Stress, Cortisol and the Modulation of Multiple Memory Systems

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Learning without thought is labor lost.

(Confucius, Chinese Philosopher)

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Contents

List of Abbreviations

ACTH	Adrenocorticotropic hormone
AMPA	α-Amino-3-hydroxy-5methyl-4-isoxalole-propionic acid
ANOVA	Analysis of Variance
AVP	Argininine Vasopressin
BLA	Basolateral complex of the amygdala
BMI	Body-Mass-Index
Ca^{2+}	Calcium
CA	Cornu amonis
CaM-KII	Calcium calmodullin kinase
CaMP	Cyclic adenosine monophosphat
CEA	Central nucleus of the amygdala
CR	Conditioned response
CREB	cAMP response element-binding protein
CRF	Corticotropin releasing factor
CRH	Corticotropin releasing hormone
CS	Conditioned stimulus
ECG	Electrocardiogram
e.g.	For example
E-LTP	Early LTP
fMRI	Functional magnetic resonance imaging
GAS	General adaptation syndrome
GR	Glucocorticoid receptor
h	Hour
HR	Heart rate
HPA axis	Hypothalamus-pituitary-adrenal axis
i.e.	That is
K^{+}	Potassium
L-LTP	Late LTP
LTD	Long-term depression
LTP	Long-term potentiation
LTS	Long-term store

M	Mean
MDBF	"Multidimensionaler Befindlichkeitsfragebogen"
MR	Mineralocorticoid receptor
ms	Miliseconds
Na^+	Sodium
NMDA	N-methyl-D-aspartate
NS	Neutral stimulus
p.	Page
PD	Parkinson's disease
PET	Positron emission tomography
PKC	Protein kinase C
PVN	Paraventricular nucleus
RMSSDibi	Root mean square successive difference of the interbeat interval
R^0	Response
S^1	Reinforcing stimulus
SAM	Sympathetic-adrenal-medullary
SD	Standard deviation
S^D	Discriminative stimulus
SEM	Standard error of the mean
SNS	Sympathetic nervous system
STS	Short-term store
TICS	Trier inventory of chronic stress
TSST	Trier social stress test
UR	Unconditioned response
US	Unconditioned stimulus

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The outline of this work

Stress is a common phenomenon in modern societies. Constantly changing challenges, evaluations and the fear of unemployment lead to a continuous pressure to succeed. This work-related stress comes along with loosening family bonds; the required flexibility and mobility make stable relations and partnerships difficult. Besides its emotional components, stress affects cognitive processes as well. This is particularly serious as continuing education is needed in all occupational fields. "Lifelong learning" is a request to each of us.

This work deals with a intersection of stress and learning, the modulation of multiple (learning and) memory systems by stress. Up to now, research focussed on stress-induced changes in the quantity of learning, i.e. *how much* people learn under stress. The present work addresses stress effects on the quality of learning, i.e. on *how* people learn under stress. It aims to provide a first answer to the following questions:

(i) Does stress modulate multiple memory systems in humans?

(ii) Is there an effect of the glucocorticoid stress hormone cortisol on the use of multiple memory systems?

(iii) Do people show a permanent tendency to prefer one kind of learning over another, irrespective of acute factors such as stress?

This work is of interdisciplinary character. Its topic is shaped by psychological, medical and neurobiological research. This has some advantages but poses the risk of communication problems. For instance, many psychologists view memory as a purely mental entity, some neurobiologists, on the other hand, consider primarily the associated brain structure. The present work applies a psychobiological approach. It focuses on both psychological concepts and their biological basis.

Multiple memory systems and stress are at the centre of this work and will be portrayed in chapters one and two, respectively. Chapter three will link these two topics, it is dedicated to the effects of stress on memory and memory system modulation. To assess the impact of stress on multiple memory systems, a paradigm is needed that allows to distinguish different memory systems. The development of a task that allows to separate hippocampus-based spatial and caudate nucleus-based stimulus response learning and memory is described in chapter 4. Using this task the influence of psychosocial stress (chapter 5) and the stress hormone cortisol (chapter 6) on the use of spatial and stimulus-response strategies was tested. In a third and final study, it was hypothesized that people have a durable proneness to use

either spatial or stimulus-response learning (chapter 7). This work ends with some overall remarks (chapter 8).

1 Learning and Memory: Psychological and Neurobiological Aspects

1.1 The relationship between learning and memory

Imagine you were asked to name the capital of Italy. Presumably, you know that the correct answer is Rome. Why are you able to answer correctly? First, you have learned at school that Rome is the capital of Italy. Second, you remember what you have learned. Even this little example demonstrates how close the relationship between learning and memory is. If nothing is learned, there is nothing to memorize. On the other hand, if something is not stored in memory you cannot say that it has been learned. Memory is a necessary prerequisite of learning and vice versa. Despite this, the close relationship between learning and memory is often neglected within psychology text books (Mazur 2004, Wilhite and Payne 1992). Only few authors addressed the question how learning and memory relate to each other (Schermer 2002, Spear and Riccio 1994). Although the close relationship between learning and memory is obvious a synonymous use of both terms is not reasonable, since they correspond to different issues. Learning refers to the acquisition of information or skills, which leads to experience- or training-based changes in behavior and thinking. These changes have to outlast a longer time (Schermer 2002, Weidenmann and Krapp 2001). Memory can be defined either as an internal representation of what a person has learned or as a process, which leads to remembering (Spear and Riccio 1994). The author of the present work views memory as a process that comprises encoding, consolidation, storage, and retrieval. Following this view learning can be considered as an early part of the memory process.

Central psychological and neurobiological concepts of learning and memory will be described below. This is seen as very important as both some psychologists and neurobiologists working on learning and memory seem to neglect developments in the respective other discipline, which impedes a fruitful synergism. Since learning and memory have developed as relatively independent fields of research within psychology, the psychological aspects of learning and memory will be depicted separately. It should be noted that it is not the aim of this work to report the progress within the psychological research of learning and memory during the last century in detail, but to give a short overview of significant developments. In contrast to psychology, neurobiology has not distinguished

clearly between learning and memory. Therefore the neurobiological aspects of learning and memory will be described together. Again, only selected aspects will be specified. Since molecular mechanisms underlying learning and memory are not directly relevant within the present work they won't be addressed in detail. The focus will be mainly on memory systems in the brain.

1.2 Psychological aspects of learning and memory

1.2.1 Learning from a psychological perspective

Learning is necessary for the adaptation to environmental challenges and thus for the survival of the organism. Basic principles of learning belong to the most fundamental questions about human nature. Early ideas about learning can be found in Greek antiquity already. The concepts of association and contiguity, for instance, were introduced by the philosopher Aristotle (Kluwe et al. 2003). The scientific examination of learning became of increasing importance during the first decades of the 20th century when the until then dominating method of introspection became an object of growing criticism and the focus of interest changed from thinking to learning (Davison and Neale 1998). As the researchers concerned with learning in those years dealt with observable behavior only, they were called "behaviorists". The behaviorists studied which stimuli lead to which responses. Other mental processes were almost completely ignored. For several decades the behaviorism had been the prevalent paradigm in the study of learning. However, during the 1950s, criticism on the behavioristic paradigm and its neglecting of mental processes arose. A concurrent approach that put emphasis on how information is received, stored, and processed emerged – the cognitive paradigm ("cognitive revolution", see Miller 2003).

During the last century three theories of learning have been especially influential: classical conditioning, operant conditioning, and social-cognitive learning. These will be described briefly.

1.2.1.1 Classical conditioning

The basic principle of classical conditioning was found rather coincidentally by the Russian physiologist Ivan Pavlov (1849-1936) when he investigated the mechanisms of digestion. Pavlov studied the salivation of dogs during feeding. Thereby he noticed that dogs, which were tested repeatedly, started to salivate already before they saw the food. The

Russian physiologist concluded that there must have been a stimulus, which always preceded the presentation of food (e.g. the investigator) and led to the precipitated salivation. Based on his observations Pavlov formulated the foundations of classical conditioning (see e.g. (Domjan 1998, Mazur 2004, Schwartz 1984): The repeated pairing of a neutral stimulus (NS) and an unconditioned stimulus (US) leading to an unconditioned response (UR) changes the quality of the NS (then called conditioned stimulus, CS) so that he is able to evoke the UR (then called conditioned response, CR) without the presence of the US (see figure 1.1). The term unconditioned indicates that the association between stimulus and response is not learned, but innate. Whereas the term "conditioned" points to a learned relationship between stimulus and response. Conditioned responses will be reduced after the CS was presented repeatedly without the US (extinction). But after a resting time a spontaneous recovery may sometimes be observed (Domjan 1998), so it is questionable whether a relationship between stimulus and response once learned can be extinguished completely.

The learning of an association between two stimuli is called excitatory conditioning. A second principle introduced by Pavlov is inhibitory conditioning. Inhibitory conditioning means that a CS signals, that an US will *not* occur. Although this is important in daily life (“no entry”, “out of order”), it has not received as much attention from psychologists as excitatory conditioning (Domjan 1998). As inhibitory conditioning is of little relevance within the present work, it won’t be discussed further.

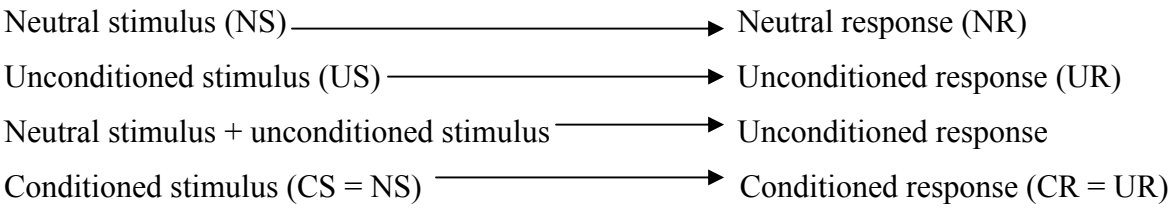


Figure 1.1: *Basic principle of Pavlovian classical conditioning.*

An example of (excitatory) classical conditioning that has become very famous is the case of “little Albert” (Watson and Rayner 1920). Watson and Rayner (1920) presented a white rat to the 11 month old infant Albert B.. At the same time they struck a bar of steel. The resulting noise led to intensive fear reactions in Albert. After repeated pairings of the white rat and the noise the rat alone caused fear in the infant (see figure 1.2). Interestingly, Watson and Rayner (1920) observed that the fear triggering quality was not restricted to the rat, but was also found for a rabbit, a dog, a fur coat, cotton wool and a Santa Claus mask. The ability of stimuli similar to the CS to provoke responses comparable to the CR is known as stimulus

generalization (Mazur 2004). Pavlov‘s ideas about classical conditioning (today also referred to as Stimulus substitution Theory) had an enormous impact on modern psychology. Nevertheless there are some problems with the paradigm of classical conditioning as proposed by Pavlov. Three of them are mentioned by Mazur (2004). First, UR and CR often differ regarding their intensity and time characteristics. Second, the US causes usually many responses and not all of them follow the CS. Third, in some cases the UR and CR differ even in regard to their direction.

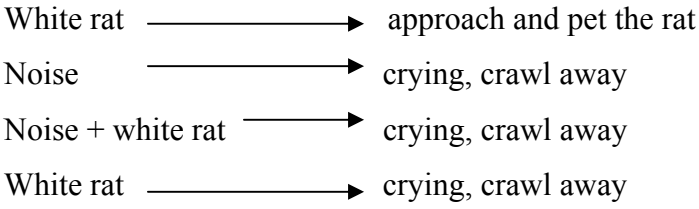


Figure 1.2: *Fear conditioning in "little Albert". The white rat becomes a conditioned stimulus leading to fear reactions after being paired repeatedly with noise.*

Another aspect to criticize is that Pavlov neglected the significance of cognitive processes during learning. The importance of the informativeness of the CS referring to the occurrence of the US for a subject's reaction to the CS, however, has been demonstrated by several authors (e.g. Rescorla 1966, Seligman 1968).

Although it seems reasonable to assume that the majority of our learned behaviors are not based on classical conditioning, its relevance should not be underestimated. Recent studies present evidence that classical conditioning processes have amongst others an impact on immune reactions (e.g. Irwin and Livnat 1987, Spector et al. 1994), taste aversion (e.g. Bills et al. 2003, Masaki and Nakajama 2005) and attention (Beaver et al. 2005).

1.2.1.2 Instrumental conditioning

Same as in habituation and sensitization organisms have no control over stimuli in classical conditioning (Domjan 1998). However, in the type of learning to be described now the presented stimuli depend on the reactions of the subject. The behavior of most people is instrumental, i.e. it occurs to achieve a certain goal. Instrumental conditioning describes the process by which an individual learns how to react to reach a certain consequence.

One of the first who investigated the question how behavior is shaped by experience was Edward L. Thorndike. He studied the behavior of animals such as cats, dogs and chickens, when being hungry and captured in a "problem-cage" (Thorndike 1911). Thorndike

observed how long it took the animals to get out of the cage. The Columbia psychologist noticed that the animals have shown instinctive behavior (as for example clawing) when put in the cage. Rather coincidentally they showed reactions defined as goal behavior leading to escape. After several successful movements the connection between the situation (being captured in a cage) and the movements got stronger. In consequence of that, the escape latency decreased with increasing number of trials. Based on these findings Thorndike formulated the law of effect: "Of several responses…those which are…closely followed by satisfaction…will be more likely to recur; those which are…closely followed by discomfort…will be less likely to recur" (1911, Chapter 5).

The test arrangement of Thorndike was slightly altered by Burhus F. Skinner. He studied responses that could be done repeatedly by the animals, not only once as in the experiments of Thorndike. Skinner (1938) was the first who used the term operant conditioning (also termed instrumental conditioning) to refer to the consequence dependent strengthening of behavior. Moreover, he developed the fundamental principle of instrumental conditioning displayed in figure 1.3. Three components are essential for instrumental conditioning: the discriminative stimulus (S^D), the response of the subject (R^0), and the reinforcing stimulus (S^1). Their relationship was stated by Skinner (1938) as follows: "only in the presence of S^D is R^0 followed by S^1" (p. 178). A controversially discussed aspect was the relationship between R^0 and S^1. Is temporal contiguity between R^0 and S^1 sufficient or is a causal contingency between both required? Skinner (1948) interpreted findings obtained in the study of pigeons as evidence for the assumption that temporal contiguity is the main responsible factor for learning. This was questioned by Staddon and Simmelhag (1971) who interpreted the results they gained in a replication of Skinner's study in favor of the more cognitive contingency hypothesis. In line with their view, Hammond (1980) found that the response frequency of rats was directly related to the level of contingency between response and reinforcer. To sum it up, the contingency hypothesis has been shown to be more adequate.

Four procedures have been distinguished within the paradigm of instrumental conditioning: positive reinforcement, negative reinforcement, punishment and omission training. Positive reinforcement refers to the presentation of appetitive stimuli. The removal of aversive stimuli is called negative reinforcement. Presenting aversive stimuli is known as punishment. Omission training, finally, means the removal of appetitive stimuli. While the former are to strengthen certain behavior, the latter two shall weaken it.

A special form of operant conditioning is shaping. It refers to the successive building up of behavior. In shaping behavior in direction of the objective is reinforced. This is especially important when an individual is not able to achieve a goal in one step.

$$S^D \rightarrow R^0 \rightarrow S^1$$

Figure 1.3: *The basic principle of instrumental/operant conditioning.*

A significant area of application of instrumental conditioning is behavior therapy (e. g. token economies, see Margraf 2000). Further fields of application are for example the control of slow cortical potentials in epilepsy patients (Birbaumer and Lachenmeir 1997, Sterman 2000), the treatment of chronic pain (Flor et al. 2002, Linton 1994) and the modification of students classroom behavior (Dunn and French 1982, Sharpley 1985).
Here it should be noted that behavior is (as one could get the impression from the preceding sections) not completely determined by the reinforcement history of a person. As Breland and Breland (Breland and Breland 1961) have pointed out, it is always a mixture of learned and inherited factors.

Instrumental conditioning has also been referred to as **stimulus-response learning** (Domjan 1998). Stimulus-response learning will be of great importance in this work. In chapter 3.2.2.1 a brain system will be portrayed that has been shown to be involved in this kind of learning. This system is one of the two which are in the centre of the discussion of stress effects on multiple memory systems.

1.2.1.3 Social-cognitive learning

Albert Bandura (1979) claimed that most behavior patterns are not acquired via classical or operant conditioning. In his social-cognitive theory of learning he considered the impact of associative learning on behavior, but argued that the majority of the behavior shown by individuals can be ascribed to the observation of others (models) in comparable situations. The proposed form of learning was called observational or imitative learning. It is noteworthy that imitative learning does not require direct observation. Verbal reports by others can be sufficient for learning. Bandura (1979) suggested that observational learning is affected by four processes. First, *attention* has to be focused on the relevant behavior aspects. Second, the observed behavior must be stored in *memory*. Third, the cognitive representation has to be transferred in action (*motor reproduction*). Finally, as people do not realize everything they

learn, the *motivation* to act is required. Looking at these processes makes it clear that – in contrast to classical and operant conditioning – in Bandura's theory cognitive processes play an important role. An advantage of the social cognitive theory of learning is that it can account for the first time people behave in a certain way. According to Bandura people show certain behavior, because they have observed it in others.

In a famous study Bandura, Ross and Ross (1961) presented evidence for the influence models have on the aggressive behavior of children. They found that children, who had observed an adult maltreating a doll, showed in a subsequent situation significantly more aggressive behavior compared to control children and children, who observed a non-aggressive adult. The aggressive behavior shown by the children resembled clearly the behavior exhibited by the adult models. This study is often cited when the influence of the media on violent behavior of youths is discussed. Principles of observational learning are also an important part of behavior therapy. For instance, Pfingsten and Hintsch (2002) used modeling to teach anxious people adequate behavior in social situations.

Within the present work observational learning will be of no importance. Nevertheless it seemed reasonable to give a short overview of Bandura's theory, since it has been of great significance within the psychology of learning.

1.2.2 Memory from a psychological perspective

Humans have been dealing with questions concerning memory since millennia. Early societies believed even in gods and goddesses governing memory. In ancient Rome for example Minerva was deified as the goddess of learning, memory and wisdom (Searleman and Herrmann 1994). Plato and Aristotle were the first who thought intensively about memory. The former gave several metaphors of memory. For instance, he described it as a wax tablet (Herrmann and Chaffin 1988). During the middle ages there was less work on memory (mostly spiritual like the work of Augustinus). This changed during the 16th and 17th century, when scholars as Kant, Locke, Bacon or Mill were interested in the nature of memory. A milestone in the study of memory can be seen in the investigations of Hermann Ebbinghaus in the late 19th century. The German scholar was the first who studied memory with the help of experimental methods. He learned lists of nonsense syllables by heart and tried to remember as many of these syllables as possible after varying retention intervals. Ebbinghaus plotted the percentage of savings against the retention interval. The resulting forgetting curve was characterized by a substantial loss over the first hours and days and a more gradual loss in the following time. Moreover, Ebbinghaus noticed that forgetting was

less after multiple repetitions of the lists (Bower 2000). Today, it is known that there is not one but many forgetting curves, since forgetting depends on many personal and environmental factors (Adams 1980). Nevertheless, Ebbingshaus' investigations had an enormous impact on memory research. During the 1940s and 1950s, when behaviorism dominated the psychological research especially in America, memory processes were neglected. However, from the 1960s on memory has been a topic of intensive research.

In the following, three models of memory that have been especially influential will be described briefly: the Multiple-Store Model by Atkinson and Shiffrin, the Working Memory model by Baddeley and Hitch and the levels of processing approach by Craik and Lockhart. Furthermore some discussed distinctions of types of knowledge represented in memory will be resumed. Here special emphasis will be put on spatial memory as this is of great relevance within the present work.

1.2.2.1 The multiple-store model

The most popular memory model of the late 1960s and the early 1970s was proposed by Atkinson and Shiffrin (1968). They postulated a memory system composed of three distinct components (figure 1.4): the sensory register, the short-term store (STS) and the long-term store (LTS).

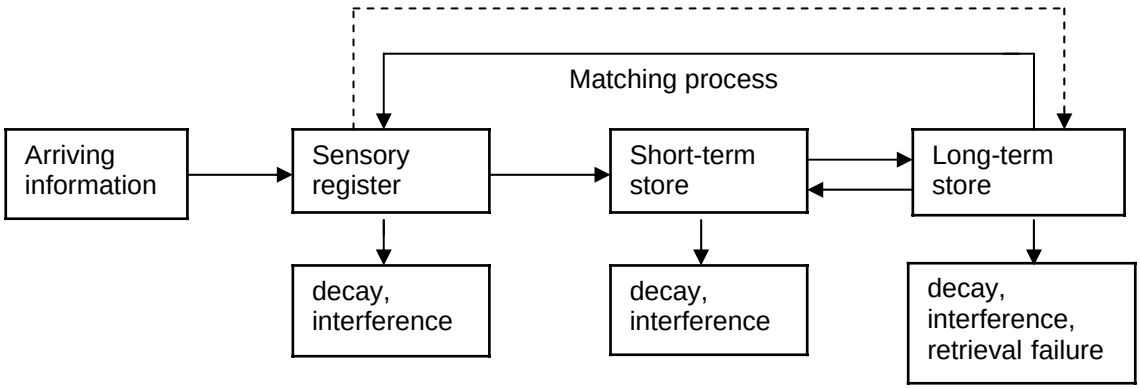


Figure 1.4: *The multi-store model by Atkinson and Shiffrin.*

Incoming information is hold for a very short time (several hundred milliseconds), in which the arrived stimuli are scanned. As each element is scanned a matching process is carried out in which information stored in the LTS and related to the present stimuli (e. g. the verbal name) is activated. Stimuli attended to and identified are transferred to the STS. Atkinson and Shiffrin (1968) speculated that there may be a direct transfer from the sensory

register to the LTS as well. This is indicated by the dashed line in figure 1.4. Rapid decay and interference with new incoming material lead to loss from the sensory register.

The STS is a temporary store of limited capacity (5 to 8 items). However, it is not as temporary as the sensory register. Atkinson and Shiffrin (1968) suggested that stimuli decay and get lost from STS after a period of 15 to 30 seconds. Another cause of forgetting postulated by Wilhite (1992) is interference with incoming stimuli similar to the previous ones. The transfer of material to LTS depends on the time the material is hold in STS (Adams 1980). This time can be lengthened by rehearsal, the repetition of the relevant information, which was thought to rely upon a subdivision of STS called rehearsal buffer. Further control processes governed by the subject are chunking, coding and organizing.

Information transferred to LTS can be stored permanently. Moreover, the LTS has an (virtually) unlimited capacity. As mentioned above the LTS is in constant communication with both the sensory register and the STS. Its functions are – besides storing stimuli – to search for and retrieve particular information. Material transferred to LTS can also be forgotten, but this happens much slower than in the sensory register or the STS. Loss from LTS is mainly due to decay, interference or as Atkinson and Shiffrin (1971, see Wilhite and Payne 1992) concluded three years after their original formulation of their memory model to retrieval failure.

The multi-store model postulates an information flow between the three stores that follows definite rules. The real innovation of the model was the assumption of deliberately applicable control processes to memorize, retain, reproduce and process information as well as to govern the information flow between the system components.

It is to be emphasized that STS and LTS are not to be confused with the terms short-term memory and long-term memory. As Atkinson and Shiffrin (1968) pointed out both the STS and the LTS contribute to short-term memory as well as to long-term memory. Evidence consistent and evidence inconsistent with the multi-store model is listed elsewhere (e.g. Adams 1980, Bower 2000, Eysenck and Keane 2000, Kluwe 1997, Squire et al. 1993, Wilhite and Payne 1992).

1.2.2.2 Working memory

Atkinson and Shiffrin (1968) ascribed the key role within their memory system to the STS. They suggested that it is probably more multifarious than they had conceptualized it and has to be differentiated. This was done by Baddeley and Hitch (1974). They used a “dual task” method, in which subjects had to perform two tasks simultaneously, to investigate the

STS. Contrary to their expectation, Baddeley and Hitch observed that - despite the additional task - no or only moderate impairments of cognitive performance occurred. Therefore the assumption of a unitary STS responsible for storage and processing of material seemed unlikely.

The multicomponent working memory system proposed by Baddeley and Hitch (1974) is composed of two slave systems, the phonological loop and the visuo-spatial sketchpad, and a super ordinate instance, the central executive. The phonological loop is responsible for the manipulation and storage of auditory stimuli. It is similar to the rehearsal buffer postulated in Atkinson and Shiffrin's model. However, in contrast to Atkinson and Shiffrin, Baddeley and Hitch claim that rehearsal is useful but no necessary component of the memory system. The phonological loop is subdivided into a phonological store and an articulatory control process. Within the former memory traces are irretrievable after a period of about 2 seconds, but can be activated when read in by the articulatory control process, which feeds back to the phonological store. The articulatory control process can also receive visual material via articulation (phonological coding).

The visuo-spatial sketchpad is a visual equivalent to the phonological loop. It is responsible for the manipulation and storage of visual-spatial images and is loaded either directly by perception or indirectly by creating visual images (Baddeley 1999). Logie (1995) suggested differentiating between two subsystems within the visuo-spatial sketchpad: a visual cache responsible for storing information about color and form and a visual scribe dealing with movement and spatial information.

The central executive, which is modality-free and has a limited capacity (Baddeley 2000), plays the key role in the working memory system. Despite this, only little is known about this component. Its main function is the coordination of the slave systems. This is done via running off of scripts and supervising attention processes (Baddeley 1992). Further functions attributed to the central executive are planning, deciding, correcting mistakes and interrupting semiautomatic processes (Kluwe 1997).

One implication of the model by Baddeley and Hitch (1974) is that two activities can not be accomplished simultaneously when they need the same component, while they can be carried out in parallel when they require different components (Eysenck and Keane 2000). Thus, individuals are, for example, able to watch a movie and listen to music via headphones at the same time, but not to watch a movie and read a newspaper.

The working memory model has some advantages compared to the multi-store model. For instance, it can account for the observation that some people with STS deficits show only

little impairment in long-term storage. A finding the Atkinson and Shiffrin model can not explain (Baddeley and Hitch 1974). One problem of the model proposed by Baddeley and Hitch is that the exact function and functioning of the central executive remains - after a period of three decades – still unclear.

1.2.2.3 Levels of processing

Atkinson and Shiffrin (1968) as well as Baddeley and Hitch (1974) emphasized the structure of the memory system. An alternative approach was suggested by Craik and Lockhart (1972). They concentrated on processes rather than structures. Craik and Lockhart postulated different levels of information processing varying between the physical analyses of stimuli (e. g. Is the word written in capital letters?) and the deep semantic processing (e.g. What does the word mean?). The core assumption of the proposed framework is that the depth of information processing relates to the memory for the information whereby a deeper level of processing leads to more durable memory traces. Though, they focused on memory processes Craik and Lockhart (1972) continued to distinguish between a short-term (STM) and a long-term memory (LTM). Two functions have been attributed to STM: maintenance and elaborative rehearsal. As its name suggests maintenance rehearsal simply holds information without deeper processing. It is assumed to prevent forgetting at the time of maintenance, but not to lead to long-term learning. Elaborative rehearsal should increase the depth at which information is processed and therefore the durability of the memory traces. The LTM was thought to depend on the kind and the amount of elaboration.

The levels of processing framework as it was originally conceptualized by Craik and Lockhart (1972) was criticized by many authors. Two famous critics were the British Michael Eysenck and Alan Baddeley. They considered the lack of independent measurement of processing depth as the main problem of Craik and Lockart's approach. As Eysenck (1978, cited from Eysenck and Keane 2000) stated: "There is a danger of using retention-test performance to provide information about the depth of processing, and then using the putative [alleged] depth of processing to 'explain' the retention-test performance, a self-defeating exercise in circularity" (p. 166). Further points of criticism were the neglecting of the retrieval situation and the assumption that deep processing is always necessary for retention (see Baddeley 1999, Eysenck and Keane 2000). Although the adequacy of the levels of processing framework as a whole was questioned, Baddeley (1999) appreciated two statements of it as "important generalizations about human memory" (p. 120). First, that semantic processing enhances memory. And second, that two forms of rehearsal, which have different effects on

the durability of memory traces, can be distinguished. A simple repetition of information on the one hand and an integration of new stimuli into already existing structures on the other hand.

1.2.2.4 Organization of information in long-term memory

Numerous forms of memory or memory systems within long-term memory have been discussed. There seems to be a broad consensus that a distinction between declarative and non-declarative (or procedural) memory, as proposed by Anderson (2001) makes sense (see also Squire 1992). Declarative memory refers to knowing "that" (e.g. …Rome is the capital of Italy). It is representational and allows contrasting and comparing remembered material (Squire 2004). Procedural memory refers to knowing "how" (e.g. …to ride a bike) and is rather dispositional. Wilhite (1992) mentions three differences between these memory forms. Firstly, declarative knowledge is possessed in an all-or-none fashion while procedural knowledge can be possessed in degrees. Secondly, declarative knowledge is (mostly) learned rapidly whereas procedural knowledge requires (mostly) repeated practice. Finally, declarative knowledge can be reproduced verbally while procedural knowledge is to be concluded from performance. Although, declarative and non-declarative memory can be seen as distinct systems they are not completely independent, but do interact. The declarative knowledge determines when and under which circumstances procedural knowledge becomes activated. Parallel to the distinction between declarative and non-declarative memory explicit and implicit memory are distinguished (Anderson 2001). Explicit knowledge can be consciously recalled whereas implicit knowledge does not tap awareness. According to Anderson (2001) explicit memory can be equated with declarative memory and implicit memory equals procedural memory.

Within declarative memory a further distinction was made between episodic and semantic knowledge (Tulving 1972). The distinction between these forms of memory is more complicated (and also more controversial, see (Wilhite and Payne 1992) than the one between declarative memory and procedural memory. Episodic memory contains knowledge of incidents of the individuals past (e.g. the first kiss). It is similar to daydreaming or introspection and allows the subject reflections about his or her past experiences. In contrast to this, semantic memory refers to knowledge of facts (e.g. the author of "King Lear") and concepts of the world. Wheeler (2000) argues that the central distinctive feature between episodic and semantic memory is that the former is associated with the "feeling to relive a […] previous episode" (p. 598) while the latter is not.

In procedural memory different forms as for example motor learning, conditioning and perceptual priming can be distinguished. Figure 1.5 gives an overview of the memory systems described and their relationship.

One particular form of episodic memory is the memory for spatial information. Since this is of special interest within the present work, it will be characterized in the next section, separately.

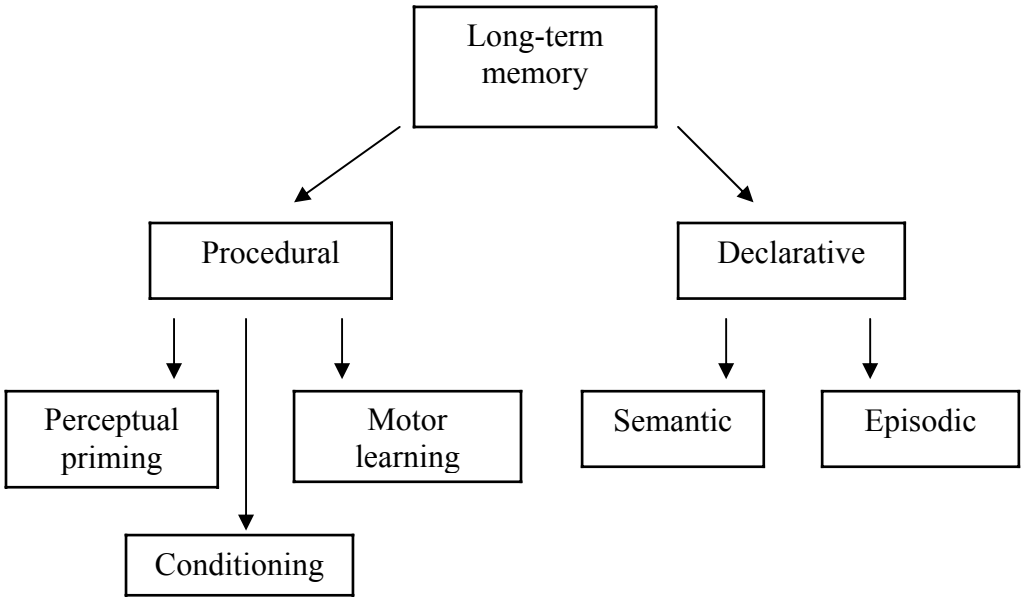


Figure 1.5: *Organization of knowledge in long-term memory (following Wilhite, 1992).*

1.2.2.5 Spatial memory

Remembering spaces is highly adaptive. Finding one's way to food or one's way back home are only two examples for this. Humans as well as animals are capable of extraordinary spatial navigation performances. In some south sea cultures open-sea navigation is well developed, enabling those folks traveling across thousands of miles of open sea (Nadel 1992). Migratory birds fly to their breading areas – often located on another continent - every year. Both the south sea folks and the migratory birds use their relative location to stimuli of the environment (e.g. stars) to accomplish these activities.

Spatial memory can be defined as the cognitive representation of spatial arrangements in the environment. It requires knowledge of relationships between multiple environmental landmarks (O'Keefe and Nadel 1978) and is acquired by direct exploration, by studying maps or by verbal descriptions. In the late 1940s during the height of behaviorism the American

psychologist Edward Tolman (1948) studied as one of the first the spatial behavior of rats. He put hungry rats at the entrance of a maze consisting of true paths and blind alleys and provided food at its end. Tolman observed that the error rate (times the rat moves to a blind alley) decreased with the number of trials. This finding was discussed in the light of a stimulus-response and a cognitive interpretation. According to stimulus-response theory the rat was responding to external stimuli (e.g. sights, smells) leading to the runnings and turnings shown by the rat. In contrast to that, the cognitive view held that "in the course of learning something like a field map of the environment gets established in the rat's brain" (Tolman 1948, p. 193). Further results gained by Tolman (1948) clearly supported the cognitive interpretation. For instance, rats satiated for food and water were put several times in a Y-maze, in which water was at the end of the right arm and food at the end of the left arm. In a test trial the trained rats were divided into two groups, one deprived of water and one deprived of food. It was found that the water-deprived rats turned right more frequently while the food-deprived rats did the opposite. This indicated that the rats learned in a non-rewarding training condition where water and food were located. In Tolman's words: „they had acquired a cognitive map" (p. 197). Three decades after Tolman's work O'Keefe and Nadel (1978) got back to the idea of cognitive maps. They distinguished between a taxon and a locale system. O'Keefe and Nadel argued that spatial information is always part of what is processed in the locale system, while the processing in the taxon system is based on the taxonomic principles of category inclusion and generalization (1994). The taxon system was assumed to be focused on single stimuli. The locale system, on the other hand, should generate place hypotheses and exploration. It was seen as a cognitive mapping system. Maps were thought to be built up by exploration merely. And curiosity was viewed to act as the motivational force behind exploration. It was stated that new stimuli are encoded with regard to their spatial relation to other stimuli in the environment. In contrast to the taxon system the locale system should be sensitive to changes in the environment, but independent of time and repetition. Map-like representations within the locale system were assumed to provide – because of their flexibility – a basis for the generation of novel outputs. Moreover, due to the uniqueness of the map-like representations, there should be less interference in the locale than in the taxon system. Nadel (1994) argued that the locale system provides a context, in which the context-free information of the taxon system can be integrated. A dysfunction in the locale system – so was supposed by O'Keefe and Nadel (1978) – would lead to loss of exploration and place learning: Subjects would be forced to rely on their taxon system. The work of O'Keefe and Nadel will be taken up when the function of the hippocampus is discussed (see 3.2.1.1).

Barbara Tversky (2000) pointed out that mental spaces differ from "real" spaces. Mental spaces were often incomplete, inconsistent, distorted and mostly multimodal. Therefore, she recommended speaking of cognitive collages rather than cognitive maps as Tolman (1948) and O'Keefe and Nadel (1978) did. It should be noted here, however, that Tolman as well as O'Keefe and Nadel used rats as subjects whereas Tversky investigated humans. Slightly different findings, accentuations and methods are probably due to the different species studied.

Spatial memory was sometimes referred to as "cognitive" memory, in contrast to stimulus-response memory, which was labeled "habit" memory (Nadel 1994, Packard and Cahill 2001, White and McDonald 2002). This terminology emphasizes that spatial memory is seen as cognitively more demanding than stimulus-response memory.

1.3 Neurobiological aspects of learning and memory

So far the focus was on psychological concepts of learning and memory. Now neurobiological aspects will be discussed. Before introducing the multiple-memory-systems hypothesis and the memory systems most relevant in this work a short overview of cellular mechanisms underlying learning and memory will be given.

1.3.1 Cellular mechanisms underlying learning and memory

Learning is not a simple process of accumulating new experiences in memory like putting new books in a bookcase. It is rather a change in the way a person behaves, feels, perceives and thinks. The basic mechanism underlying learning and memory is synaptic plasticity, the changes in the structure or biochemistry of synapses that alter their postsynaptic effects (Carlson 2001). At the end of the 1940s the Canadian psychologist Donald E. Hebb published his ideas about how synaptic plasticity contributes to the organization of single cells to what he called "cell assemblies". Hebb (1949) postulated a dual-trace mechanism. He assumed that a sensory event would lead to reverberatory after-effects, which should constitute the physiological basis of a "transient" memory for the stimulus. Moreover, the reverberatory after-effects were supposed to prolong the time for structural changes at synapses necessary for memory consolidation. Hebb's central postulation regarding cellular changes was as follows:

> "When an axon of cell A is near enough to excite a cell B and repeatedly or persistently takes part in firing it, some growth process or metabolic change takes place in one or both cells such that A's efficiency, as one of the cells firing B, is increased" (p. 62).

The most discussed form of synaptic plasticity and best model of the cellular basis of learning and memory is synaptic long-term potentiation. In 1968, the young Norwegian Terje Lømo observed that high-frequency electrical stimulation (tetanus) of hippocampal neurons led to a steeper slope of the excitatory synaptic potential in response to a subsequent single pulse (Bliss and Lomo 1973). The phenomenon that "a brief burst of high-frequency activation of presynaptic fibers leads to an enhancement of excitatory synaptic efficacy lasting hours to weeks or longer" (Wigtström and Gustafsson 1992) has become known as **long-term potentiation (LTP)**. After a latency of a few seconds, LTP reaches its peak within a minute. It attains then at a stable level after 10 to 30 minutes of decay (Wigtström and Gustafsson 1992). There are six characteristics which make LTP an attractive model of learning and memory: (a) LTP seems to be a feature of the hippocampus, a brain region often associated with learning and memory (see below), (b) LTP develops very fast, (c) it can be long-lasting, (d) LTP is specific, only relevant synapses are changed, (e) LTP is induced by a stimulation rhythm comparable to the rhythm (theta-activity) recorded in the hippocampus during exploration behavior and finally (f) LTP is associative that means a potentiation results only from the simultaneous income of multiple inputs (Eichenbaum and Cohen 2001, Lynch 2004). The associative character of LTP is linked to the fact that two conditions have to be fulfilled simultaneously for the occurrence of LTP: the stimulation of the synapse and the depolarization of the postsynaptic neuron (Carlson 2001). This is due to the features of a glutamate receptor, which is of great relevance for memory processes – the N-methyl D-aspartate (NMDA) receptor. The NMDA receptor can be seen as a "contingency detector" (Wigtström and Gustafsson 1992) since it requires the presence of glutamate and the depolarization of the postsynaptic cell at the same time for its activation. Activation of the NMDA receptor leads to calcium (Ca^{2+}) influx into the cell. When Ca^{2+} enters the postsynaptic cell it activates protein kinases as calcium Calmodullin Kinase (CaM-KII), which then "wake up" previously "sleeping" AMPA receptors. AMPA receptors are same as NMDA receptors glutaminergic receptors. However, in contrast to NMDA receptors, AMPA receptors show no increased permeability for Ca^{2+} when activated, but for potassium (K^{+}) and sodium (Na^{+}). The increased AMPA conductance is followed by an increased responsiveness to glutamate (Lynch 2004). Another effect of Ca^{2+} influx is the synthesis of

new proteins, which is necessary for LTP maintenance. Eichenbaum and Cohen (2001) suggested the following cascade: Ca^{2+} influx leads to the activation of adenyl cyclase, which in turn activates ATP to cyclic AMP (cAMP). This activates protein kinase C (PKC) leading to the phosphorylation of various proteins such as the CaMP responsive transcription factor CREB that relates to LTP as shown by genetically manipulated mice lacking CREB. Further postsynaptic mechanisms contributing to the maintenance of LTP have been proposed. These were (amongst others) an increase in the number of active zones (Edwards 1995), a change in the size and the form of the dendritic spines as well as discontinuities in the postsynaptic density (Greenough 1992) and the growth of new dendritic spines (Eichenbaum and Cohen 2001). Many authors argue that besides the mentioned postsynaptic changes presynaptic changes play a role, too. Particularly, an increase of the presynaptic transmitter release is discussed (Medina and Izquierdo 1995, Reid et al. 2004, Tsien 1992). Since the initial effects of simultaneous pre- and postsynaptic activity evoke cellular mechanisms localized at the postsynaptic site, changes in the physiology of the presynaptic cell require a retrograde messenger traveling from the activated postsynaptic site to the presynaptic site. Several studies point to the gas nitric oxide as a promising candidate taking this part (e.g. Bon and Garthwaite 2003, Ferry and McGaugh 1999, Medina and Izquierdo 1995, O'Dell et al. 1991).

Two phases of LTP have been distinguished, an early one (E-LTP) lasting up to 2 hours and a late one (L-LTP) that is more long-lasting (Baudry and Lynch 1992, Frey and Morris 1998). While the former is thought to be independent of protein synthesis, the latter requires the synthesis of new proteins.

LTP has mostly been studied in the hippocampus. However, it occurs in other brain regions such as the neocortex, the neostriatum, the cerebellum and the amygdala as well (Eichenbaum and Cohen 2001). Moreover, LTP is not always dependent on NMDA receptors. Eichenbaum and Cohen (2001), for instance, describe a form of LTP in the mossy fiber between dentate gyrus and CA 3 that is entirely mediated by an increased presynaptic transmitter release.

Here, it is to be emphasized that LTP is not to be equated with memory. Three strategies have been applied to investigate the relationship between LTP and memory: (a) Is there a change in synaptic efficacy after a learning experience? (b) Is there an association between neural activity patterns and activation parameters for LTP induction? (c) Is learning prevented by manipulating LTP? (Morris 1992) Although LTP is not memory, optimism that there is a common mechanism shared by LTP and memory seems to be justified (for an overview of relevant results see Eichenbaum and Cohen 2001 and Morris 1992). This view is

supported by a recent study by Baker and Kim (2002) who tested stress effects on (hippocampal) LTP and memory in an object recognition task in rats. They obtained a stress-induced memory impairment which was accompanied by impaired LTP. More important, Baker and Kim (2002) showed that these memory impairments were transient, they disappeared 48 h after training - same as the LTP impairments.

A mechanism that was associated with the decay of memories is long-term depression (LTD). LTD refers to a type of synaptic plasticity in which the efficacy of the synaptic transmission is reduced. It is caused by low-frequency stimulation and implies (at least in the hippocampus and the neocortex) a reduced Ca^{2+} level (Ito 1992). According to Carroll et al. (1999) the weakening of the synaptic transmission might be due to a decrease of the number of AMPA receptors caused by LTD. Rosenzweig et al. (2001) view LTD as an active destruction of memories. That LTD is no passive process, but requires the activation of NMDA receptors was shown by Villarreal and colleagues (2002). They demonstrated that the decay of LTP was blocked by an NMDA antagonist (CPP). So it seems as if NMDA receptors reverse LTP actively. Beyond this, Villarreal et al. (2002) could present further evidence for the link between LTP and memory; the prolongation of the LTP led to an enhanced spatial memory.

Although numerous studies have been conducted and substantial progress has been made within the topic of learning and memory since the seminal work of Hebb, research is still far away from a full understanding of the processes underlying learning and memory.

1.3.2 Multiple memory systems

During the past decades strong evidence has emerged that memory is no unitary entity, but organized in multiple functionally and anatomically distinct systems. If memory were a single faculty, one would expect to observe for all persons high correlations between their memory performances for different materials. That this is not the case has been demonstrated in studies with amnesics. At the end of the 1950s Scoville and Milner (1957) reported on the memory impairments of the neurological patient H. M., who had the medial temporal lobe removed and is today probably the most famous amnesic. H. M. was severely impaired in retaining new memories while he was able to retrieve remote memories or retain memories over short delays. Over 20 years after Scoville and Milner's investigation Cohen and Squire (1980) presented data suggesting that amnesics are also capable of acquiring new skills such as mirror writing. More recent studies confirmed this finding indicating that

amnesics' learning capabilities are not reduced to pure perceptual and motor learning (Haist et al. 1991, Squire and Frambach 1990).

Considerable evidence supporting the idea of multiple memory systems has also come from dissociation studies. Double dissociations exist when damage to brain region A leads to impairment in task x but not in task y whereas damage to brain region B leads to the opposite pattern. Numerous studies were successful in demonstrating double dissociations between brain structures (Bechara et al. 1995, Bills et al. 2003, Gabrieli et al. 1995, Knowlton et al. 1996, McDonald and White 1994, Myers et al. 2003a, Packard et al. 1989, Packard and White 1991, Packard and McGaugh 1992, Packard and McGaugh 1996,). And triple dissociations have been shown as well (Kesner et al. 1993, McDonald and White 1993, White and McDonald 2002).

Although there is now broad consensus that memory manifests in multiple systems, it is not really clear what exactly a memory system is. Squire (2004) argues that the view of memory as an exclusively psychological function is not consistent with biology while Nadel (1997) emphasizes that a memory system is more than a particular brain area. In line with these positions Kim and Baxter (2001) defined a memory system as a psychological and biological entity being determined by its processed information and performed operations on the one hand and by its neural structures and connections operating with particular information on the other hand. Neurobiologists proposed that a memory system is the place of both processing and storage of material (Nadel 1994).

Most multiple memory system views have been dualistic. Distinctions have been made, for instance, between a taxon and a locale system (O'Keefe and Nadel 1978, see above), a declarative and a non-declarative system (Squire and Zola-Morgan 1988, Squire et al. 1993, Squire 1994), a reference and a working memory system (Olton et al. 1979), or a simple and a configural association system (Sutherland and Rudy 1989). However, these dualistic views are too simple; reality is more complex. Memory systems consist of subsystems and subfunctions (Eichenbaum and Cohen 2001). An approach taking these complexities into account is shown in Figure 1.6.

According to Sherry and Schacter (1987) distinct memory systems have evolved whenever there was a functional incompatibility between memory demands. This implies that memory involves adaptive specializations.

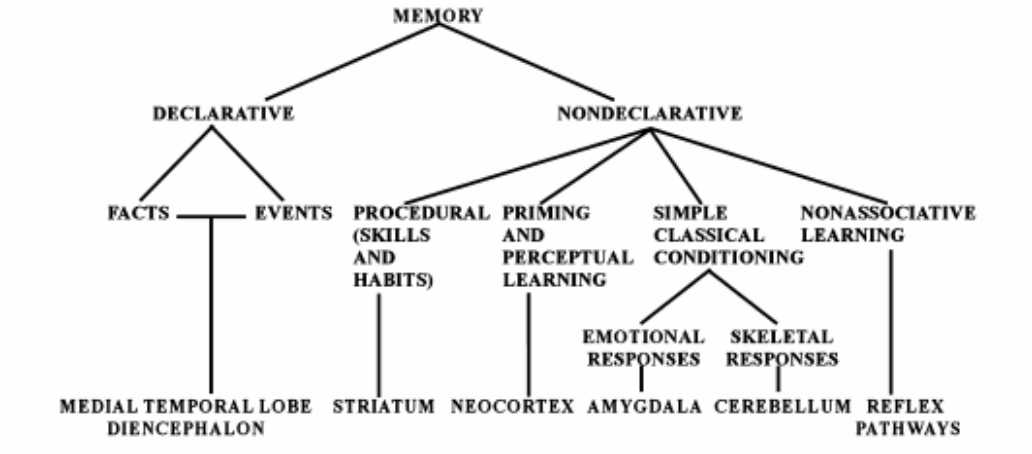


Figure 1.6: *Overview multiple memory systems (from Squire 2004).*

Below, three memory systems which have been at the centre of the multiple memory systems discussion and are most relevant for the present work will be portrayed: the medial temporal lobe system, the basal ganglia, and the amygdala. Further memory systems are for example the cerebellum (Christian and Thompson 2005, Gabrieli 1998) the occipital (Gabrieli et al. 1995) and the prefrontal cortex (Eichenbaum and Cohen 2001, Lee and Kesner 2003). Since they are of minor interest within this work they will not be addressed further.

1.3.2.1 The medial temporal lobe system

Anatomy. There has been an ongoing terminological imprecision in the discussion about the medial temporal lobe system. Here, the terminology of Zola and Squire (2000) will be used, since this provides a reasonable framework within the present work. According to Zola and Squire the hippocampus consists of the cells of the hippocampus proper (CA1 – CA4) and the dentate gyrus. Together with the subiculum the hippocampus constitutes the hippocampal region, which in turn constitutes – together with the entorhinal cortex – the hippocampal formation (figure 1.7). The medial temporal lobe system refers to the hippocampal formation plus the adjacent perirhinal and parahippocampal cortices (see also Eichenbaum and Cohen 2001). Since the hippocampus is the most prominent structure with respect to memory it will be in the centre of the following description.

The hippocampus is an elongated bulge medially in the temporal horn of the lateral ventricle. It is the structure that has been most often associated with memory. Compared to neocortex the hippocampus is characterized by a rather simple pattern. Within the dentate gyrus there are mainly granule cells; in the hippocampus proper prevail pyramidal cells. The

main afferents of the hippocampus come from two sources: the entorhinal cortex and the septal nuclei. Although there are only relative few septohippocampal pathways, they lead to important modulatory effects by long-lasting depolarizations. Further afferents come from the raphe nuclei, the locus coeruleus, the thalamus and the gyrus cinguli (Brodal 1992, Trepel 2004).

Hippocampal efferents project to the subiculum, the entorhinal area and the septum. So the hippocampus acts mainly on these structures from which it receives information. However, the hippocampus projects - indirectly via the subiculum and the entorhinal cortex - also to the hypothalamus and various cortex areas. Most of the hippocampal efferents run through the fornix. The fimbria-fornix is one of the two main routes connecting the hippocampus bidirectionally to subcortical regions as the nucleus accumbens, the mammilary bodies or the ventral medial hypothalamus.

Starting from the fornix the Papez-circuit arises: the hippocampus projects via the fornix to the mammilary bodies; these send information to the anterior nucleus of the thalamus, which transfers the information to the cingulum that projects back to the hippocampus (Trepel 2004). A second route is the so called “retrohippocampal output”, which connects the hippocampus via the subiculum to the cingulum, the entorhinal and prefrontal cortex (White and McDonald 2002). The latter is of special interest, since the prefrontal cortex has been often associated with consciousness (Badgaiyan 2005, Dehaene et al. 2003) .

Another important transmission route runs within the hippocampal formation. Axons from the entorhinal cortex, which receives extensive input from all sensory association areas, project via the perforant path to the dentate gyrus. Mossy fibers lead from dentate gyrus to pyramidal cells of CA3, which sends Schaffer collaterals to apical dendrites of CA1. From CA1 traffic goes on to the subiculum, which projects back to the entorhinal cortex (Brodal 1992). All these links are excitatory. Moreover, the involved synapses are places of plasticity (see 3.1).

Commissural fibers connect the hippocampi of both hemispheres, so that a close cooperation between them is ensured.

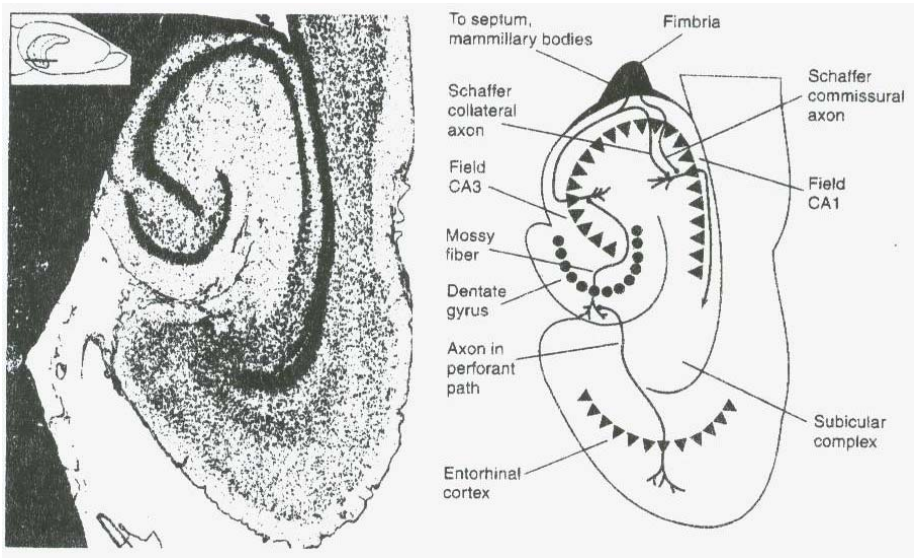


Figure 1.7: *The hippocampal formation (from Carlson 2001).*

1.3.2.1.1 The hippocampus and spatial ("cognitive") memory

The major contribution of Nadel and O'Keefe's (1978) cognitive map theory (see 1.2.2.5) was to ascribe spatial memory to a defined brain region – the hippocampus. They derived their thesis from two converging lines of evidence: neuropsychological findings indicating that hippocampal damage leads to severe impairment in spatial memory and the discovery of "place cells" within the hippocampus. Place cells are neurons "that fire in association with the rat's place in the environment, independent of any particular stimulus or ongoing behavior" (Eichenbaum 1996). After O'Keefe and Dostrovsky's (1971) first mention of hippocampal place cells, many authors confirmed the notion of hippocampal neurons sensitive to a subject's location in the environment (Battaglia et al. 2004, Breese et al. 1989, Eichenbaum et al. 1989, Knierim et al. 1995, Lenck-Santini et al. 2002, Mizumori et al. 2004, Sharp and Green 1994, Wiener et al. 1989).

Further support for the idea that the hippocampus is responsible for spatial memory came from animal studies using radial maze (Olton and Samuelson 1976) or water maze tasks (Morris 1984). A radial maze consists of a central platform from which eight arms run out. The animals are mostly required to collect food pellets placed at the end of the arms. In a water maze task rats swim in a circular pool filled with opaque water and try to find a hidden or visible escape platform placed in one of four (imaginary) quadrants. Both, radial and water mazes are mostly surrounded by a number of extramaze cues. Several authors demonstrated

spatial memory impairments in radial maze (Kesner et al. 1993, McDonald and White 1993) and water maze tasks (McDonald and White 1994, Micheau et al. 2004, Packard and McGaugh 1992, Whishaw et al. 1995) following inactivation or lesion of the hippocampus of rodents. McDonald and White (1993), for instance, tested rats one week after neurotoxic lesion of the fornix – the major output region of the hippocampus – in a radial maze task. Rats were placed at the centre of the maze and allowed to choose one of eight arms each containing a Froot Loop in the food well at its end. Since the food wells were not refilled, it was most efficient to choose each arm only once. Animals performance was assessed as the number of revisits to arms from which they had already obtained food and expressed as number of errors. As predicted by the spatial memory hypothesis of hippocampal function, rats with fornix lesions were significantly impaired in this "win-shift" task compared with control and sham animals. The opposite way of investigating the role of the hippocampus in spatial memory was gone by Packard and Teather (1998). They did not lesion the hippocampus but enhanced its functioning by injections of the dopamine agonist amphetamine. Animals were first trained in a water maze to find an escape platform submerged at a depth of 1 cm beneath surface. Immediately after training they received an injection of amphetamine into the hippocampus. Escape latencies of rats that received intrahippocampal injections of amphetamine were significantly lower in a test trial than the escape latencies of controls. To find out whether this result is really due to an enhanced functioning of the hippocampus, a second experiment was conducted, in which rats received in addition to a post training injection of amphetamine a preretrieval injection of lidocaine into the hippocampus. If posttraining injections of amphetamine act to consolidate memory traces within the hippocampus, then preretrieval injections of lidocaine should block the expression of the memory enhancing effect of the drug. Indeed, this was what Packard and Teather (1998) observed.

Evidence for the spatial memory view of hippocampal function comes also from studies with humans. Veronique Bohbot and colleagues (2004) investigated the strategies people apply to find a destination in a virtual environment and how the use of these strategies relates to the activation of different brain regions. They found that the application of a spatial strategy was associated with a significant activation of the hippocampus. The authors administered the task also to patients with lesions to the medial temporal lobe; those patients showed an impaired ability to use the spatial strategy.

Same as Bohbot et al. (2004), Maguire et al. (1998) investigated the brain activity of people during navigation in a virtual reality town with the help of functional imaging. They

observed an especially high activity in the hippocampus during navigation. Interestingly, the more accurate the navigation was, the more activated was the hippocampus. Even more impressive were the results obtained by Maguire and colleagues (2000) in another study. Here, they analyzed the brains of persons with extensive navigational experience, licensed London taxi drivers, and compared them to the brains of controls. The only brain region in which the brains of the two groups differed was the hippocampus. Significantly increased grey matter volume was found in the hippocampi of taxi drivers compared with those of controls. Moreover, the work experience of taxi drivers correlated positively with the size of the dorsal and negatively with the size of the ventral hippocampus. In a subsequent study Maguire et al. (2006) supported these findings after controlling factors such as driving experience, self-motion and stress. The results of Maguire and colleagues are in line with those from earlier biological studies. Krebs and colleagues (1989), for example, set the volume of the hippocampus of different species of passerine birds in relation to their body size. What they found was a significantly larger volume of the hippocampus relative to the body size in species that store food than in species that do not. In other words: species that are confronted with special spatial memory demands have a (relatively) larger hippocampus.

As the results of Maguire et al. (2000) suggest, there might be different contributions of dorsal and ventral parts of the hippocampus to spatial memory. Similarly, Jung, Wiener and McNaughton (1994) found that almost 50 percent of the cells in the dorsal hippocampus had place fields, whereas only about a fifth of the ventral hippocampal cells show location specific patterns of firing. The authors proposed that the dorsal and ventral parts of the hippocampus differ regarding their modes of information processing. While the dorsal hippocampus was supposed to yield a high resolution of small environments, the ventral hippocampus was thought to provide a low resolution of large environment.

An aspect of the cognitive map theory (O'Keefe and Nadel 1978) that has often been neglected is that the processing of spatial information has been ascribed to two systems: an allocentric (or allothetic) and an egocentric (or idiothetic) spatial system (Nadel 1991). The allocentric system exploits the relationship between stable external (visual, auditory, etc.) cues. The egocentric system, on the other hand, integrates internal cues generated from own movement (as information from the proprioceptive and vestibular system). According to O'Keefe and Nadel (1978) the hippocampus should be relevant for the allocentric system only. This, however, has been questioned recently. Whishaw and colleagues (Whishaw et al. 1997, Whishaw and Maaswinkel 1998, Whishaw and Gorny 1999) presented evidence that the egocentric system depends on the hippocampus as well. They have shown that rodents

with hippocampal damage are severely impaired in “homing”, the return to a start point or a home base after exploration, which was thought to be mediated by the egocentric system. The importance of the hippocampus for the allocentric system has been demonstrated (Matsumura et al. 1999) and is widely accepted (Eichenbaum and Cohen 2001).

To summarize, there is a broad consensus that the hippocampus plays a prominent role in the processing and storage of spatial information (Jarrard 1993).

1.3.2.1.2 Further functions ascribed to the hippocampus

The hippocampus was once related to olfaction, later to emotion, and for the last forty years to learning and memory (Henke 1999). Within the last two decades there has been an ongoing discussion on whether the hippocampus is specific for the processing of a special kind of information or whether it is specific for particular learning and memory processes. As described in the previous section O’Keefe and Nadel (1978) saw the hippocampus as being responsible for the processing of spatial information. This view, however, faces some problems. First, it has been shown that hippocampal place cells do not respond to pure space, exclusively, but also to the speed and direction of movement or to vestibular information (Deadwyler et al. 1996, Eichenbaum et al. 1989, Rosenzweig et al. 2003, Sakurai 1994, Sharp and Green 1994). Additionally, Save et al. (1998) found that the firing patterns of hippocampal place cells of early blind rats were similar to those of control rats, suggesting that visual inputs are at least not the only factor influencing place cell firing. Second, as Nadel (1991) had to admit, cognitive map theory (O'Keefe and Nadel 1978) has difficulties to account for the non-spatial memory deficits of amnesics (Cohen and Squire 1980) and animals with hippocampal damage (Clark et al. 2002, Eichenbaum et al. 1996a, Vargha-Khadem et al. 1997).

These findings led Squire and colleagues (Squire 1994, Squire 2004) to conclude that the hippocampus is concerned with declarative memory in general. Another conclusion was drawn by Eichenbaum and colleagues (Eichenbaum et al. 1990, Eichenbaum et al. 1996a, Eichenbaum et al. 1999a ; see also Sutherland and Rudy 1989). They argued that the hippocampus is not specific for a particular content, but for the representation of relations between stimuli. The key feature of this representation was thought to be its flexibility (Cohen and Eichenbaum 1991). Eichenbaum, Stewart and Morris (1990) mention four characteristics of the memory deficits that follow hippocampal damage: (a) they are not restricted to a particular content, but depend on the representational demands of the task, (b) they are severe when a representation between multiple cues is requested, (c) the acquisition

of basal processes required for task accomplishment is still possible, and (d) the flexible use of information is disturbed. Following the relational view, spatial memory is only one kind of hippocampus-dependent memory. Eichenbaum and colleagues (1996) propose to extend the cognitive map theory (O'Keefe and Nadel 1978). The map-like representation should not be restricted to space, but include almost all kinds of information provided that they are to be expressed flexibly in new situations.

A recent study by Kumaran and Maguire (2005) pit the relational and the spatial view of hippocampal information processing against each other. During functional magnetic resonance imaging (fMRI) subjects performed two tasks placing similar demands on relational processing: navigation within either a spatial or a non-spatial, social domain. The authors showed that the hippocampus was only engaged by relational processing in the spatial domain. This was interpreted as evidence in favor of the cognitive map theory. Contrary results were reported by Moses, Cole and Ryan (2005). They studied the performance of rats with hippocampal lesions in a spatial water maze task and a relational object preference task and found that hippocampal damage led to impaired memory in *both* tasks. It was therefore concluded that the hippocampus is essential for processing all types of relational information. Thus, there is still no final answer to the question how the information processing of the hippocampus is best characterized.

Both, Eichenbaum (2000) and Squire (1994) associated hippocampus-dependent memory with explicit memory. This assumption, however, was challenged by recent data. Chun and Phelps (1999) observed impairments of patients with medial temporal lobe damage in a context learning task that was supposed to be implicit. The authors concluded that the medial temporal lobe memory system is also important for implicit learning which requires the binding of multiple cues.

Besides memory some other (memory related) functions have been ascribed to the hippocampus. Knight (1996) points to the role of the hippocampus in novelty detection; Jarrard (1993) names eating and nocturnal activity as further areas that might depend, at least partly, on the hippocampus.

The central problem in the search for the function(s) of the hippocampus lies in differences among studies in the locus and the extent of damage within the medial temporal lobe; in addition to an imprecision in terminology (as reflected in the headings of this and the previous section). Rempel-Clower et al. (1996) demonstrated in amnesic patients that the kind and extent of memory deficits depend on the locus and extent of the brain damage. And Tulving and Markowitsch (1997) stress that memory (and non-memory) functions of medial

temporal lobe regions other than the hippocampal region have become more and more a focus of interest. That different regions of the medial temporal lobe serve different functions has been illustrated by many authors (Düzel et al. 2003, Haist et al. 2001, Hunt et al. 1994, Malkova and Mishkin 2003, Suzuki 1996, Vargha-Khadem et al. 1997). Vargha-Kadem et al. (1997), for example, suggest that the hippocampal region is necessary for episodic memory, whereas semantic memory would depend on ento- and perirhinal cortices. Brown and Aggleton (2001) and Düzel et al. (2001) agree that the hippocampus is important for recollection-based memory ("remembering"), while the perirhinal cortex supports familiarity-based memory ("knowing"). Moreover, Moser, Moser and Anderson (1993) presented evidence that there are not only functional differences between different regions of the medial temporal lobe, but also between different parts of the hippocampal region. They described much more severe spatial memory impairments after damage of the dorsal hippocampus than after damage of the ventral hippocampus. To make a long story short: future research is required to lesion the hippocampus proper or other medial temporal lobe structures selectively and to name the damaged region more precisely. This would allow conclusions about the function(s) of the medial temporal lobe structures that are more reliable.

A further question regarding the function of the hippocampal region concerns its temporal role in the memory process. Squire and Alvarez (Alvarez and Squire 1994, Squire and Alvarez 1995) postulated a time-limited role of the hippocampal region in memory. Based on results from patients with temporally-graded retrograde amnesia (i.e. memories acquired recently are more affected than memories acquired longer ago) they suggested that the hippocampal region is relevant for the consolidation but not for the long-term storage of information. It was assumed that memories become gradually fixed. During consolidation the hippocampal region should activate a particular representation within the neocortex. This in turn was thought to lead to neocortical associations, which make memory independent from the hippocampal region. Contrary to Squire and Alvarez (1995), Nadel and Moscovitch (1997) argued that the hippocampal formation is not only involved in the consolidation of memories but also in the reactivation of remote memories. According to Nadel and Moscovitch's (1997) multiple trace theory the hippocampal formation and the neocortex interact constantly; *both* would be responsible for the storage and retrieval of information throughout life. There was a heated debate between the proponents of the standard consolidation model and those of the multiple trace theory (see Knowlton and Fanselow 1998, Moscovitch and Nadel 1998). Winocur and colleagues (2005a) presented data that shed some light on this issue. They reared rats in a complex environment and tested the effects of

hippocampal lesions on spatial memory for that environment. By showing that rats with hippocampal lesion which had extensive preoperative experience in a complex environment performed well in a spatial memory test for this environment, the authors provided evidence that a map-like representation of a complex environment can survive hippocampal damage. Yet, the same authors showed also that forgetting curves in hippocampus lesioned rats were comparable to forgetting curves in controls, i.e. that there were no signs of temporally graded amnesia in hippocampus damaged rats (Winocur et al. 2005b). A very recent study by Winocur, Moscovitch and Sekeres (2007) tested the transformation hypothesis implicated in multiple trace theory. This hypothesis states that with time the original, detailed and context-dependent memory is transformed to one which is context-free and schematic (semantic). This gist memory would be mediated initially by the hippocampus but represented in extrahippocampal structures once it is acquired (Moscovitch et al. 2005). By manipulating the context (similar vs. different to learning) in a food-preference and a fear conditioning task Winocur et al. showed in rats that context-sensitivity of memory decreased from 1 to 8 days after training which was interpreted as evidence for the transformation view. Nevertheless, a final decision in favor of one of the two competing theories, standard consolidation versus multiple trace theory, is not possible yet.

Although it is not completely clear for which kind of information and/or information processing the hippocampus (and other medial temporal lobe structures) is specific, there seems to be no doubt, that the hippocampal region is relevant for spatial memory. For the purpose of this work it is crucial that the hippocampal region has *not* been associated with stimulus-response memory.

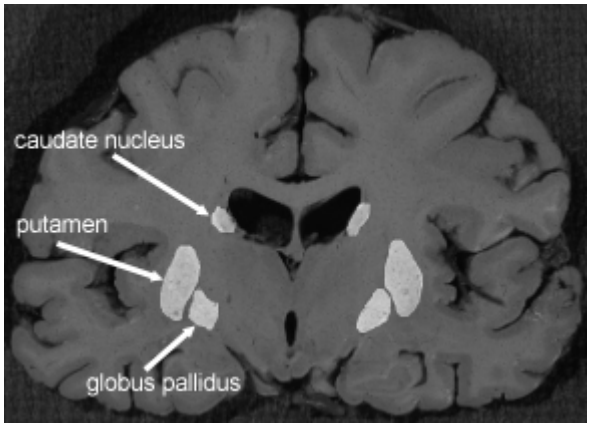
Though, this work focuses on hippocampal memory functions mainly, it is important to note that the hippocampus is also involved in the regulation of the hypothalamic-pituitary-adrenal (HPA) axis (see chapter 2.2.2).. The hippocampus displays highest levels of glucocorticoid and mineralocorticoid receptors of any brain structures suggesting a high degree of glucocorticoid receptivity. Lesion studies indicated that hippocampal damage potentiates stress-induced glucocorticoid secretion (Herman et al. 1989). Conversely, stimulation of the hippocampus led to reduced HPA axis-activity (Jacobson and Sapolsky 1991). Thus, these studies suggest an inhibitory effect of the hippocampus on the HPA axis (Herman and Cullinan 1997).

1.3.2.2 The basal ganglia

Anatomy. The basal ganglia are a collection of subcortical nuclei in the forebrain between the anterior portions of the lateral ventricles (figure 1.8a and b). They consist of three major parts: the caudate nucleus, the putamen and the globus pallidus or pallidum (Packard and Knowlton 2002, Trepel 2004). If the basal ganglia are seen as a group of *functionally* related neurons, the substantia nigra, which divides into substantia nigra pars compacta and substantia nigra pars reticulata, and the subthalamic nuclei should be included (Brodal 1992). Latterly, the nucleus accumbens and the olfactory tubercle have been imputed to the basal ganglia as well. They were referred to as the ventral striatum, complementary to the dorsal striatum (or neostriatum) composed of caudate nucleus and putamen.

Within the dorsal striatum there are about six kinds of neurons (Brodal 1992). Many of them project out of the neostriatum while some do not suggesting that the neostriatum is not a pure relay station, but processes information, too.

(a)



(b)

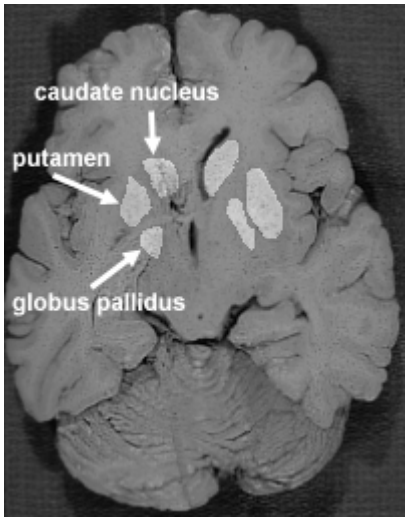


Figure 1.8: *The basal ganglia: (a) sagittal and (b) horizontal view (from http://www.sci.uidaho.edu/med532/basal.htm, 20.10.05).*

Both, the neostriatum and the pallidum receive their major input from the neocortex (Trepel 2004). Thereby, corticostriatal connections show a high degree of convergence. Small cortex areas project to large striatal domains (Wise, Murray and Gerfen 1996). The caudate nucleus and the putamen differ, however, regarding the cortical regions they receive their input from. While the input of the caudate nucleus come primarily from association cortices related to higher cognitive functions, the putamen receives somatotopically organized inputs from somatosensory and motor cortex areas. Further basalganglionaric afferents come from the thalamus and dopamine-containing cell groups in the mesencephalon (Brodal 1992). The

output of the basal ganglia leaves mainly from the internal segment of the pallidum and the substantia nigra pars reticulata. It is inhibitory and goes primarily to the motor regions of the cortex, the thalamus and the brain stem (Squire et al. 2003). An exception is the caudate nucleus, which projects to prefrontal cortex areas and seems to be involved in cognitive rather than motor functions (Brodal 1992).

There are several neuronal circuits within the basal ganglia between which the flow of information is thought to be separated. This implicates that information are processed in parallel within the basal ganglia (Brodal 1992, but see Squire et al. 2003).

Since the dorsal striatum is the most relevant part of the basal ganglia for the purpose of the present work, the following section will focus on it mainly.

1.3.2.2.1 The dorsal striatum and stimulus-response ("habit") memory

Decades of research on the basal ganglia have focused on its role in motor functioning (Packard and Knowlton 2002). However, the view of the basal ganglia as a pure motor system has been challenged by neurobehavioral data. It is suggested that especially the neostriatum is important for learning and memory processes. Support for this concept comes from three converging lines of evidence: rodent studies, neuroimaging studies and studies investigating patients with Parkinson's disease (PD).

Packard, Hirsh and White (1989) lesioned the caudate nucleus of rats before testing the animals in a "win-stay" task. In this task rats were placed in a radial maze, in which four arms were lit and baited, while the other four arms were neither lit nor baited. A lit arm was refilled after a first visit, but remained dark and without food after a second visit of the rat. To obtain all the food available in the maze most efficiently, rats had to learn the association between the light and the correct response. Visits to unbaited arms were scored as errors. What Packard et al. (1989) found was a significant impairment of caudate lesioned rats in learning the association. This result has been replicated in a series of similar studies by Mark Packard (Packard and McGaugh 1992, Packard and McGaugh 1996, Packard and Teather 1998, Packard 1999), Robert McDonald (McDonald and White 1993, McDonald and White 1994) and other authors (Kesner et al. 1993). It led to the hypothesis, that the dorsal striatum is involved in a form of learning, in which stimulus-response associations are incrementally formed. A further interesting investigation supporting this hypothesis was conducted by Jog et al. (1999). They presented auditory cues to rats in a T-maze signaling the rats which direction to choose. During training neuronal activity was recorded with multiple electrodes. The authors obtained "large and widely distributed changes in the neuronal activity patterns … in

the … striatum during behavioral acquisition" (Jog et al. 1999, p. 1745). Moreover, Blazquez and colleagues (2002) identified in macaque monkeys (a) striatal neurons responsive to cues that signal rewards and (b) striatal neurons whose response to a sensory stimulus reflects the probability that a reaction will follow the stimulus.

Evidence indicating that the neostriatum mediates stimulus-response memory comes also from human studies using neuroimaging techniques. For instance, Iaria et al. (2003) observed that subjects who used cues to navigate in a virtual radial maze showed an increased activity within the caudate nucleus. Neuropsychological studies with PD patients, i.e. patients with damage to the substantia nigra (the major output region of the neostriatum), provide some support for a role of the dorsal striatum in response learning, too. Myers et al. (2003), found in PD patients in a latent learning task, which required them to "remember" that they had been exposed to a stimulus already, a reversal of the effect shown by control subjects.

Besides these experimental data, some anatomical and physiological considerations suggest an involvement of the dorsal striatum in stimulus-response learning as well. First, Middleton and Strick (1996) have shown that the corpus striatum projects via the substantia nigra to cortex areas involved in higher-order processing of visual information. Second, various forms of long-term synaptic plasticity (LTD, LTP) have been identified within the dorsal striatum (Calabresi et al. 1992, Calabresi et al. 1996). Third, it has been shown that reward information is processed within the substantia nigra (Schultz et al. 1997), which contains a great many of dopamine-releasing neurons. The release of dopamine is central for the neurobiology of reward and hence of fundamental importance for stimulus-response learning (White 1997). Finally, as White and McDonald (2002) summarized: "…information about the sensory environment and (possibly) two forms of efference copy from the motor system … are available [within the neostriatum] to form S-R associations" (p.162).

Thus, based on the presented evidence it seems reasonable to relate the neostriatum to stimulus-response memory. This is, however, not the only cognitive function ascribed to the caudate-putamen. Several authors suggested an involvement of the dorsal striatum in the building, storage, retrieval and optimization of action plans (Dagher et al. 2001, Graybiel 1995, Graybiel 2005, Lewis et al. 2003, Salmon and Butters 1995). Furthermore, Knowlton, Mangels and Squire (1996) described deficits of PD patients in a weather prediction task requiring probabilistic classification. Some studies indicate a role of the neostriatum in attentional set-shifting and even in working memory (for a review see Brown, Schneider and Litsky 1997). The functional heterogeneity within the dorsal striatum corresponds to the fact, that it receives inputs from various cortex areas. Beyond this, the diversity in striatal functions

found in different investigations is probably due to the consideration of different regions of the neostriatum. Similarly to the hippocampal formation (see 3.2.1.2), it has been proposed to view the dorsal striatum as a heterogeneous structure in which different regions contribute to different functions (Devan and White 1999, Levy et al. 1997, Mair et al. 2002, Sage et al. 2003, Yin and Knowlton 2004). Devan and White (1999), for instance, found different effects of dorsomedial and dorsolateral striatum lesions in a water maze task. While the medial caudate-putamen lesion led to a preponderance of a cue response, the lateral lesion produced a preference for the spatial response. And Yin and Knowlton (2004) suggested that there is a functional heterogeneity even within the dorsomedial striatum with anterior regions related to response learning and posterior regions relevant for spatial learning. Based on these results Yin and Knowlton (2006) proposed recently that it could not longer be maintained that the dorsal striatum as a whole is a substrate for habit learning. Rather, the (posterior) dorsomedial striatum was assumed to be crucial for goal-directed action-outcome learning, whereas the dorsolateral striatum was thought to mediate stimulus-response learning. However, despite the impairments in spatial learning after damage to the posterior dorsomedial striatum it cannot be concluded for sure that this region belongs to the hippocampus formation-based "cognitive" learning system. As Devan and White (1999) suppose the spatial deficits observed after fimbria-fornix lesion and lesion to the dorsomedial striatum have different reasons. Whereas fimbria-fornix lesions should lead to a general impairment in the acquisition of cognitive-spatial information, damage to the dorsomedial striatum was thought to produce a deficit to acquire responses based on learned spatial information.

So what are the cognitive functions of the dorsal striatum? The picture emerging from the research described above suggests that the neostriatum is involved in planning, skill and habit learning. All these functions require the gradual acquisition of responses by "trial and error" (Dagher et al. 2001). The caudate-putamen based learning is assumed to progress automatically and unconsciously (White and McDonald 2002); it is thought to be fast, but hardly transferable to novel situations (Myers et al. 2003a). Therefore the dorsal striatum can be labeled as a "habit" learning system. Habits develop through the formation of simple associations by which a particular stimulus leads to a particular (motor) response (Salmon and Butters 1995). This is a function of repeated reinforcement. In sum, the neostriatum seems to be concerned with a "less cognitive, more rigid" (White 1997) form of memory.

Although it was primarily the neostriatum that has been related to cognitive functioning, few studies describe also cognitive functions of the ventral striatum (Roullet et al. 2001) and pallidum (Lombardi et al. 2000).

At this point it is to be emphasized, that the deficits observed after striatal damage did not occur after damage to the hippocampal formation suggesting that the neostriatum and the hippocampus formation are dissociable learning and memory systems (for references see 3.2).

1.3.2.3 The amygdala

Anatomy. The amygdaloid complex is located within the temporal lobe, at the rostral end of the caudate. It consists of different groups of nuclei, each with diverse inputs and outputs and discriminative functions (Carlson 2001). For the purpose of this work it is sufficient to distinguish four structures within the amygdala: the medial nucleus, the lateral/basolateral, the central and the basal nucleus (Carlson 2001; but see Amaral et al. 1992 for a more specific distinction).

The medial nucleus receives sensory inputs including information about odors and pheromones. Its outputs terminate mainly in the medial basal forebrain, the thalamus and the hypothalamus. The lateral/basolateral nucleus receives sensory information, too. These, however, come primarily from the neocortex, the hippocampus, the hypothalamus and the sensory thalamus. Moreover, the lateral/basolateral nucleus receives afferences from regions known to process affective and visceral information such as the substantia nigra and the nucleus accumbens (White and McDonald 2002). The efferences of the lateral/basolateral nucleus project back to the ventral striatum, to the caudate-putamen, the dorsomedial thalamus and the central nucleus of the amygdala, which in turn projects to the thalamus, the substantia nigra and autonomic centers such as the hypothalamus, the pons, the medulla and the tegmentum. Finally, the basal nucleus receives sensory inputs from the basolateral nucleus and relays information to the striatum and the periaqueductal gray matter (Amaral et al. 1992, Carlson 2001; see Figure 1.9).

It is important to highlight, that the amygdala holds connections to both the dorsal striatum and the hippocampal formation; albeit the connection to the latter is not really reciprocally. While the basal and lateral/basolateral nuclei project to the subiculum and hippocampus proper (especially field CA1) via the entorhinal cortex, the transfer into the opposite direction is definitely less (Amaral et al. 1992). Besides these extrinsic connections there is a considerable flow of information within the amygdaloid complex. This is primarily unidirectional following a lateral to medial direction.

In sum, there are two major kinds of information converging in the amygdala: sensory information from the thalamus and the neocortex as well as information about rewards and aversive events (White and McDonald 2002). A look to its efferences shows that the

amygdala is endued with "a myriad of routes through which it can influence behavior" (Amaral et al. 1992, p.54).

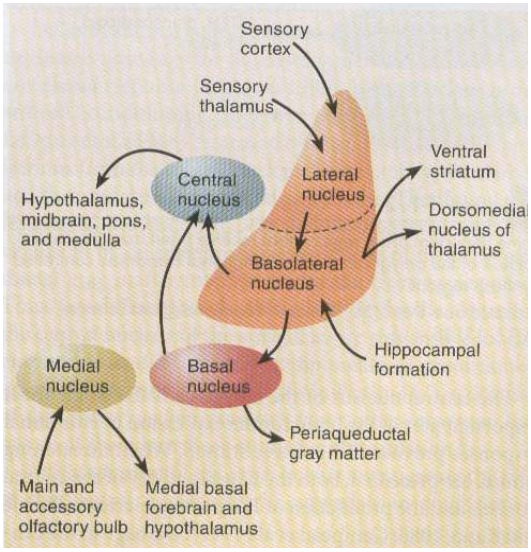


Figure 1.9: *A simplified diagram of the nuclei of the amygdala and their connections (from Carlson 2001).*

1.3.2.3.1 Functions ascribed to the amygdala

A great many of different functions has been related to the amygdala, including for example the processing of reward stimuli (Baxter and Murray 2002, Gaffan 1992, Holland and Gallagher 2004, Kalivas and Nakamura 1999, O'Doherty 2004) or influencing sexual (Aggleton 1992, Canli and Gabrieli 2004) and social behavior (Adolphs et al. 1995, Kling and Brothers 1992, Rolls 1992). Two directions in the search for the role(s) of the amygdaloid complex, however, have received particular attention: the involvement of the amygdala in the processing of emotional stimuli (especially faces) as well as in emotional memory (see Phelps and Anderson 1997).

It has been proposed that the amygdala is a central part of a neural system for recognizing emotions (Adolphs 2002). Supporting this view several studies presented evidence suggesting impairments in the recognition of emotions in facial expressions after damage to the amygdala (Adolphs et al. 1994, Adolphs et al. 1995, Adolphs et al. 1999, Broks et al. 1998). The observed deficits were most striking for expressions of fear (Adolphs et al. 1994, Adolphs et al. 1999), but also expressions of anger or surprise were affected (Adolphs et al. 1995, Adolphs et al. 1999). Remarkably, these impairments occurred while the recognition of the personal identity from faces remained intact. Furthermore, it has been shown that the processing of emotional faces is accompanied by changes in the activity of the amygdala (Blair et al. 1999, Breiter et al. 1996, Thomas et al. 2001, Whalen et al. 1998).

Interestingly, Whalen et al. (1998) reported different levels of amygdala activation depending on the emotional valence of the external stimuli. While fearful faces led to increased amygdala activity, happy faces caused a decrease in the activity of the amygdala. These findings point to the importance of the amygdala for the processing of positive emotions, which is especially interesting since research on functions of the amygdala has focused primarily on negative emotions.

There is an extensive body of evidence suggesting a role of the amygdala in emotional memory tasks (Davis 1992, LeDoux 2000, Phelps and Anderson 1997). The paradigm most often employed to demonstrate the involvement of the amygdala in emotional memory is fear conditioning. Conditioned fear is a construct used to explain the cluster of behavioral effects that are provoked by a formerly neutral stimulus, which had been consistently paired with an aversive stimulus (Davis 1992). In a typical experiment an auditory or visual stimulus (NS) is paired with an electric shock (UCS). After several pairings the NS alone produces (almost) the same fear responses that formerly followed the UCS (see 1.2.1.1 for a description of classical conditioning). It has been assumed that the amygdala receives information about the NS and the UCS and controls fear responses via its outputs to behavioral, autonomous and endocrine centers within the brain stem (LeDoux 2000). Many authors demonstrated impairing effects of amygdala lesions on fear conditioning in rats (Campeau and Davis 1995, Davis 1992, LaBar et al. 1998, LeDoux et al. 1988). And Bechara (1995) provided data from patients with bilateral amygdala damage indicating that fear conditioning necessitates an intact amygdala in humans as well. Koo, Han and Kim (2004) identified the basolateral complex of the amygdala (BLA) as being of special importance for the expression of conditioned fear; BLA projections were thought to run via the central nucleus of the amygdala (CEA) to downstream fear response structures. Similarly, Campeau and Davis (1995) viewed the BLA as necessary to relay sensory information from cortical areas to the CEA. Further evidence for the importance of the BLA in fear conditioning comes from studies showing that posttraining stimulation of the BLA by noradrenalin or oxotremorine leads to increased conditioned fear responses (LaLumiere, Buen and McGaugh 2003, Vazdarjanova and McGaugh 1999).

Within the traditional fear conditioning paradigm fear is acquired by direct confrontation with an aversive stimulus. This, however, neglects that in every day life fear is mostly not acquired by direct contact with the fear provoking stimulus, but by language. It is not necessary to be bitten by the neighbor’s dog to be afraid of it. Taking the importance of verbal instructions into account, Phelps et al. (2001) told subjects that a particular picture

would be followed by a mild electroshock (what indeed never happened). What Phelps et al. (2001) found was an arousal reaction and significantly increased amygdala activation when the announced "threat stimulus" was presented. These findings point to an involvement of the amygdala in "non-experiential" fear.

An ongoing debate concerns the question whether an intact amygdala is really necessary for conditioned fear. Is amygdala damage sufficient to block fear conditioning? Most of the authors cited above seem to have a clear answer: "yes". As Cahill, Weinberger and McGaugh (2001) argue there is, however, a central problem with many of the studies on fear conditioning. They criticize that most authors take freezing as the only indicator of conditioned fear. This would be problematic since amygdala lesions do also affect locomotor activity. Therefore it would be not allowed to infer impaired fear conditioning from freezing deficits. To avoid this problem Cahill et al. (1999) recommend to operationalise conditioned fear independent of freezing behavior. Vazdarjanova and McGaugh (1998) observed besides freezing further parameters indicative of conditioned fear, such as the latency of rats to enter a maze arm, in which they were previously shocked or the total number of entries into this maze arm. They obtained a freezing deficit in BLA-lesioned rats relative to control rats. Regarding the other fear conditioning parameters BLA-lesioned rats showed weaker signs of conditioned fear relative to non-lesioned controls, but significantly stronger fear responses compared with BLA-lesioned rats that did not receive any shocks during training. These findings suggest that fear memory does not depend upon an intact amygdala (see also Berlau and McGaugh 2003). Although there is still no widely accepted answer to the question whether amygdala damage is sufficient to block fear conditioning, there seems to be a broad consensus that conditioned fear is reduced by amygdala lesions.

A phenomenon often observed is an enhanced memory for emotional relative to neutral stimuli (Adolphs et al. 1997, Adolphs et al. 1999, Dolcos et al. 2004, Hamann et al. 1999). Larry Cahill and colleagues (1996a), for instance, presented subjects two videos, an emotional one and a neutral one, each consisting of twelve film clips. Immediately after watching the videos subjects were scanned (PET). Three weeks later participants were called and asked which of the films they could remember (they were not told before that they would be tested on memory for the films). Cahill et al. (1996a) found that subjects remembered significantly more emotionally arousing films than neutral ones. Moreover, the authors reported an association between the number of remembered films and the level of amygdala activation during encoding. Other authors have shown that the amygdala is especially active during watching emotional stimuli (Canli et al. 2000, Ochsner et al. 2002, Schaefer et al.

2002) and that this activity is related to the enhanced memory for emotional stimuli (Canli et al. 2000, Dolcos et al. 2004, Hamann et al. 1999).

Further evidence supporting the view that the amygdala is involved in the enhanced memory for emotional material comes from studies with patients suffering from amygdala damage. Several studies demonstrated that amygdala damaged patients do not show the memory increase for emotional stimuli observed in controls, while they are not impaired relative to controls in remembering neutral stimuli (Adolphs et al. 1997, Adolphs et al. 2000, Cahill et al. 1995, Richardson et al. 2004). Kensinger and Corkin (2004) distinguished between emotionally arousing and emotionally valent but non-arousing stimuli to investigate whether the valence of a stimulus alone can account for the memory enhancing effect. They found an increased memory performance for both emotionally arousing and emotionally valent but non-arousing stimuli. Using fMRI Kensinger and Corkin (2004) observed that there was an increased activation in the amygdaloid complex only during encoding of arousing stimuli, whereas encoding of valent but non-arousing stimuli was correlated with an increased activity of the hippocampus and prefrontal cortex.

There seems to be no doubt that the amygdala contributes significantly to the enhanced memory for emotional material. But when does the amygdala exert its impact on memory? A recent study by Anderson and Phelps (2001) suggests that the amygdala influences processes preceding memory consolidation. The authors employed the attentional blink paradigm to investigate whether affective words are better identified than neutral words when presented shortly after another word. Anderson and Phelps (2001) obtained a recognition enhancing effect of emotional relative to neutral words in healthy subjects, but not in patients with amygdala damage. This portends to an influence of the amygdaloid complex on initial perceptual encoding processes, which might increase the probability that stimuli become conscious. Evidence supporting the idea that the amygdala has an impact on early sensory processes comes also from a study by Vuilleumier et al.(2004) indicating that the amygdala modulates the activity in the fusiform “face processing” cortex. But what about the rather late stages in the memory process? Does the amygdala act as a locus of permanent memory storage? Showing molecular processes underlying learning and memory (LTP, LTD, see 3.1) to occur in the amygdala, Maren (1999, Maren and Fanselow 1995) suggested that memories might be stored in the amygdala.

Another view on the role of the amygdaloid complex in memory storage that is highly relevant within the present work was developed by McGaugh (2004, McGaugh et al. 1992, McGaugh et al. 1993, McGaugh et al. 1996, McGaugh and Cahill 1997, see chapter 3.1). He

argues that memory storage is regulated by neuromodulatory systems activated by experiences. It has been demonstrated that injections of drugs or hormones affect memory (Ferry and McGaugh 1999, McGaugh 2003, McIntyre et al. 2003b). These neuromodulatory effects on memory are at least partly mediated by the amygdala. It has been shown that amygdala lesions block the memory modulating effects of drugs injected peripherally (McGaugh and Roozendaal 2002, Roozendaal and McGaugh 1996) or centrally (Roozendaal and McGaugh 1997). McGaugh (McGaugh et al. 1992, McGaugh 2002a) proposed that the amygdala exerts its impact on memory via the modulation of the memory storage in other brain regions. This assumption was confirmed in several studies (Hatfield and McGaugh 1999, Packard et al. 1994, Packard and Teather 1998). Packard and colleagues (1994), for instance, tested the effects of posttraining intracaudate, intrahippocampus and intraamygdala injections of the catecholamine agonist amphetamine on retention in a spatial or cued water maze task. As expected intrahippocampus and intracaudate injections of amphetamine enhanced retention in the spatial and cued task, respectively (see 1.3.2.1 and 1.3.2.2). Intraamygdala injections of amphetamine led to better retention in both water maze tasks. To investigate if this was due to memory storage within the amygdala or to modulation of memory storage in other brain regions, Packard et al. (1994) injected lidocaine immediately before retention testing into the amygdala – additionally to posttraining amphetamine. The effect of posttraining amphetamine was *not* blocked by pre retention test injections of lidocaine, neither in the spatial nor in the cued task. These data speak against the possibility that the amygdala is a locus of memory storage (at least for the kind of information required in the tasks used) and support the memory modulation hypothesis of amygdala functioning. Moreover, Packard et al. (1994) reported that amygdala damage did not impair the acquisition of one of the two water maze tasks. Phelps (2004) concluded that the amygdala is not required for the formation of episodic memories, but strengthens hippocampus-based memory by emotions. This is probably true for caudate-dependent memory as well.

In sum, the amygdala is important for the coding of emotional material. It should be emphasized that the amygdala seems to be not (directly) involved in memory for motor responses as well as spatial and sensory-perceptual information (see Kesner 1992), it rather modulates memory processes in other brain areas (Kim and Diamond 2002, McGaugh et al. 1993).

1.3.2.4 Interactions between memory systems

In the previous sections it was argued that memory is not a single entity, but consists of multiple anatomically and functionally distinct systems. Three memory systems have been portrayed: a spatial or (more general) "cognitive" memory system based upon the hippocampal formation and adjacent cortices, a stimulus-response or "habit" memory system dependent upon the dorsal striatum, and an amygdala-based memory system mediating the effects of emotion on memory. How do these memory systems interact? Most authors assume that information is processed simultaneously and in parallel within the different memory systems (McDonald and White 1994, McDonald et al. 2004a, Squire 2004, White and McDonald 2002). Three ways of interaction between the distinguished memory systems could be imagined: independence, synergism, and competition (Kim and Baxter 2001a).

Although a task can be acquired after one system is damaged (McDonald and White 1994, Packard and Teather 1998, White and McDonald 2002) a complete independence of the different memory systems has been ruled out (McDonald et al. 2004a, Voermans et al. 2004). McDonald et al. (2004a), for instance, argued that even if a system is not necessary for the acquisition of a task, it processes information which might be important for future behavior. The question of interactions between memory systems was illuminated in a study by Packard and McGaugh (1996). They trained rats to find food in a cross maze. After 8 and 16 days of training a probe trial was given, in which rats started from the arm opposite to the arm they started from during training. If rats moved to the place where the food was located during training, this was interpreted as a spatial strategy. If rats made, on the other hand, the body turn they had to make during training (e.g. turn left), this was viewed as a response strategy. Immediately before the probe trials rats received injections of either lidocaine or saline into caudate nucleus or hippocampus. In the probe trial on day 8 both rats that received saline injections and those which received intra-caudate lidocaine injections used mainly a spatial strategy. Rats that received lidocaine injections into the hippocampus showed no preference for one of the two strategies. In the probe trial on day 16 rats that were injected saline as well as rats that received intra-hippocampus lidocaine injections employed primarily a response strategy, while rats which received lidocaine infusions into the caudate nucleus used mainly a spatial strategy. These findings suggest that early learning is driven by hippocampus-dependent place learning. Later in training a shift seems to occur and learning becomes more and more dominated by the caudate nucleus. However, the hippocampal system is not inactivated in later stages of training. It remains active and capable of substituting the caudate-dependent system if this is blocked. Similar results were obtained by Chang and Gold

(2003), who used the ACh-level within memory systems as an indicator of their activation (Gold 2003, Gold 2004). Chang and Gold (2003) reported that hippocampal activation rose at the beginning of training to its maximum and remained constant in the following. The ACh-level in the caudate rose much more slowly than in the hippocampus. The changes in the relation between ACh-release in the hippocampus and ACh-release in the caudate were temporarily contingent to the observed switch in the behavioral strategies employed by the rats. Comparable results were found in other studies (Iaria et al. 2003, Packard 1999), so that the assumption seems to be justified that hippocampus-dependent and caudate-dependent memory systems contribute to learning at different times.

Packard and McGaugh (1996) as well as Chang and Gold (2003) suggested that the hippocampal formation can substitute the caudate in its memory function when the latter is damaged. This points to cooperation in the relationship between hippocampus-based and caudate-based memory systems. Cooperation between those memory systems was also demonstrated in an excellent study by Voermans and colleagues (2004). The authors combined naturally occurring brain lesion (Huntington's disease) with neuroimaging techniques. They investigated whether a different extent of caudate damage leads to a different degree of compensatory activity within the hippocampus. Patients were asked to memorize routes in familiar houses and retrieve them later. What Voermans et al. (2004) found was that *all* subjects (even those with severe caudate degeneration) performed above chance level in a recognition test. Moreover, they obtained a positive correlation between severity of Huntington's disease and hippocampal activity during recognition, whereas disease severity and caudate activity were negatively correlated. This indicates that the hippocampus is able to compensate for caudate damage in spatial navigation. There seems to be, however, an asymmetry in the abilities of the hippocampal and caudate system to compensate for damage in the other. While the hippocampus is – due to its flexible memory representations – able to substitute the caudate, the caudate can compensate damage to the hippocampus in very specific situations only (Burgess et al. 2002; see also Hartley and Burgess 2005).

Voermans et al. (2004) describe the relationship between caudate-based and hippocampus-based memory as cooperation, other authors refer to it as competition. It has been shown that damage to one memory system can enhance the learning of a task depending on the other system (Matthews and Best 1995, McDonald and White 1993, McDonald and White 1995, Poldrack et al. 2001, Poldrack and Packard 2003, Poldrack and Rodriguez 2004, Schroeder et al. 2002). Matthews and Best (1995), for instance, investigated the effects of

fimbria/fornix lesions on performance in a spatial and a non-spatial radial maze task. They obtained a significant lesion × task interaction effect indicating that lesioned rats learned markedly slower than controls in the spatial task but faster than controls in the non-spatial task. The enhancing effect of fimbria/fornix lesion on performance in the response task was thought to be due to the elimination of interfering spatial information not required in the response task. Poldrack et al. (2001) identified three features of the hippocampus-dorsal striatum interaction: (a) the use of the systems is modulated by the requirements of the task, (b) the activity in both structures is negatively correlated, and (c) fast, reciprocal changes in the dominance of the systems. Competition between memory systems was viewed by Poldrack et al. (2001) as an adaptive mechanism leading to the optimization of experience-based behavior and mediating between the need for flexibly accessible knowledge and the acquisition of fast, automatic responses in specific situations.

If one accepts that there are multiple memory systems which compete in some situations the question arises, what mechanism determines which system gains the upper hand. Since the brain does not produce contradictory responses at the same time, information processed simultaneously has to be integrated. Factors proposed to be involved in the modulation of memory systems are experience, motivation, hormones (Mizumori et al. 2004), task characteristics (Matthews and Best 1995, Schroeder et al. 2002), task conditions such as distraction (Foerde et al. 2006), movement, temporal and stimulus factors (White and McDonald 2002). An interesting suggestion regarding the modulation of multiple memory systems was made by Packard and Wingard (2004). They injected rats peripherally anxiogenic drugs (Yohimbine or RS 79948-197) prior to training in a plus-maze task which can be acquired using either hippocampus-dependent place learning or caudate-dependent response learning. The drug injection did not impair the learning of the task per se. It had, however, an effect on the strategy employed by the rats. While controls showed primarily spatial learning, rats that were injected anxiogenic drugs showed mainly response learning. The same findings were obtained when the anxiogenic drugs were injected directly into the BLA. Packard and Wingard (2004) concluded that the emotional state during learning modulates the use of multiple memory systems and that these effects are mediated by the noradrenergic activity within the BLA (see 3.2.3.1 for a discussion of the modulatory effects of the amygdala). The thesis that emotions modulate the use of multiple memory systems is the core of the present work. In chapter 3 it will be argued that it is the *stress* evoked activity within the amygdala that "helps" to solve the conflict between multiple memory systems in favor of one system, the caudate-dependent "habit" system. After introducing the concept of

stress and its biology (chapter 2), the effects of stress on memory, in general, and on multiple memory system modulation, in particular, will be described (chapter 3).

2 Stress: Concept and Biology

2.1 Of adrenaline and appraisal: different concepts of stress

The man who laments the death of his wife. The young girl who has to run to school since she missed the bus. The bride celebrating her wedding. They are all stressed. The student who has to prepare for his final examination. The women that sees the big dog approaching her. The man who is told that he has cancer. They are all stressed. The football player who shoots the deciding penalty in the last minute of the match. The girl who prepares for the first date with the boy she is in love with since years. The child that suffers from an infectious disease. They are all stressed.

The term “stress” has become part of our everyday speech. It is used in newspapers and topic of TV discussions. As the above examples show, we speak of “stress” in very different situations. What are the common features of these situations? Or asked differently: what is stress?

With today’s use of the word “stress” in mind, it is surprising that the stress concept was significantly influenced by the ideas of an engineer. The 17th century physicist Robert Hooke worked on the question how man-made structures, such as bridges, have to be designed to carry heavy weights without collapsing and to withstand strong winds or earthquakes. Hooke’s analyses based on three basic concepts: “load”, the external force, “stress”, the area over which the load is applied, and “strain”, the deformation of the structure under stress (Lazarus and Folkman 1984, Lazarus 1999). These analyses should have a great impact on following models of stress.

Stress is the product of a person-environment interaction. Depending on which aspect of this interaction is emphasized, three approaches to stress can be distinguished: the biological, the psychological and the environmental (social) perspective (see Cohen, Kessler and Gordon 1995, Nitsch 1981).

The biological perspective on stress focuses on the activation of physiological systems, which respond especially to physical and psychological demands. Special attention was paid to the sympathetic-adrenal medullary system (SAM) as well as the hypothalamus-pituitary-adrenal (HPA) axis (Cohen et al. 1995). Central characteristics of the biological stress perspective are (a) the focus on the physiological effect of objective stimuli, (b) the

view of stress as a general, non-specific response pattern (this point is questioned nowadays), and (c) that stress is seen both as an indicator of disturbance and as a physiological adjustment response (Nitsch 1981).

A major contribution to the biological stress concept was made by the French physiologist Claude Bernard in the 19th century. He discovered that a substantial increase or decrease in the insulin level leads to mental confusion and ultimately to death (Lazarus 1999). The work of Bernard paved the way for modern views on adaptive processes.

The next central figure in the history of the stress concept was the Harvard physiologist Walter Cannon. Cannon was concerned with the specific response mechanisms following changes in the external environment. He (Cannon and De La Paz 1911) obtained specific changes, such as accelerated heart beat or inhibition of the intestines, in cats which were confronted with barking dogs. These changes were ascribed by Cannon to the SAM, especially to the release of adrenaline. Fear and other major emotions were thought to cause a release of adrenaline leading in turn to a higher level of blood glucose (Cannon 1914). Bodily resources, such as glucose, so argued Cannon, would be mobilized to sustain an attack or flee from danger. Purpose of this "fight-or-flight" response would be the preservation of the well-being of the organism. Cannon was the first who used the term homeostasis for the maintenance of the inner stability in the face of changes in the environment. Moreover, the Harvard physiologist suggested that the intrinsically adaptive processes can impair the homeostatic steady state (Lazarus 1999).

Building upon the work of Bernard and Cannon Hans Selye was the first who analyzed the phenomenon he called "stress" systematically. Unlike Cannon, Selye focussed on the HPA axis rather than the SAM system. Origin of his view on stress was an observation he made repeatedly during his medical studies. Selye (1956, 1974, 1981) observed that patients with various infectious diseases shared a number of symptoms as for example pain in the joints, loss of appetite and fever. This led him to postulate a "syndrome of being sick", later named "stress". Stress was defined by Selye (1956) as "…the state manifested by a specific syndrome which consists of all the *non-specifically* induced changes within a biologic system" (p. 54; emphasis added). Selye (1956, 1974) assumed individuals confronted with very different problems would all respond with a stereotyped pattern of biochemical, functional, and structural changes; three physiological markers would be characteristic: an enlargement of the adrenal cortex, an atrophy of the thymus, as well as ulcers in the stomach and duodenum (stress triad). This response was thought to proceed in a three-stage pattern referred to as the general adaptation syndrome (GAS; Selye 1956, Selye 1974, Selye 1981;

see Cohen et al. 1995 for a summary). A noxious agens initiates the first stage of the GAS, the *alarm stage*. The pituitary gland secretes adrenocorticotrophic hormone (ACTH), which leads to the release of corticosteroids from the adrenal cortex. The second stage, the *resistance stage*, involves an adaptation to the demands with the consequence of improvement. Using the resources of the body this stage is catabolic in action (Lazarus 1999). If the stressor is severe and prolonged the third stage, the *stage of exhaustion*, occurs, which symptoms are similar to those of the alarm reaction. It was supposed to lead to disease and ultimately death and was therefore seen as the physiological cost of defence. However, the syndrome does not often go beyond the second stage (Selye 1956).

McEwen (2005) argues, that the weakening of the organism is not caused by a depletion of bodily resources (as Selye thought), but due to the effects of the substances released during stress. The selective exhaustion of muscles or eyes were described by Selye (1956, 1974) as final stages of local adaptation syndromes. Several of these can occur simultaneously in the human body and may activate the GAS mechanism depending on their intensity and extent. It is Selye's merit to have worked out that the stress response is highly adaptive and necessary for the survival of the individual, but that the same mechanism can lead to negative consequences, if it is severe and prolonged. Moreover, Selye (1956, 1974) pointed out that stress is no unitary concept and that it is wise to distinguish between positive and negative stress or "eustress" and "distress" to use Selye's terminology. A distinction emphasized by present authors (see below). The major difference of Selye's stress concept and the psychological view on stress is that the Hungary-Canadian scientist claimed stress would be a stereotypical response following diverse factors.

The psychological stress perspective focuses on the subjective evaluations of the individual. It makes a distinction between the real nature of potentially stressful events and the appraisal of the event. Following the psychological view stress occurs if the individual evaluates a demand as exceeding the own competence. Thus, stress is seen as the product of the interpretation of an event and the evaluation of the adequacy of the available coping resources (Cohen et al. 1995). Some authors, however, viewed the availment of cognitive resources as stress, while others thought of stress as a change in the emotional well-being. Nitsch (1981) suggests distinguishing between cognitive and emotional demands, whereby only the latter should be referred to as stress.

The most influential psychological stress model was introduced by Richard Lazarus (Lazarus et al. 1980, Lazarus and Launier 1981, Lazarus and Folkman 1984, Lazarus 1999). Lazarus (1980) emphasizes the differences between individuals regarding their reactions to

stress. He criticizes the assumption of identical stress responses to various stressors made by Selye. Lazarus (1980) argues that the specificity of autonomic responses to different kinds of stressful situations had been shown and that the whole pattern of physiological parameters had been barely studied. He defines psychological stress as "…a particular relationship between the person and the environment that is appraised by the person as taxing or exceeding his or her resources and endangering his or her well-being" (Lazarus and Folkman 1984, p.19). In his stress model Lazarus (1999, see also Lazarus et al. 1980) differentiates three forms of appraisal. *Primary appraisal* refers to the individual evaluation of the question, whether a situation is relevant for own values, commitments, and beliefs. If the answer is "yes", Lazarus suggests distinguishing between appraisals of harm/loss, threat and challenge. In *secondary appraisal* a person evaluates its own coping skills and options. The question is: what can be done to cope with the situation? A third and often neglected form of appraising is *reappraisal*, changing one's evaluation in consequence of new information. Stress would occur, if a situation is appraised as *relevant* and if the adequacy of the coping resources is *uncertain*. The denotation "primary" and "secondary" appraisal is – as Lazarus and Folkman (1984) admit – unfortunate, since it suggests that one form of appraisal is more important than the other or precedes the other. Lazarus points out, that both processes are equally important and appear simultaneously. Cognitive appraisal intervenes between encounter and reaction. It depends on personal factors, such as individual commitments and personally formed or culturally shared beliefs, as well as situation variables, such as novelty, predictability, ambiguity and temporal uncertainty (Lazarus and Folkman 1984). The stress concept proposed by Lazarus was criticized by some as being to vague (Cohen et al. 1995). However, not at least due to the work of Lazarus psychological factors received more attention in stress research.

According to the social perspective stress is caused by a threat to the social competence and identity of a person. Three assumptions are made by the proponents of the social perspective on stress: (a) stress is socially caused, (b) stress can become manifest in social behaviour and (c) coping with stress is a social event. Although social factors are important in the stress genesis as well as in coping with stress, the social perspective on stress is by far less developed than the psychological and biological concept of stress.

In every day life stress has primarily negative connotations. And also textbooks do often focus on the – doubtless important – association between stress and illness (see for example Dohrenwend 1998, Nitsch 1981). However, as Selye (Selye 1956) emphasized already in his early writings, stress is not always deleterious. Selye (1956, 1974, 1981) distinguished between constructive "eustress" and destructive "distress". As figure 2.1

indicates as stress increases so does well-being. When the optimal stress level is reached a further increase in stress leads to negative consequences (see also Everly and Rosenfeld 1981).

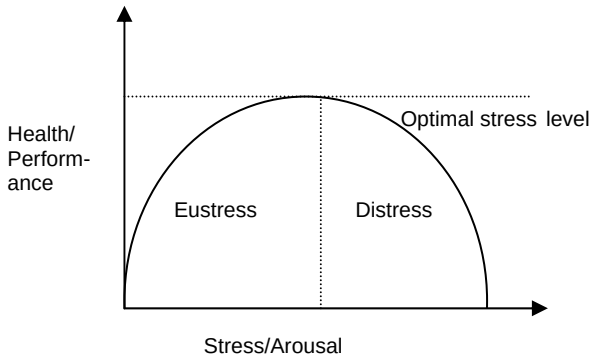


Figure 2.1:
Optimal Stress Level (adapted from Everly and Rosenfeld 1981).

Almost fifty years before Selye Yerkes and Dodson (1908) postulated an inverse u-shaped relationship between arousal and performance. Since arousal is a central component of the stress phenomenon it seems reasonable to assume that there is also an inverse u-shaped relationship between stress and performance. This would implicate that a certain level of stress improves the performance of an individual.

The Janus face of stress was nicely described by McEwen and Norton Lasley (2003) considering the example of salmon: "Every year the salmon swim upstream to spawn, battering the adverse current, leaping over rocks, travelling up to a thousand miles to return to their breeding ground. After ensuring the birth of a new generation, the salmon die" (p.10). Stress enables humans as well as animals to accomplish great achievements, but if it is to intense it might lead to fatal consequences. It was also McEwen (2000a, 2000c, 2002, 2005) who suggested to change the concept of stress that prevailed during the last century. To avoid the ambiguity associated with the term "stress", he proposed to use "stress" for an external force only – same as the 17th century physiologist Robert Hooke. McEwen (2000a) refers to the "fight-or-flight" response as *allostasis* meaning the ability to "achieve stability, or homeostasis, through change" (p. 145). This ability is critical for the survival of the individual by promoting adaptation to changes in the environment. In a dangerous situation an individual needs an increased flow of oxygen to its muscles, therefore breathing is accelerated to get more oxygen and heart rate speeds up to bring the oxygen to the muscles. To provide sufficient fuel for fight or flight glands liquidate carbohydrates to glucose (McEwen and Norton Lasley 2003). These are only two examples for the many changes in physiological systems assuring stability within vital systems such as body temperature, oxygen and glucose

levels. Goal of all these processes is to bring maximal energy to those parts of the body, which need it most. Nowadays, a "simple" fight or flight response is impossible in many stressful situations (e.g. at work). If these situations persist and the allostatic systems remain active for weeks, months or even years, changes in the body might appear that lead to disease (McEwen 2002, McEwen and Norton Lasley 2003). McEwen describes the excessive levels of mediators of allostasis in situations, in which the fight-or-flight response cannot help to speed us toward a resolution and cause wear and tear instead, as *allostatic load*. Four ways in which allostasis can become allostatic load are mentioned by McEwen (2000a, McEwen and Norton Lasley 2003): (a) allostatic processes are activated to frequently, (b) failing habituation to repeated challenges, (c) inability to turn off allostatic reactions, and (d) inadequate allostatic reactions leading to compensatory increases in other allostatic systems. The framework presented by McEwen distinguishes clearly between protective and damaging effects of responses to stressors. McEwen (2000a, 2002) emphasizes that the development of allostasis and allostatic load depends highly on the lifestyle of the individual. Dietary habits, physical activity, consume of alcohol and cigarettes are seen as behavioural factors influencing the risk of allostatic load. In contrast to Selye (1956), McEwen (2005) does not assume that all kinds of stressors cause the same response pattern. He argues, for example, that adrenergic and noradrenergic nerves show different reactions to stress and that they respond differently to different stressors. Moreover, McEwen (2005) suggests an alternative interpretation of the GAS introduced by Selye (1956). The alarm stage is seen by McEwen as a process leading to adaptation by the release of glucocorticoids and catecholamines. The stage of resistance reflects in McEwen's opinion the protective effects of the adaptation to the stressor. And the stage of exhaustion was viewed as the result of the overuse of acute reactions. Stress was defined by McEwen (2000c) as "a real or interpreted threat to the physiological or psychological integrity of an individual that results in physiological and/or behavioral responses" (p.508). If one adds changes in subjective experience and cognitive functioning (Steptoe 2000) as effects of stress this might be a definition most stress researchers could agree to.

2.2 Stress: biological fundamentals

The previous section dealt with rather general ideas about stress. Within this section the biological background of the stress response will be described.

Allostasis or the stress response begins when the hypothalamus sends an alert to the adrenal medulla, which answers by the release of adrenaline, a major stress hormone. The heart rate speeds up, breathing accelerates, and glucose is released from energy stores. Following this first wave of defence a second wave, involving the activation of the hypothalamic-pituitary-adrenal (HPA) axis, sets in (see McEwen and Norton Lasley 2003).

Below both lines of defense – the sympathetic-adrenal-medullary (SAM) system as well as the HPA axis – will be portrayed. Furthermore, glucocorticoids, the second of the major stress hormones, and their action will be described, since they are of great importance within the present work.

2.2.1 The first line of defense

The first wave of the stress response sets in immediately after the stressor occurred. Sensory inputs are transferred via cranial or spinal nerves to the central nervous system. They are relayed by the thalamus to sensory cortices, which send information via the prefrontal cortex to limbic structures (for exceptions see e.g. Pacak and Palkovits 2001, “short circuits”). Amygdaloid nuclei are activated, which in turn project to brain stem nuclei, such as the nucleus of the solitary tract, the pontine reticular formation, the locus coeruleus and raphe nuclei, as well as to the hypothalamus (Lovallo 1997, Nitsch 1981). Hypothalamic activation leads to the release of corticotropin releasing hormone (CRH), primarily from the parvocellular division of the paraventricular nucleus (PVN). The secretion of CRH initiates the activity of the HPA. It leads to the secretion of corticotrophin (ACTH) and β-endorphin from the pituitary about ten seconds after its release from the PVN. CRH exerts also extrapituitary actions; it affects, for instance, the cardiovascular system, respiration and glucose metabolism (Fisher 1991, Koob 1999, Lehnert et al. 1999).

However, hypothalamic activation leads not only to endocrine reactions. The hypothalamus is also the head ganglion of the autonomic nervous system. It activates the sympathetic nervous system (SNS) which secretes noradrenaline at its postganglionaric nerve endings. Among other effector organs the adrenal medulla is activated by the SNS. When activated the adrenal medulla releases 80 percent adrenaline and 20 percent noradrenaline. In consequence of the activation of the SAM system heart rate, respiration and glucose release from energy stores increase, contractibility of cardiac muscles is facilitated and dilatation of blood vessels enhanced (Carrasco and van de Kar 2003, Kopin et al. 1988, Lovallo 1997, McCarty and Gold 1996).

Walter Cannon (1914) viewed the SAM as decisive for the maintenance of homeostasis, as the initiator of the "fight-or-flight" response. He thought of the SAM as a system activated only in case of emergency. More recent authors, however, emphasized that the SAM is also activated in not life threatening, every day situations such as public speaking or ingestion (Goldstein 2003, Kopin et al. 1988). Moreover, Goldstein (2003) suggested to forebear from the idea of a unitary SAM system and to distinguish three catecholaminergic systems: the SNS, the adrenomedullary system and the autocrine/paracrine dopamine system. He proposed that the homeostatic system would be regulated by multiple effectors and that the response to stress would depend upon the kind, intensity and meaning of the particular stressor. Goldstein (2003) ascribed different functions to the different catecholaminergic systems. While noradrenaline (i.e. primarily the SNS) has been associated by him to active avoidance or attack, he associated adrenaline (i.e. primarily the adrenomedullary system) to passive fear and immobility.

This first line of defense, mainly mediated by catecholamines, enables us to adapt to stressful situations within seconds after stressor onset.

2.2.2 The second line of defense

The second line of defense is primarily associated with the activity of the HPA axis. Inputs from limbic and/or brain stem structures stimulate the PVN of the hypothalamus, where many CRH-containing neurons can be found, partly colocalized with arginine vasopressin (AVP). Stimulation of the PVN leads to the release of CRH and AVP into hypothalamo-hypophyseal portal vessels which constitute a specialized portal blood system responsible for the transportation of releasing hormones from the hypothalamus to the anterior pituitary. CRH causes the secretion of β-endorphin and adrenocorticotrophic hormone (ACTH) from the pituitary. AVP by itself leads only to low ACTH release, but it exponentiates the ACTH releasing effects of CRH. It was suggested that CRH-containing neurons are responsible for the basal, diurnal secretion of ACTH, while CRH/AVP-neurons would respond quickly to homeostatic changes of the axis (Hellhammer and Pirke 1996). After its secretion from the anterior pituitary ACTH moves in the blood to the cortex of the adrenal glands, where it induces the release of glucocorticoids, mainly from the zona fasciculata (see figure 2.2). The most important glucocorticoid in humans is cortisol (in rodents it is corticosterone). Cortisol will be of great relevance within the present work. Therefore an extra section will be dedicated to it (see 2.2.3). It is to be emphasized that the above description of the HPA axis is simplified. More than a dozen hormones participate in

its regulation (for an overview of the HPA axis see e.g. Hellhammer and Pirke 1996, Kirschbaum and Hellhammer 1999, Krishnan et al. 1991).

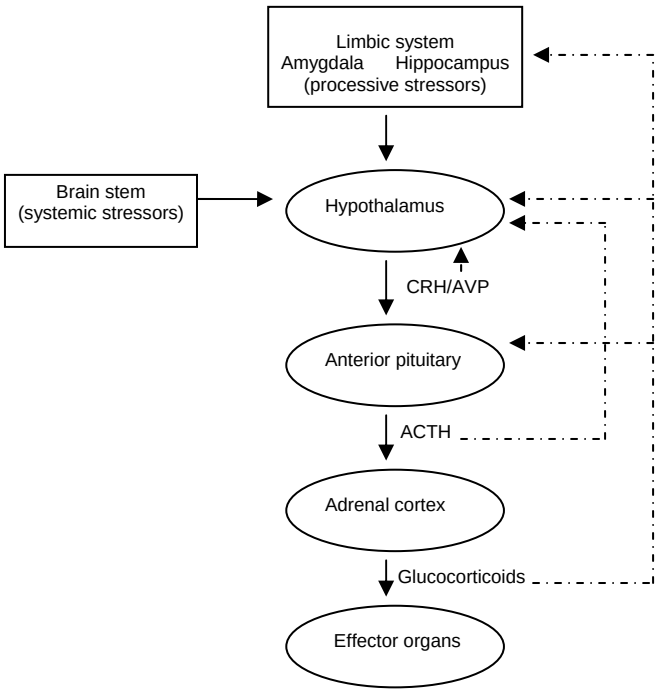


Figure 2.2:*Simplified illustration of the HPA axis (dotted lines indicate feedback loops).*

Importantly, the stress-regulatory circuits activated by a particular stressor depend strongly on stimulus attributes. Herman and Cullinan (1997) distinguished "systemic", i.e. survival threatening, stressors such as hypoxia and "processive" stressors such as exposure to a novel environment, which require processing of signals from multiple sensory modalities and comparison with previous experiences. While systemic stressors are directly relayed to the hypothalamic PVN by visceral efferents, processive stressors are transferred via limbic structures (especially the amygdala and the hippocampus) to the PVN (figure 2.2).

The importance of maintaining glucocorticoid levels within tolerable limits requires mechanisms for inhibiting stress-integrative PVN neurons (Herman and Cullinan 1997). Overshooting of the HPA axis is prevented by several feedback loops. Rhodes (2000) distinguishes an “open-loop”, the regulation of the HPA axis by structures of the central nervous system (CNS), and three types of “closed-loops”: the negative feedback of glucocorticoids to the anterior pituitary, the hypothalamus and the hippocampus (long-loop; see chapter 1.3.2.1.2), the ACTH feedback to the hypothalamus (short-loop) as well as direct feedback of CRH to the hypothalamus (ultrashort-loop). All these feedback mechanisms serve to regulate the release of CRH, ACTH and cortisol itself. Regarding the temporal

characteristics of the feedback control of the HPA axis three phases can be distinguished. Rapid feedback starts within a few minutes after a cortisol increase and lasts not longer than ten minutes. It is a response to the change in cortisol level rather than to the absolute concentration. Early delayed feedback occurring 30 to 60 minutes after an elevation in plasma steroid levels suppresses circadian and stress-induced increases in cortisol. Late delayed feedback shows a latency of 24 hours and emerges only after substantial increases in steroid level; it can last for days or weeks (Buckingham 2000).

In contrast to the SAM system the HPA axis reacts rather slowly. Its major function seems to be the supply of energy in the case of ongoing load.

Selye (1956) demonstrated that physical stress affects the HPA axis. Later, Mason (1968) provided persuasive evidence that also psychological factors influence HPA activity. Especially, the subjectively experienced novelty, uncontrollability, unpredictability and personal relevance of a situation are supposed to activate the HPA axis. However, it is to note that the HPA axis reacts not only to stressful events. Every day actions such as smoking (Matta et al. 1998, Mendelson et al. 2005, Rhodes et al. 2001), ingestion (Alexander et al. 1995, Ishizuka et al. 1983, Vicennati et al. 2002), physical exercise (Droste et al. 2003, Fediuc et al. 2006, Wittert et al. 1991), consume of caffeine (Patz et al. 2006) or alcohol (Waltman et al. 1993) as well as menstrual cycle phase in women (Kirschbaum et al. 1999, Symonds et al. 2004) influence the HPA axis activity (and its responsiveness to stress). Moreover, there is a great variance between subjects in their HPA responsiveness even if environmental factors are constant. This is due to factors such as age, sex or genetic predisposition (Kirschbaum et al. 1999).

Besides SAM and HPA systems there are other systems contributing to the stress induced physiological changes (e.g. the locus coeruleus noradrenergic system). For the purpose of this work, however, it is sufficient to look at the systems described above.

2.2.3 Glucocorticoids

The release of ACTH from the anterior pituitary, which is triggered by CRH released from the PVN of the hypothalamus, leads to the secretion of glucocorticoids from the zona fasciculata and the zona reticulata of the adrenal cortex. Cortisol is the most important glucocorticoid in humans; in rodents it is corticosterone. After its release from the adrenal cortex the steroid hormone is primarily bound to a transport protein (cortisol binding globulin, CBG). About 15 percent of the cortisol is bound to albumin. Only 5 to 10 percent are freely

circulating. This is the biological active hormone fraction (Hellhammer and Pirke 1996, Kirschbaum and Hellhammer 1999).

The cortisol secretion follows a circadian rhythm with a peak in the early morning and an evening nadir. Most glucocorticoid actions are exerted via the "classical pathway", i.e. free steroid enters the cell, bounds to an intracellular receptor and initiates changes in protein synthesis (Buckingham 2000). Cortisol carries out its actions via the broadly distributed glucocorticoid receptors (GR) and the (hippocampal) mineralocorticoid receptors (MR). De Kloet and colleagues (1998) suggested that MR, which show a 10-fold higher affinity to cortisol than GR, mediate tonic cortisol influences, while GR are activated by higher cortisol levels. Glucocorticoids contribute to the protection of the organism in a twofold manner: they prime defense mechanisms of the body (proactive role) and they prevent the overshooting of defense mechanisms (protective role) (Buckingham 2000, Munck 2000).

Effects of cortisol are manifold. In general, cortisol mobilizes energy resources, suppresses non-vital systems (digestion, reproduction), inhibits inflammatory processes, and alters pain sensitivity. An excellent overview of glucocorticoid effects is given by Sapolsky, Romero and Munck (2000). The authors mention effects of glucocorticoids on cardiovascular parameters, fluid volume, immune system, reproduction, metabolism, and neurobiology. Glucocorticoids exert permissive effects on the cardiovascular system; they increase blood pressure and cardiac output. In case of hemorrhage glucocorticoids inhibit the release of AVP. Effects of glucocorticoids on immune system function are inconsistent. Both facilitating and suppressive effects are reported (see also Chrousos 1995). Reproductive behavior and physiology are inhibited by glucocorticoids; the release of gonadotropins is reduced. Of particular importance are glucocorticoid effects on metabolism. The blood glucose increasing effect of the steroid hormone is what gave it its name. Glucocorticoids increase the blood glucose level by enhanced gluconeogenesis, stimulation of glycogen use, inhibition of peripheral glucose transport, and the mobilization of free fatty acids. Thereby glucocorticoids counteract the hypoglycaemic effects of insulin. Furthermore, glucocorticoids impact emotion and cognition, especially via GR and MR in limbic structures (for further overviews of glucocorticoid effects see Kirschbaum and Hellhammer 1999, Pearson Murphy 2000). Effects of cortisol on cognition (with a focus on memory) will be a key aspect of the following chapters.

3 Stress Effects on Memory

3.1 Stress and memory: general considerations

Most people have problems to remember every day events even if they happened only a few days before, while other situations, although long ago, remain remarkably vivid in their memory. We hardly remember what we had for lunch last Tuesday, but still know the color of the house from which the dog came who bit us twenty years ago. Stress makes lasting memories. This had already been known in earlier times when children sometimes had to witness historical events and were afterwards thrown in a river. The stress associated with the fear of drowning should strengthen the memory for the historical event and preserve this thereby for the posterity. Although these examples suggest a facilitating impact of stress on memory, the relationship between stress and memory is less clear.

Albeit, Bartolomucci and colleagues (2002) found an enhancement of specific memory functions after chronic psychosocial stress, most authors agree that chronic stress exerts an impairing effect on hippocampus-dependent learning and memory (Bodnoff et al. 1995, Kleen et al. 2006, Luine et al. 1994, Wright and Conrad 2005). Luine and colleagues (1994), for instance, demonstrated that restraint stress, 6 hours/day for 21 days, affects spatial memory performance in an eight arm radial maze. These impairments are accompanied by altered neuroplasticity, alterations of synaptic terminal structures and dendritic retraction in the hippocampus proper (Artola et al. 2006, Magarinos et al. 1997, McEwen 1999, Pavlides et al. 2002). As argued by Conrad (2006) CA3 dendritic retraction affects spatial memory indirectly: the chronic stress-induced dendritic retraction in the CA3 was supposed to disturb the HPA axis regulation and to elevate the glucocorticoid secretion, which in turn should impair spatial memory. The influence of chronic stress on non-hippocampal memory seems to be different. Working memory was not affected after three weeks of daily restraint stress (Kleen et al. 2006). Fear conditioning was even enhanced following a prolonged stress period (Conrad et al. 1999). Wright and Conrad (2005) demonstrated in chronically stressed rats that impairments in a spatial Y-maze task disappeared after salient intramaze cues were added that allowed for stimulus-associated learning. Thus, non-hippocampal memory is - if at all - less affected by prolonged or repeated stress than hippocampus-dependent forms of memory.

More diverse is the literature on the effects of acute stress on learning and memory. Cahill, Gorski and Lee (2003) reported that subjects showed improved memory performance

for emotionally arousing slides compared to controls when cold-pressure stressed after viewing the slides. Similarly, Payne et al. (2006) obtained a facilitating effect of psychosocial stress on the memory for emotional aspects of an event. Time-dependent retrieval impairment was observed by de Quervain, Roozendaal and McGaugh (1998) who gave rats footshocks 30 minutes before a water maze retrieval test. That stress might affect physiological processes underlying learning and memory has been suggested by a study of Kim and colleagues (1996). The authors observed that NMDA-receptor dependent changes occur during stress in the CA1 of the hippocampus. These changes were assumed to alter the inducibility of LTP and LTD. Corroborating these results, Akirav and Richter-Levin (1999) provided evidence that the development of LTP by high frequency stimulation is blocked 30 minutes after behavioral stress.

Many of the studies which were dedicated to shed light on the impact of stress on memory focus on the effect of glucocorticoids as a major stress correlate. According to McEwen (1999) corticosteroids are involved in three kinds of plasticity in the hippocampus: (a) the modulation of the excitability of hippocampal neurons and the strength of the LTP, (b) they act together with amino acids on the neurogenesis in the dentate gyrus, and (c) they act together with amino acids on (reversible) stress induced atrophy in the CA3.

A number of studies indicated a detrimental effect of cortisol on memory in humans. Buss et al. (2004) asked subjects to recall autobiographic memories and found that these memories were less detailed in people who received a moderate dose of hydrocortisone than in untreated controls. Kuhlmann, Kirschbaum and Wolf (2005) obtained impaired memory in women after they were administered cortisol. De Quervain and colleagues (2000) administered cortisol either before or immediately after the learning of neutral words or before a retention test 24 hours later and observed an impairing effect of cortisol only when administered before retrieval. Furthermore, Putman et al. (2004) as well as Kirschbaum and colleagues (1996) reported negative correlations between cortisol levels and explicit memory.

By implementing cortisol pellets in the hippocampi of monkeys Sapolsky et al. (1990) investigated the effect of chronic cortisol on hippocampal cell structures. After one year of heightened cortisol levels deformed somata, neurodegeneration and irregularities in zonal arrangements were found (see also Stein-Behrens et al. 1994 and Uno et al. 1989). The “glucocorticoid cascade hypothesis” (Sapolsky 1986) which proposes a significant relationship between high cortisol levels, impaired memory functions and hippocampal atrophy, has been addressed in a very elegant study by Issa et al. (1990). They studied the HPA-activity, spatial memory performance and the number of hippocampal neurons in aging

rats. Basal ACTH concentrations as well as corticosterone concentrations were significantly higher in cognitively impaired rats than in cognitively unimpaired rats. Moreover, hippocampal neuron loss was significantly higher in the former ones. Similar results were obtained by Lupien and colleagues (1998) in aging humans. The authors measured basal plasma cortisol levels in aged healthy volunteers annually for five to six years. They demonstrated that aged humans with prolonged cortisol elevations showed a reduced hippocampal volume and deficits in hippocampus-dependent memory tasks relative to normal-cortisol controls. Moreover, the degree of hippocampal atrophy was found to be correlated significantly with the degree of cortisol elevation over time and current basal cortisol levels. The authors concluded that basal cortisol elevation may lead to hippocampal damage and deficits in hippocampus-dependent learning and memory (see also Lupien et al. 2005, Lupien et al. 1994).

Besides studies indicating impairing effects of glucocorticoids on memory there are also results suggesting memory enhancing glucocorticoid effects. Buchanan and Lovallo (2001), for instance, reported that subjects who were administered cortisol before viewing pictures showed a better memory for emotional pictures in a retention test one week later. And Roozendaal and McGaugh (1997) demonstrated that posttraining injections of a glucocorticoid agonist facilitated the memory performance in an inhibitory avoidance task, while pretraining injections of a glucocorticoid antagonist were associated with memory impairments in the water maze (see also Quirarte et al. 1997). Similarly, Newcomer et al. (1994) described a positive correlation between plasma cortisol concentrations and correct recall during a paragraph recall task. An impairing effect of decreasing cortisol levels on delayed recall was observed by Lupien and colleagues (2002) in subjects who were administered metyrapone, a glucocorticoid synthesis inhibitor, before neuropsychological testing. Akirav and colleagues (2004) replicated the findings of Sandi et al (1997) that rats trained in cold water for a spatial task showed higher corticosterone levels as well as better acquisition and retention performance than rats trained in warm water. Furthermore, Akirav et al. (2004) demonstrated that pretraining administration of corticosterone led to better performance in rats trained in warm water, while the administration of metyrapone, a glucocorticoid synthesis inhibitor, before training impaired the performance of rats trained in cold water. The authors concluded "…that corticosterone is instrumental in the acquisition and retention of the spatial learning task" (p.188).

Several authors argued that the effect of glucocorticoids on learning and memory is neither purely enhancing nor purely impairing, but that there is an inverted u-shaped

relationship between corticosteroids and memory. While moderate levels should lead to improved memory performance, high and (too) low levels were assumed to have disruptive effects on memory (e.g. Abercrombie et al. 2003, McEwen and Sapolsky 1995, Roozendaal, Williams and McGaugh 1999). Diamond and colleagues (1992) suggested that also an inverted u-shaped relationship between cortisol levels and primed burst potentiation, the prolonged increase of the amplitude of CA1 spikes in response to hippocampal stimulation.

De Kloet, Oitzl and Joels (1999) argued that the paradox that corticosteroids are essential for cognitive performance on the one hand, but have damaging effects on memory formation on the other hand, can be explained by considering the specific roles of GR and mineralocorticoid receptors (MR) in the various stages of information processing. Selective MR blockade has been shown to affect the applied learning strategy, while selective GR blockade led to impaired memory consolidation (Oitzl and de Kloet 1992). Thus, MR were viewed as being responsible for the behavioral reactivity and the responses to environmental cues, whereas GR were assumed to influence primarily the consolidation of acquired information (de Kloet et al. 1999). That MR and GR affect the information processing in different ways has been confirmed by Sandi and Rose (1994) by administering MR and GR antagonists, respectively. It was proposed by de Kloet, Oitzl and Joels (1999) that "if imbalance between MR- and GR-mediated actions on crucial neuronal networks that underlie behavioral adaptation persists … this imbalance might contribute to deterioration of cognitive function" (p.426). Conrad and colleagues (1997) found that MR but not GR agonists improved the performance of adrenalectomized rats in the water maze. This led the authors to conclude that GR require a concomitant activation of MR to affect learning and memory. In the same line, Joels and de Kloet (1993) proposed that at least MR have to be activated to maintain synaptic transmission in the CA1 region of the hippocampus.

A metaanalysis by Het, Ramlow and Wolf (2005) shed light on a further factor that may account for the diverse results found in the literature on how corticosteroids impact memory: The time of day seems to influence the effect of glucocorticoids given prior to learning. While studies that administered cortisol in the morning found memory impairments, studies applying cortisol in the afternoon obtained small but significant memory enhancement (see Lupien et al. 2002).

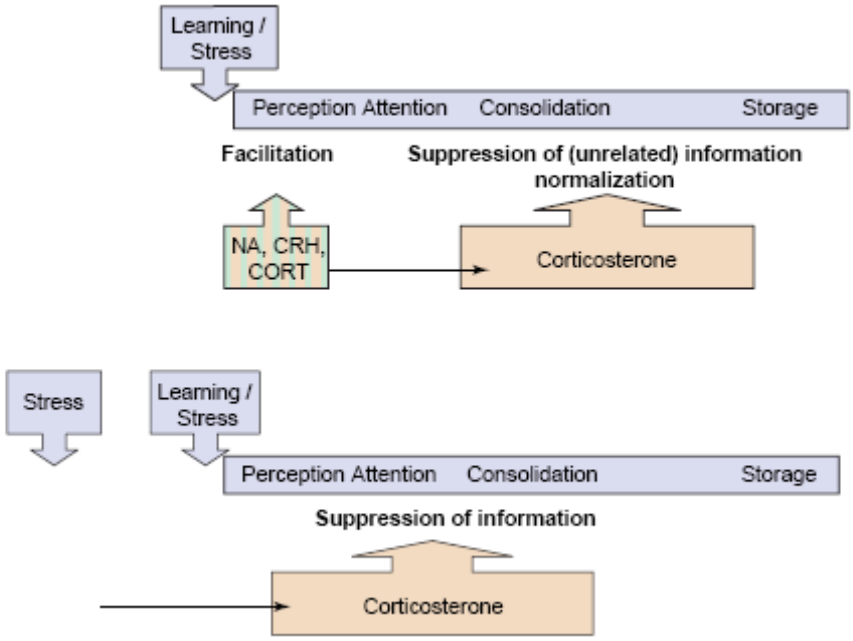


Figure 3.1: *Antagonising effects of stress and glucocorticoid administration depending on the timing of the events (from Joels et al. 2006).*

Taking the circadian rhythm of the corticosteroid release into account (morning peak and evening nadir), this finding fits well to the view that there is an inverted u-shaped relationship between corticosteroids/stress and memory performance.

Altogether, the following picture emerges from the literature on the effects of stress (or glucocorticoid administration) on learning and memory: Effects of pre-learning stress are ambivalent, both impaired and enhanced memory was found (Buchanan and Lovallo 2001, Kirschbaum et al. 1996, Newcomer et al. 1994). Stress within a certain time window after learning facilitates memory consolidation (Cahill et al. 2003, Roozendaal 2000, Roozendaal 2002), while stress prior to a retention test impairs memory retrieval (Buss et al. 2004, De Quervain et al. 1998, de Quervain et al. 2000, Kuhlmann et al. 2005; for a review see Het, Ramlow, Wolf 2005).

Joels and colleagues (2006) suggested recently a model that provides an explanation for the converse stress effects (figure 3.1). The authors propose that stress will facilitate learning and memory only when "… (i) stress is experienced in the context and around the time of the event that needs to be remembered, and (ii) when the hormones and transmitters released in response to stress exert their actions on the same circuits as those activated by the situation…" (p. 152). That is, Joels et al. (2006) assume that CRH, noradrenalin and glucocorticoids facilitate ongoing cognitive processes. However, glucocorticoids initiate also

a gene-mediated pathway, which elevates the threshold for interfering processes such as the acquisition of new or the recall of old material. Thus, the seemingly destructive effect of stress on learning of new and retrieval of previously learned information is actually adaptive as it ensures that ongoing memory processes are not disturbed.

Similarly, Roozendaal and colleagues (McGaugh, Cahill and Roozendaal 1996, Roozendaal 2002) proposed that glucocorticoids and noradrenalin released during stressful experiences converge in the BLA, which coordinates in concert with other brain regions such as the hippocampus or the prefrontal cortex the antagonising effects of stress on acquisition, consolidation and retrieval (figure 3.2). This model is well supported by several studies (Cahill et al. 1994, De Quervain et al. 2007, Roozendaal et al. 1996b, Roozendaal et al. 2004a, Roozendaal et al. 2006).

Here it is to note that the above mentioned studies refer to effects of stress/corticosteroids on hippocampus-based declarative memory. Those studies that addressed the impact of stress on non-declarative memory found no effect of stress (Kirschbaum et al. 1996, Lupien et al. 1994).

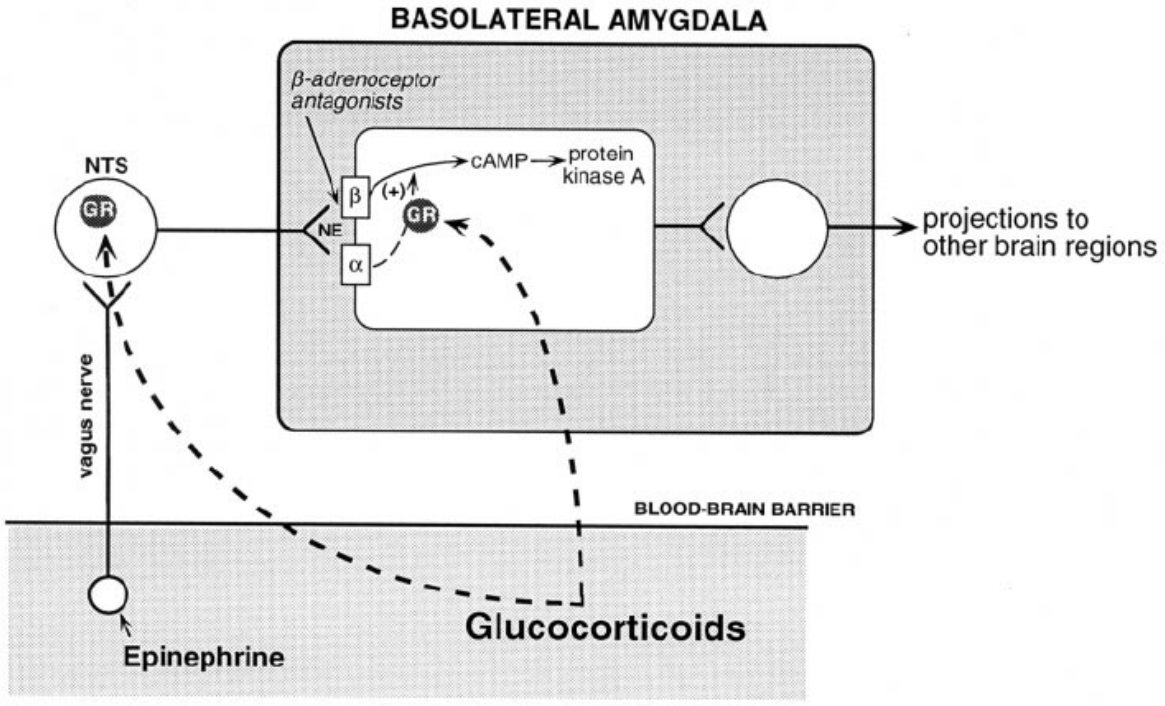


Figure 3.2: *Interactions of glucocorticoids and the noradrenergic system in the basolateral amygdala (BLA): the Roozendaal and McGaugh model (from Roozendaal 2002).*

3.2 Modulatory effects of stress on multiple memory systems and the scope of this work

Subsequent to an overview of psychological theories of learning and memory the multiple memory systems view has been introduced and the medial temporal lobe (hippocampal) system, the dorsal striatum system as well as the amygdala were portrayed (chapter one). The hippocampus was associated with declarative or "cognitive" memory and thought to process relations between multiple cues. In contrast, the dorsal striatum was assumed to focus on single cues and to be responsible for the rather simple stimulus-response ("habit") memory. The amygdala has been related to emotional memory, but seems to be no site of memory storage. It rather influences memory processes in other brain areas (Kim and Diamond 2002, McGaugh 2006, Roozendaal and McGaugh 1997a).

In chapter 1.3.2.4 it was argued that information is processed in parallel and simultaneously in the hippocampus and neostriatum. While the two memory systems cooperate in some situations (McIntyre et al. 2003a, Voermans et al. 2004), they compete in others (Matthews and Best 1995, Poldrack et al. 2001, Schroeder et al. 2002). This raises the question how one system comes to dominate behavior in situations of conflict between memory systems. In the present work it is argued that stress exerts a modulatory effect on multiple memory systems. The concept and the biology of stress have been described in chapter two. In the previous section it has been shown that stress affects memory in general. That the emotional state prior to learning influences the use of multiple memory systems was suggested in a study by Packard and Wingard (2004). They showed that rats which received an injection of anxiogenic drugs used significantly more often a stimulus-response strategy in a test trial after training on two consecutive days in the plusmaze compared to placebo controls (see also 1.3.2.4). In a study that is of great importance for the present work, Kim and colleagues (2001) investigated the effect of stress on spatial and stimulus-response memory. They stressed rats (restraint stress and 60 tail shocks) 30 to 60 minutes before eight massed training trials in a fixed location – visible platform task. In this task rats are supposed to find a submerged platform coupled with a salient pole in a circular tank filled with opaque water. The platform can be found either by orientating on the pole, i.e. by using a dorsal striatum-dependent stimulus-response strategy or by taking the spatial arrangement of the environment into account, i.e. by applying a hippocampus-based spatial strategy. Starting points were randomly distributed. The next day, a retention test was given in which the platform (coupled with the pole) was moved to a novel location. What Kim and colleagues obtained was that

animals stressed before training showed a significantly shorter latency to find the platform than unstressed controls. The observed difference was due to the fact that control animals swam first to the location, where the platform had been during training, while half of the stressed animals moved directly to the new platform location (see figure 3.3). This indicates a modulatory effect of stress on the use of spatial versus stimulus-response memory.

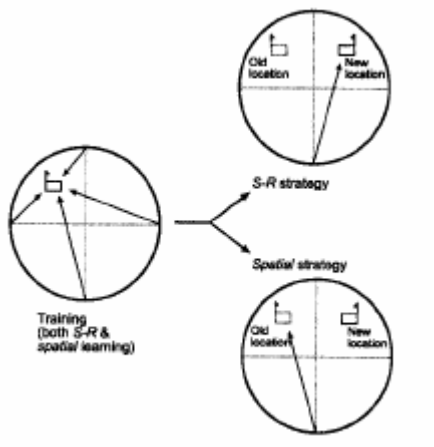


Figure 3.3: *Fixed location – visible platform task to assess the effects of stress on spatial and stimulus-response memory (from Kim et al. 2001).*

Comparable data from humans are missing. Indirect evidence for the hypothesis that stress modulates multiple memory systems in favor of the nucleus caudate-based "habit" system comes from a recent study by Foerde, Knowlton and Poldrack (2006). In their study participants were given a probabilistic classification task (weather-prediction task) that can be solved by the engagement of the medial temporal lobe or the caudate-nucleus. While working on this task participants were presented high and low-pitched tones. In one set of blocks high-pitched tones should be counted during weather prediction (dual-task condition, DT), in the other the tones could be neglected (single task condition, ST). During task-processing functional imaging was performed with a head only scanner. After the weather prediction task was finished, participants were given a declarative memory task; they were asked about cue-outcome associations. Foerde et al. (2006) observed that learning proceeded normally under DT conditions. However, the test of declarative knowledge showed that the performance of a secondary task impaired acquisition of flexible knowledge about cue-outcome associations. Interestingly, although no differences regarding the classification accuracy were observed between DT- and ST-conditions, there were significant differences in neural activity between conditions. Activity in the right hippocampus was significantly correlated with performance of items learned under DT-conditions; the putamen showed the opposite pattern. This

suggests that the presence of a demanding secondary task modulates the degree to which declarative and habit learning systems are used to solve a task.

If it is assumed that the performance of a secondary demanding task is associated with a higher stress level, the study by Froede and colleagues (2006) can be seen as evidence for the modulating effect of stress on multiple memory systems. However, this evidence is (at best) indirect, direct evidence for a memory system modulation by stress in humans is missing. It is the primary goal of this work to close this gap and to investigate whether stress modulates learning and memory in favor of the caudate nucleus-dependent “habit” system and at the expense of the hippocampus-dependent “cognitive” system in humans. Such a memory modulating effect might have important implications for education, social life and the treatment of psychiatric disorders. To be able to investigate the modulatory effect of stress on multiple memory systems a first step is to develop a paradigm that allows a differentiation between spatial and stimulus-response memory in humans. This first step will be described in the following chapter.

4 Development of a Paradigm to Distinguish Spatial and Stimulus-response Learning and Memory in Humans

To test the impact of stress on the use of multiple memory systems a paradigm is to be developed that permits a differentiation of spatial ("cognitive") and stimulus-response ("habit") learning and memory. Task requirements are (i) the possibility to acquire the task by means of the hippocampal (medial temporal lobe) "cognitive" system as well as by means of the caudate nucleus-based "habit" system and (ii) the chance to "dissociate" the two systems in a test trial to determine which strategy is/was used.

In a first step a simple task that was thought to fulfil the required criteria and could be executed at the computer was developed and tested in a preliminary study. Since there were several problems with the task in this form, it has been advanced and put into a different context; a 3D-model of a room was used. This more elaborated version of the task was tested in a second preliminary study.

In the following, the task as well as the belonging pilot studies will be described.

4.1 Pilot study I

4.1.1 Methods

4.1.1.1 Subjects

Forty healthy volunteers (21 females, 19 males) agreed to participate in this study (age mean: 23.9 years; age range: 20-32 years). All of them were students at the University of Trier. Participants received a moderate monetary incentive on completion of the experiment; the exact amount depended on how often the "win-field" was chosen by an individual.

4.1.1.2 The learning task

Participants were presented a configuration consisting of six fields, each labelled with a letter (R, C, Q, M, B, K), on a common computer screen (see figure 4.1 a). They were told that there is a prize of 50 Cent behind one of the fields, while there are blanks behind all other fields. It was the participants' task to click on the field behind which they assumed the prize

to be. Immediately after subjects clicked on a field they received a feedback about the result of their choice (50 Cent versus blank); then the next trial started. The arrangement of the fields and letters was constant during training. What the subjects did not know was that the prize had been in all trials behind one and the same field. This field could be identified both by its position (second column, second row) and by the letter ("M"). In a subsequent test trial the arrangement of the letters was changed (see figure 4.1 b). If subjects clicked on the letter ("M") in the novel position this was interpreted as a sign of stimulus-response learning/memory. Whereas choosing the field in the position, where the prize had been during training, was seen as indicating spatial learning/memory.

The task was programmed using E-Prime software (Psychological Software Tools, Inc.; Pittsburgh, USA).

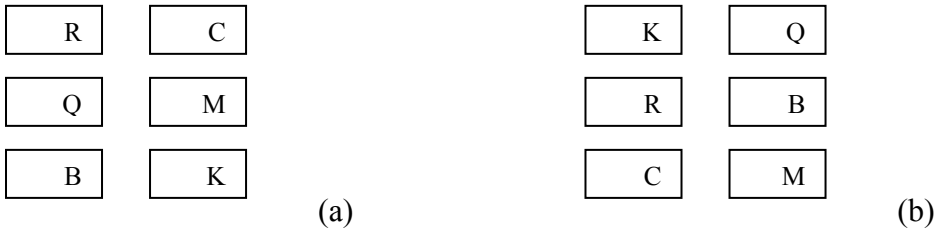


Figure 4.1: *Six-field configuration (a) during training and (b) in the test trial.*

4.1.1.3 The Trier Inventory of Chronic Stress (TICS)

The Trier Inventory of Chronic Stress (TICS; Schulz and Schlotz 1999, Schulz, Schlotz and Becker 2004) is a valid and reliable German 57-item questionnaire that was designed to measure 9 aspects of chronic stress: "work overload", "social overload", "pressure to succeed", "work discontent", "excessive work demand", "lack of social recognition", "social stresses", "social isolation" and "chronic concern". Items are descriptions of experiences such as "I have to finish too many things" and people are asked to specify on a 5-point rating scale ("never", "infrequent", "sometimes", "frequent", very frequent") how often they made the referring experience within the last 3 months. The time required to complete the TICS is 10 to 15 minutes.

4.1.1.4 Procedure

Participants performed 14 training trails of the task as described above. Thereafter subjects were asked to fill out the TICS (Schulz et al. 2004) to control for differences in individual stress levels. After filling out the TICS subjects were given one test trial (see above). Before they received feedback on their choice, participants were asked how certain they felt that they chose the field behind which the prize is (on a scale from 0 to 100, where "0" means "absolutely uncertain" and "100" means "absolutely certain"). All in all the investigation took about 35 minutes.

4.1.2 Results[1]

Learning strategy, performance and TICS scales: Twenty-six out of 40 participants (65 percent) used a stimulus-response strategy (field with letter M), 9 (23 percent) employed a place strategy, 5 (12 percent) chose neither the stimulus-response nor the spatial option. Participants' sex did not affect the chosen strategy ($\chi^2(1) = 0.47$, $p = .49$; $C = 0.12$). While there was no main effect of the learning strategy (spatial vs. stimulus-response) on the TICS scales ($F(1,32) = 0.48$, $p = .49$), a significant interaction of learning strategy and TICS scales was found ($F(8,256) = 2.48$, $p = .03$). As indicated in table 4.1 those participants who chose the stimulus-response option had significantly higher values on the TICS scales "work overload" and "chronic concern" (both p's = .03). Furthermore, stimulus-response learners tended to show higher values on the scales "excessive work demand" ($p = .08$) and "lack of social recognition" ($p = .11$).

Table 4.1: *TICS scores of spatial and stimulus-response learners.*

TICS scale	Spatial learners	Stimulus-response learners	P
Work overload	43,50 ± 2,23	53,64 ± 2,83	.03
Social overload	44,10 ± 2,87	46,04 ± 1,97	.60
Pressure to succeed	47,90 ± 1,75	49,16 ± 1,58	.65
Work discontent	56,00 ± 2,48	55,40 ± 1,83	.86
Excessive work demand	51,20 ± 3,10	57,48 ± 1,86	.08
Lack of social recognition	45,50 ± 2,99	50,68 ± 1,64	.11
Social stresses	55,80 ± 3,10	50,60 ± 2,50	.25
Social isolation	51,50 ± 2,77	51,36 ± 2,11	.97
Chronic concern	45,50 ± 2,09	52,52 ± 2,32	.03

Data represent means ± SEM.

[1] If not stated differently, **two-tailed** p-values will be reported in this work.

A mixed design ANOVA on the reaction times revealed a significant time effect (greenhouse geisser $F_{(2,52)} = 4.17$, $p = .03$, partial $\eta^2 = 0.11$) but neither a main effect of the applied learning strategy ($F_{(1,33)} = 0.45$, $p = .51$, partial $\eta^2 = 0.01$) nor an interaction effect of time and strategy (greenhouse geisser $F_{(2,52)} = 0.98$, $p = .33$, partial $\eta^2 = 0.03$) indicating that both groups of learners improved over trials but did not differ in their learning gradients (figure 4.2). Spatial and stimulus-response learners did also not differ regarding their reaction times in the test trial ($t_{(32)} = 0.08$, $p = .94$, $d = 0.02$).

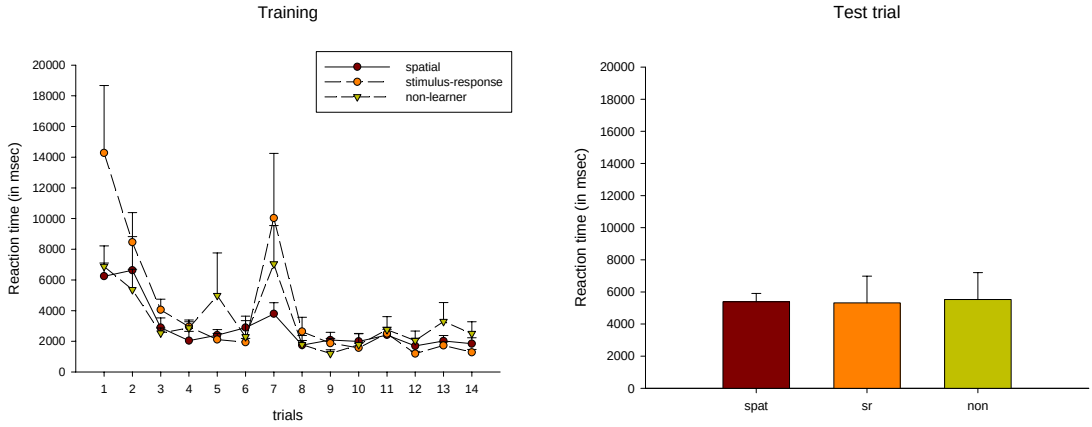


Figure 4.2: *Reaction times of spatial, stimulus-response and non-learners (a) during training and (b) in the test trial.*

Verbal report: All participants that were classified as "learner" described the applied strategy in line with the chosen card. Non-learners stated typically that the position of the win-field was completely random and that there was no consistency. Interestingly, stimulus-response learners (M = 56) tended to be more certain that the chosen field is the win-field than spatial learners (M = 44; $t_{(33)} = 1.68$, $p = .11$, $d = 0.63$).

4.1.3 Discussion

This study was conducted to test the feasibility of a new learning and memory task developed to distinguish spatial and stimulus-response learning and memory in humans. About 63 percent of the participants based their choice on a single stimulus (“M”), 25 percent chose a strategy that might be interpreted as spatial (but see below), 12 percent chose none of the options that were assumed to be indicative for spatial and stimulus-response learning, respectively. Thus, indeed interindividual differences in the strategy applied to “solve” the task were observed.

An association was found between the applied strategy and two scales of the TICS. The direction of this association was in line with the hypothesis that stress enhances the use of stimulus-response learning and memory. Those subjects who employed a stimulus-response strategy had higher scores on the three TICS scales. However, since the sample size of this study was rather low, this association is not to be overemphasized.

This pilot study revealed several problems of the developed learning and memory task. First, there was a clear imbalance in the strategies used. Since the paradigm was developed to test the effects of stress on multiple memory systems and it was hypothesized that stress enhances stimulus-response memory at the expense of spatial memory, ideally unstressed people should have employed a spatial strategy more often or at least the strategies should have been used equally often. However, almost two third of the participants employed the stimulus-response strategy. It is to be emphasized that the TICS scores of the subjects were at most moderate, not high. Thus, it can not be argued that the imbalance is due to the high stress level in the sample. Second, there were 5 participants who used neither the spatial nor the stimulus-response option. It might be speculated that they viewed the test trial as a completely new task, unrelated to the previous training. Finally, the most severe problem with the paradigm is that it still remains unclear whether the choice of the field where the prize had been during training can be interpreted as indicative for a spatial learning strategy. Spatial learning has been defined as relational learning, as a representation of the spatial relationships between pairs of cues (Eichenbaum et al. 1999a). In the developed task there are no cues that allow for spatial orientation. It might be argued that the room in which the study was conducted can provide these cues. As subjects, however, focused on the monitor while working on the task, it seems unlikely that they used room cues for spatial orientation. Moreover, other studies (Kim et al. 2001, Packard et al. 1994) varied the starting point to avoid the development of a simple motor response. That subjects who clicked on the old position of the “win-field” did so because of a “motor habit” can not be ruled out in the paradigm tested here. Because of these conceptual weaknesses, the task is not applicable for the investigation of stress effects on spatial versus stimulus-response learning and memory.

4.2 Pilot study II

The main problem of the previous task was that it remained questionable whether a spatial strategy could be applied to solve the task or not. To overcome this problem the task has been modified and put into another context. The most important modifications were that "starting points", i.e. the sides from which subjects looked into the model, were varied and that subjects were asked to describe why they chose the card they have chosen, how certain they feel that the chosen card is the correct card and whether there would be a reasonable alternative. Moreover, the task was not presented on a computer screen, but a 3D model of a room was used.

4.2.1 Methods

4.2.1.1 The spatial learning task ("card task")

Subjects were presented a wooden model of a room (box 50x50x50 cm; figure 4.3). In the center of the room is a square table on which four identical cards (white side up) are placed exactly in the middle of one of the four quadrants. There is a small plant in one of the corners of the table. Each wall contains one cue: door, window, picture, or clock. These cues are exactly in the middle of the walls. Therefore a direct association of one of these cues to one of the four cards is not possible. A chair is placed in a corner of the room. All these symbols should allow spatial orientation. The box is revolvable; the walls can be removed (see figures 4.3 a-e).

Subjects were told that they will see a 3D model of a room, containing amongst other things four cards lying on a table. One of the four cards would be a "win-card" (word "win" written on the card); while the other three cards would be "no-win" cards (word "blank" written on the card). The backside of the card was white and visible. One wall of the box was removed. The participant sat directly in front of the model and was asked to point with the finger at the card which he/she thought to be the "win card". The experimenter turned this card in such a way that the subject saw the text on the card. So subjects received an immediate positive or negative feedback. For locating the "win-card" subjects got 50 Cent. Thirteen trials were given. Eyes had to be closed between the trials. The experimenter turned the box, replaced one and removed another wall after each of the trials (same sequence for all participants). In this way, each trial provided a different view into the same room, with all objects in a fixed position. In trials one to twelve subjects looked three times from each of the

four sides into the room. The participants were not told that the “win-card” was in all trials at the same position (field A and D, respectively; see figure 4.4). Subjects could acquire the position of the “win-card” either by learning that the “win-card” was always next to the plant (stimulus response) or by learning the position of the “win-card” relative to other room cues (spatial). We concluded that a subject had learned the position of the “win-card”, if the “win-card” had been chosen in three consecutive trials, and the subject did not change his/her choice in the subsequent trials.


a


b


c


d

Figure 4.3: *3D Model of the room: look from (a) the “clock”, (b) the “picture”, (c) the ”window”, (d) the “door” , and (e) above.*

This is a rather strict criterion, but since the probability to find the correct card by chance is 25 percent, such a strict criterion is required. By determining from which trial on a subject could be classified as a learner, we concluded the learning speed of an individual. In trial 13, the plant was moved to another location.

To exclude the possibility that the decision in this trial is influenced by the side from which subjects look into the room, the latter was varied between subjects. Furthermore, the position of the plant was varied between subjects during training. While the plant was located in field A during training for the one half of the participants, it was located in field D for the other half (see figure 4.4). The use of a spatial strategy was accepted, if a participant pointed at the card in the quadrant in which the "win-card" had been located in trial 12. Choosing the card next to the novel position of the plant was considered as a stimulus-response strategy. After subjects made their choice in trial 13, but before they received feedback, they were asked which strategy they applied to find the "win-card", how certain they felt that the chosen card is the "win-card" (on a scale from 0 to 100, where 0 stands for "absolutely uncertain" and 100 for "absolutely certain") and if they have a reasonable alternative in mind. All in all the test took about 25 minutes.

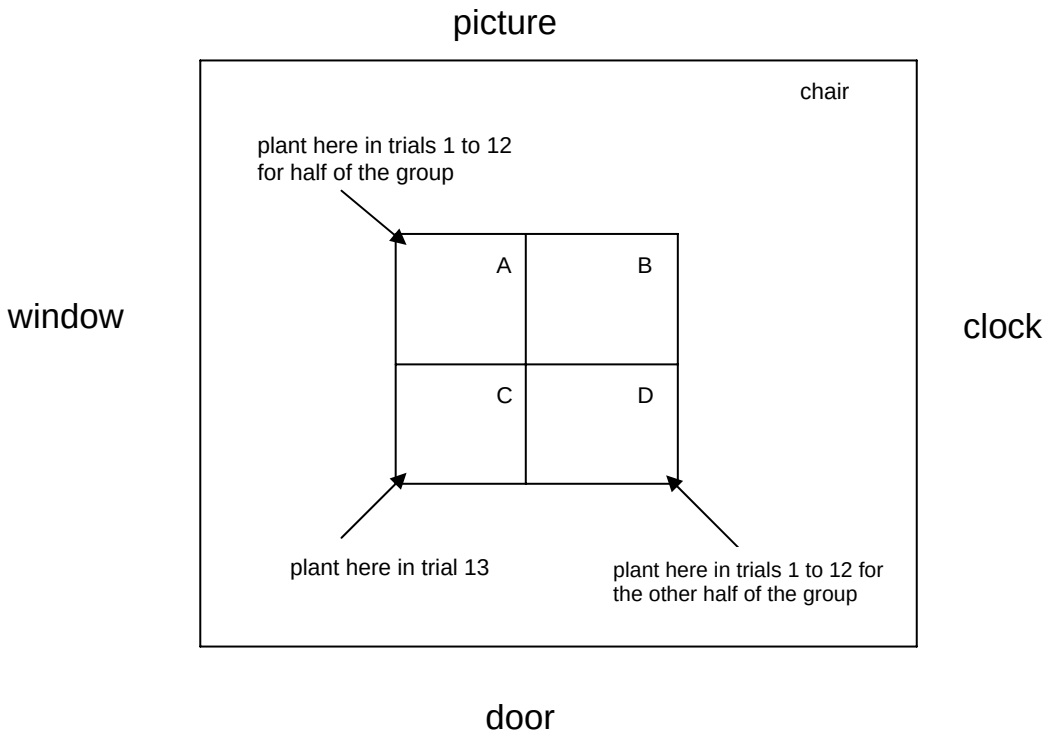


Figure 4.4: *Schematic view of the model of the room.*

4.2.1.2 Subjects

Twenty-two young, healthy volunteers (9 females, 13 males) agreed to participate in this study (age mean: 24.0 years; age range: 19-34 years). All of them were students at the University of Trier. Subjects received a moderate monetary incentive for participation in this study; the exact amount of the incentive was dependent on how often the "win-card" was chosen.

4.2.1.3 Procedure

After subjects arrived they were given a standardized, written instruction and had the opportunity to explore the model of the room. Then, participants performed 12 training trials as described above (with the plant in a constant location). Afterwards subjects were asked to fill out the "Trier Inventory of Chronic Stress" (TICS; Schulz et al. 2004; see 4.1.1.3). Finally, the test trial (trial 13) was given, in which the position of the plant was changed. Before subjects received feedback in this trial, they were briefly interviewed about the strategy employed, their certainty and alternative strategies they have in mind. All in all the investigation took about 45 minutes.

4.2.2 Results

Of the 22 participants 11 chose the card besides the plant (stimulus-response learners), 7 chose the card in the position where the "win-card" had been during training (spatial learners) and 4 chose none of the two options.

These differences in strategy use (spatial versus stimulus-response) were not associated with one of the TICS scales ($p > .10$).

Spatial and stimulus-response learners differed significantly with respect to the possible strategies mentioned ($\chi^2(1) = 7.90$; $p < .01$; $C = 0.55$). While 6 out of 7 spatial learners (86 percent) were aware of the spatial *and* the stimulus-response strategy, only 2 out of 11 stimulus-response learners (18 percent) were aware of both strategies.

On average subjects needed 6 to 7 trials to acquire the position of the "win-card"; there was no difference between spatial and stimulus-response learners ($t(16) = 0.45$; $p = .66$; $d = 0.20$).

Stimulus-response learners were more certain (mean: 65) in their choice than spatial learners (mean: 56). This trend, however, failed to reach significance ($t(16) = 1.10$; $p = .29$; $d = 0.53$).

No effect of sex on the used learning strategy was observed ($\chi^2(2) = 2.65$; $p = .45$; $C = 0.33$).

Furthermore, there was no significant effect of the side from which subjects looked into the room model in the test trial on the decision in this trial ($\chi^2(6) = 7.12$; $p = .31$; $C = 0.49$). However, if only spatial and stimulus-response learners were considered, the effect of the view in the test trial would be close to significance ($\chi^2(3) = 7.06$; $p = .07$; $C = 0.53$).

The position of the plant during training had no significant impact on the used learning strategy ($\chi^2(2) = 0.23$; $p = .89$; $C = 0.10$).

4.2.3 Discussion

In pilot study I it remained unclear whether it was possible to assume the use of a spatial learning strategy or not (see 4.1.3). Here, subjects were asked to identify the correct card out of four cards presented in a 3D model of a room. This paradigm parallels major characteristics of the water maze task as used by Kim and colleagues (2001): (a) a single stimulus close to the "win-card" as well as "environmental" cues were provided, so that the "win-card" could be identified either with the help of the single stimulus or by means of the relationship between (at least two) environmental cues, (b) the environmental cues were arranged in a manner that did not permit a direct association between the "win-card" and one single cue, (c) starting points were varied, thus a simple motor response could be excluded as a strategy to identify the "win-card", (d) the arrangement of the cues remained constant during training and was changed in the test trial; the acquisition of the position of the correct card was possible by means of a spatial and a stimulus-response strategy during training and the strategies can be distinguished in the test trial. Thus, it is assumed that the present paradigm is appropriate to differentiate between spatial and stimulus-response learning and memory.

In this pilot study 50 percent of the subjects used a stimulus-response strategy, 32 percent a spatial strategy and 18 percent none of these two options. So the ratio of the spatial and stimulus-response strategy was still different from the ideal of a complete balance of the two strategies or a prevalence of the spatial strategy, but much better than in the previous task.

In contrast to pilot study I, there was no association between the used learning strategy and one of the TICS scales in this study. Furthermore, there was no effect of sex on the employed strategy and the used learning strategy was not associated with decision certainty or learning speed.

Interestingly, it was observed that the majority of the spatial learners (86 percent) were aware of both possible learning strategies, whereas the majority of the stimulus-response

learners (82 percent) named the strategy they used as the only option. This might be interpreted as a sign for the higher simplicity and rigidity of stimulus-response learning and memory. However, since the sample size of this preliminary study is very low (N = 22; learners: n = 18), these results should not be interpreted seriously. The t-test to investigate whether spatial and stimulus response learners differ in learning speed, for instance, has a power (1-β) of only 0.30 to detect a medium effect of d = 0.50.

The obtained results suggest that the position of the plant has no effect on the used learning strategy, while there might be an influence of the side from which subjects look into the 3D model in the test trial. Therefore, the latter should be controlled in a subsequent study.

This pilot study aimed to test the feasibility and some methodological aspects of the developed spatial learning and memory task. Since both a stimulus-response *and* a spatial learning strategy seem applicable in the present paradigm and there are – until this point – no problems with its feasibility, this paradigm is seen as appropriate to investigate the modulatory effect of stress on spatial ("cognitive") and stimulus-response ("habit") learning and memory. On the basis of this pilot study, it might be speculated that a prevalence of stimulus-response learning and memory might be found in both stress and non-stress groups and that there is rather a relative difference in the learning strategies used between the groups.

A first study that investigates the impact of stress on multiple memory systems in humans with the help of the paradigm tested here will be described in the next chapter.

5 Study I: The Modulatory Effect of Stress on the Use of Spatial and Stimulus-response Learning Strategies[3]

5.1 Research question and hypotheses

Memory consists of multiple anatomically and functionally distinct systems (Eichenbaum and Cohen 2001, Gabrieli 1998, Squire 1994, White and McDonald 2002). Evidence supporting this view comes from animal studies using brain lesion (Kesner et al. 1993, McDonald and White 1994, Packard and McGaugh 1992, Packard and Teather 1998, Packard et al. 1989, Teng et al. 2000) or stimulation techniques (Packard et al. 1994, Packard 1999) as well as from human studies investigating brain damaged patients (Bechara et al. 1995, Haist et al. 1991, Knowlton et al. 1996) or employing functional neuroimaging (Bohbot et al. 2004, Iaria et al. 2003). Two systems received special attention in the multiple memory systems literature: one based on the hippocampus and adjacent cortices and one depending on the basal ganglia, specifically the dorsal striatum (see chapter 1).

Mishkin and Petri (1984) suggested that the dorsal striatum mediates a "less cognitive, more rigid" form of memory termed "stimulus response" or "habit" learning (for reviews of the cognitive dorsal striatum functions see Packard and Knowlton 2002, White 1997). Since O'Keefe and Nadel's (1978) "cognitive map" theory the hippocampus has often been associated with spatial memory (Burgess et al. 2002, Maguire et al. 1998, Nadel 1991, Rosenzweig et al. 2003).

A recent study by Kim, Lee, Han and Packard (2001) suggested that stress is a critical factor modulating the use of the two memory systems thought to work in parallel (White and McDonald 2002). Rats received tail shocks 30 minutes before training in a Morris water maze to find a submerged platform, which location was marked by a pole. One day later a retention test was given in which platform and pole where moved to a novel location. Swimming to the location where the platform had been during training was interpreted as a hippocampus-based spatial strategy. Swimming to the pole in the new location was seen as a dorsal striatum-based stimulus response strategy. Kim et al. (2001) observed that all non-shocked rats used a spatial strategy in the retention test, whereas half of the stressed rats employed a stimulus-response strategy. Similarly, Packard and Wingard (2004) found that injections of anxiogenic drugs

[3] This study was published in *Learning and Memory* (2007), 14: 109-116. Authors: L. Schwabe, M.S. Oitzl, C. Philippsen, S. Richter, A. Bohringer, W.Wippich, H. Schachinger.

into the amygdala or periphery modulated the use of memory systems in a way that favors caudate-based stimulus response learning over hippocampus-based spatial learning. Thus, being either stressed or extremely anxious prior to learning affects the use of multiple memory systems. Interestingly, in both studies the modulatory effect of the emotional state on memory systems was concluded from rat's performance in the retention test 24 hrs later (see chapter 3). It is likely that stress and anxiety affected the strategy to acquire the task as well as memory consolidation.

The present study was designed to prove in humans that stress modulates the use of multiple memory systems. As described in the previous chapter, we specifically developed a task that allows differentiating spatial from stimulus-response learning strategies. The task shares its central characteristics with the well known spatial learning task for animals, the Morris water maze.

We hypothesized that previous stress will result in the use of dorsal striatum-dependent "habit" at the expense of hippocampus-dependent "cognitive" learning strategies. Stress was realized by the well-known psychosocial stress test, the Trier Social Stress Test. Autonomic (heart rate) and endocrine (cortisol) measurements verified the efficiency of the stress procedure. The used learning strategy was derived from the actual performance of the participants as well as their verbal report at the end of the training session.

5.2 Materials and methods

5.2.1 Subjects

Eighty-eight (62 females, 26 males) students of the University of Trier in the age of 19-35 years (mean = 23,2 years; SD = 3,14) agreed to participate in the investigation. All participants were medication free and none of the subjects has shown evidence of drug abuse. They had to refrain from smoking, drinking caffeine or having severe physical exercise on the test day. Participants received a monetary incentive on completion of the experiment. Written informed consent was obtained from all subjects.

5.2.2 Experimental design

Subjects were pseudo-randomly assigned to the control (31 females, 13 males) and the experimental condition, whereupon sexes were counterbalanced (n = 31 females and n = 13 males per group). The two groups differed only with respect to the stress manipulation; memory testing was exactly the same within the two groups.

The sequence of events is shown in figure 5.1. All the testing (TSST/control task and learning task) was performed in the afternoon between 2 pm and 6 pm.

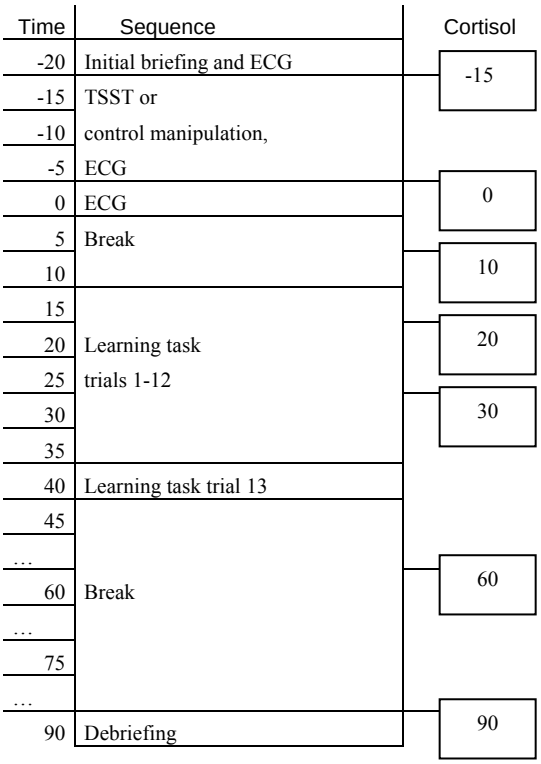


Figure 5.1: *Sequence of events in the experiment.*

5.2.3 Psychosocial stress

To induce psychosocial stress the Trier Social Stress Test (TSST) was used. In the TSST subjects have to deliver a free speech and perform mental arithmetic in front of an audience (Kirschbaum et al. 1993, Kirschbaum and Hellhammer 1994).

As has been shown, this protocol leads to significant sympathetic activation (e.g. Schommer et al. 2003). Subjects were introduced to the task and had 3 minutes to prepare a presentation in which they were to promote their candidacy for a job that was tailored to their interests and qualifications. The audience consisted of a man and a woman. To increase task engagement, subjects were told, that for later analyses their talk would be tape- and video-recorded. After the 5 minutes of job presentation, subjects had to subtract 17 serially from 2023. They were asked to do this as accurately and as fast as possible. Whenever they made a mistake, subjects had to stop and begin again from 2023. The mental arithmetic task took 5 minutes. Participants were not told how long the TSST and its single elements would take.

Subjects in the control group stood 3 minutes quietly in the room, read then a standardized text for 5 minutes and read afterwards, again for 5 minutes, a standardized list of four digit numbers. No audience was present and no video recordings were taken.

To verify the efficiency of the stress manipulation beat-to-beat heart rate data were recorded for 5 minutes immediately before the TSST/control manipulation (pre-stress), for the 13 minutes of the TSST/control manipulation and during the 5 minutes immediately after the TSST/control manipulation (post-stress). Moreover saliva cortisol samples were collected immediately before the stress manipulation (baseline) as well as 1, 10, 20, 30, 60 and 90 minutes after the end of the TSST/control manipulation.

5.2.4 Spatial learning task ("card task")

The card task has been applied as described in chapter 4.2.1 (see figures 4.3 a-e). The only difference to the task as used in preliminary study I was that the position of the plant has not been varied between individuals during training.

5.2.5 Cardiovascular analyses

Heart rate was derived from a single standard lead II ECG configuration employing telemetric HP 78100A transmitter and HP 78101A receiver system (Hewlett Packard Corp.). ECG was sampled by 1 kHz with 12bit resolution. Beat detection was performed offline by WinCPRS (Absolute Aliens Oy, Turku, Finland) as was artifact control. The following parameters, which have been used successfully in stress research (e.g. Buchholz et al. 2003), were derived: mean heart rate and the root mean square successive differences of the interbeat interval ($RMSSD_{ibi}$). The latter being a sensitive index of stress-induced vagal withdrawal.

5.2.6 Saliva sampling and biochemical analyses

Saliva samples were collected with a customary straw directly into standard Eppendorf tubes (1,5ml, Eppendorf, Hamburg; Germany), stored at room temperature until completion of the session, and then kept at -20°C until analysis. After thawing for biochemical analysis, the fraction of free cortisol in saliva (salivary cortisol) was determined using a time-resolved immunoassay with fluorometric detection, as described in detail elsewhere (Dressendorfer and Kirschbaum 1992).

5.2.7 Statistical analysis

Statistical analyses were done with the help of SPSS-Software (version 13.0; SPSS Inc., Chicago, Illinois). P-values smaller than 0.05 were considered significant. Due to technical failure some ECG data got lost: baseline ECG for three subjects of the stress and one of the control group; stress ECG and post-stress ECG for 3 and 2 subjects of the stress group, respectively. Furthermore, Cortisol data were missing for eight subjects of the stress group and eight subjects of the control group.

5.3 Results

5.3.1 Cardiovascular reactivity

As displayed in figure 5.2, heart rate was significantly enhanced in response to the Trier Social Stress Test (TSST) compared to controls ($t_{(79)} = 3.82$, $p < .001$, $d = 0.85$) , while groups did not differ in their pre-stress ($t_{(82)} = 0.27$, $p = .79$, $d = 0.06$) and post-stress ($t_{(80)} = 0.58$; $p = .57$, $d = 0.13$) heart rates (group × time interaction: $F(2,152) = 70.76$, $p < .0001$).

The root mean square successive differences of the interbeat interval ($RMSSD_{ibi}$) tended to be lower in stressed subjects than in controls ($t_{(79)} = 1.90$; $p = .06$, $d = 0.43$). Moreover, all participants of the stress group (n = 44) reported during debriefing that they felt stressed during the TSST, while none of the controls (n = 44) described the control manipulation as stressful.

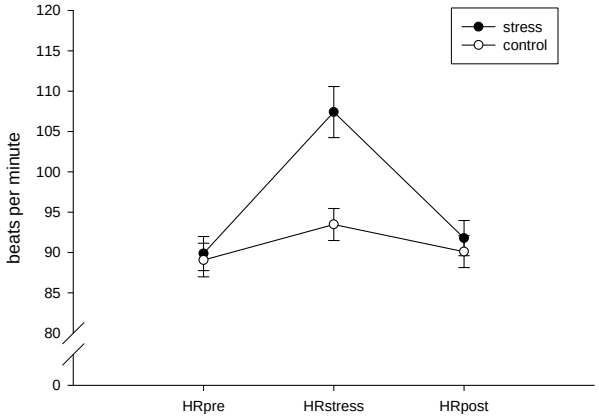


Figure 5.2: *Heart rates of stressed and control subjects before (HRpre), during (HRstress) and after (HRpost) the experimental manipulation. Bars represent means ± SEM.*

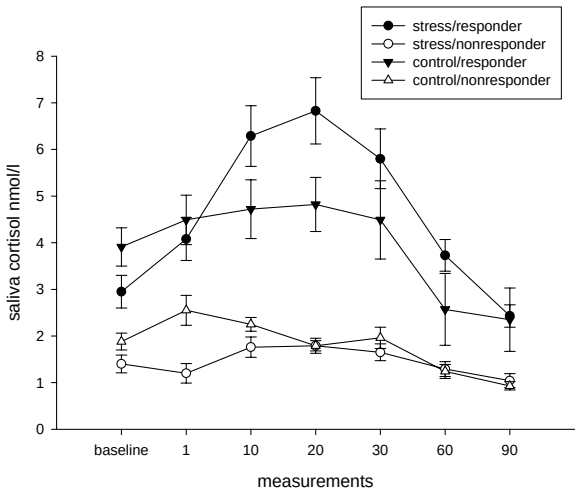


Figure 5.3: *Cortisol responses to the experimental manipulation. Bars represent means ± SEM.*

5.3.2 Cortisol reactivity

Depending on whether they showed a cortisol level of at least 3 nmol/l or not 20 minutes after the end of the stress manipulation participants were classified as cortisol responder and cortisol non-responder, respectively. Stress and control groups differed significantly with respect to the number of cortisol responders and cortisol non-responders ($\chi^2(1) = 11.54$, $p < .001$, $C = 0.35$). While 26 out of 36 subjects in the stress group showed a cortisol response, only 7 out of 36 subjects of the control group were classified as cortisol responder. As displayed in figure 5.3 only the cortisol responder in the stress group show an increase in the cortisol level in response to the stress manipulation. Cortisol responders in the control group, however, show only a very small increase in the cortisol level, but had a rather high cortisol level at the beginning of the experiment.

Cortisol responder and cortisol non-responder in the stress group did not differ with respect to heart rate (Mann-Whitney U = 159.5, p = .70) and RMSSDibi (Mann-Whitney U = 146.0, p = .44). The same was true in the control group (heart rate: Mann-Whitney U = 130.00, p = .87; RMSSDibi: Mann-Whitney U = 122,5, p = .67).

5.3.3 Performance in the learning task and verbal data

The strategies used by the stressed and control subjects in the test trial (trial 13) are shown in figure 5.4. A χ^2-test computed on the strategies of the stressed and control subjects that had learned the position of the "win-card" revealed a significant effect of experimental condition on the used learning strategy ($\chi^2(1) = 8.66$, $p < .03$, $C = 0.32$). In the stress group, 5

subjects employed a spatial and 34 a stimulus-response strategy, while in the control group 15 participants used a spatial and 23 a stimulus-response strategy.

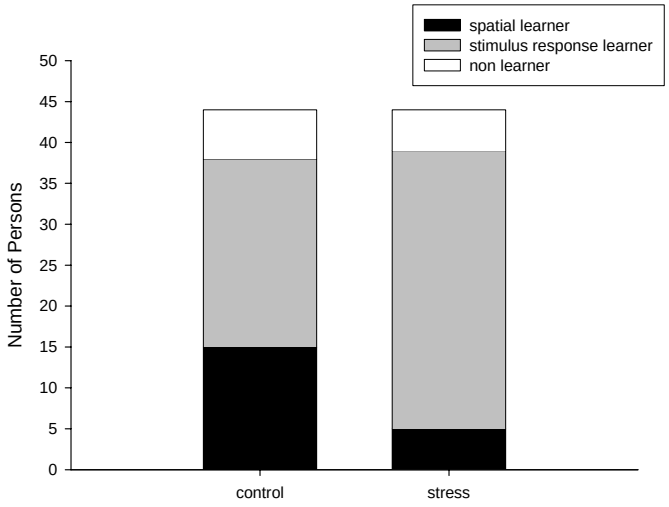
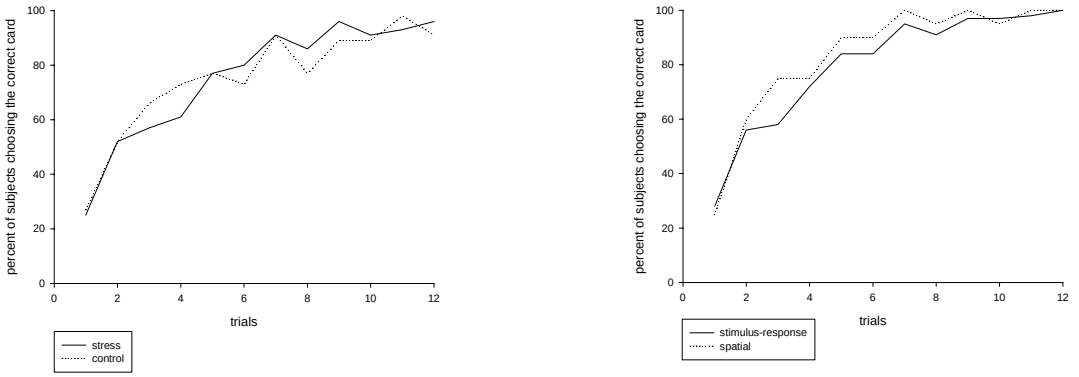


Figure 5.4: *Number of stressed and control subjects classified as spatial learners, stimulus response and non-learners.*

The number of participants that did not acquire the position of the "win-card" ("non-learners") was similar in the stress (n = 5) and the control (n = 6) groups ($\chi^2_{(1)} = 0.10$, p = .75, C = .03).

Stress and control group had a comparable learning speed ($t_{(75)} = 0.35$, p = .73, d = 0.08). The learning gradient was also similar in the two groups as indicated by a Kaplan-Meier survival analysis (Log rank $\chi^2(1) = 0.09$, p = .76). The learning curves of the stress and control groups are displayed in figure 5.5a. Likewise, spatial and stimulus-response learners showed a comparable learning speed ($t_{(75)} = 0.56$, p = .58, d = .16) and did not differ in their learning gradient (Kaplan-Meier: Log rank $\chi^2(1) = 1.04$, p = .31). The learning curves of spatial and stimulus-response learners are presented in figure 5.5b.

Spatial and stimulus-response learners differed significantly with respect to the possible strategies mentioned ($\chi^2(3) = 47.75$, p < .001, C = 0.62). All spatial learners reported the use of a spatial strategy and 17 out of 20 (85%) spatial learners were also aware of the card besides the plant as a possible option. All 57 stimulus-response learners reported the use of the stimulus-response strategy, however only 9 of them (16%) were also aware of the spatial option.



(a) (b)

Figure 5.5: *Percentage of subjects choosing the correct card plotted against the number of trials: (a) stressed subjects versus control subjects; (b) spatial versus stimulus-response learners.*

Stressed subjects who used a stimulus-response strategy (mean ± SD: 67.3 ± 4.0), stressed subjects who used a spatial strategy (mean ± SD: 76.0 ± 13.4), control subjects who employed a stimulus-response strategy (mean ± SD: 63.9 ± 5.2) and control subjects who used a spatial strategy (mean ± SD: 61.5 ± 5.6) did not differ in their certainty (Kruskal-Wallis $\chi^2(3) = 2.09$, $p = .55$).

The employed learning strategy was neither correlated with heart rate (Spearman $r = 0.06$, $p = .62$) nor with $RMSSD_{ibi}$ (Spearman $r = 0.01$, $p = .92$) when the experimental condition was partialed out. There was also no significant correlation between heart rate and learning speed (Pearson $r = 0.06$, $p = .60$), certainty (Pearson $r = 0.02$, $p = .86$) or the number of possible strategies mentioned (Pearson $r = 0.11$, $p = .35$). Similarly, the $RMSSD_{ibi}$ was neither correlated with learning speed (Pearson $r = 0.14$, $p = .24$) nor with certainty (Pearson $r = 0.16$, $p = .19$) nor with the number of possible strategies mentioned (Pearson $r = 0.06$, $p = .60$).

Independent of the experimental condition, there was no significant correlation between salivary cortisol 20 minutes after the end of the TSST and control manipulation and the used learning strategy ($r = 0.12$; $p = .30$). However, as shown in table 5.1 the mean salivary cortisol levels 20 and 30 minutes after the end of the TSST, i.e. during the learning task, tended to be higher in stimulus-response than in spatial learners - both in the stress (Cortisol +20: $U = 38.5$; $p < .05$; Cortisol +30: $U = 41.0$; $p < .06$) and the control group (Cortisol +20. $U = 73.0$; $p = .12$; Cortisol +30: $U = 77.5$; $p = .17$).

Cortisol levels 20 minutes after the stress manipulation did not correlate significantly with learning speed (Pearson $r = 0.10$, $p = .44$), certainty (Pearson $r = 0.03$, $p = .81$) or the number of possible strategies mentioned (Pearson $r = 0.18$, $p = .16$).

There was no effect of sex on the used strategy ($\chi^2_{(1)} = 1.15$, $p = .29$, $C = 0.12$). Furthermore, performance in trial 13 was independent of the side from which subjects looked into the room; in the stress ($\chi^2_{(6)} = 1.75$, $p = .94$, $C = 0.20$) as well as in the control condition ($\chi^2_{(9)} = 12.83$, $p = .17$, $C = 0.48$).

Table 5.1: *Saliva cortisol in nmol/l during the learning task, i.e. 20 min (cortisol 20) and 30 min (cortisol 30) after the TSST or control manipulation. N denotes the number of participants of the stress and control groups using the spatial or stimulus-response strategy with cortisol data at all time points. There is a trend that stimulus-response learners have a higher level of cortisol than spatial learners.*

	stress		control	
	spatial (n = 5)	stimulus-response (n = 30)	spatial (n = 11)	stimulus-response (n = 18)
Cortisol 20	3.0 ± 1.1	5.6 ± 0.7	1.9 ± 0.3	2.4 ± 0.4
Cortisol 30	2.6 ± 1.0	4.8 ± 0.6	1.8 ± 0.2	2.8 ± 0.5

*Data represent means ± SEM. $p < 0.05$ * between stress and control groups, # between spatial and stimulus-response learners in the stress group.*

5.4 Discussion

The study by Kim and colleagues (2001) provided evidence that stress enhances dorsal striatum-dependent "habit" memory at the expense of hippocampus-dependent "cognitive" memory in rats. Our study provides the first evidence that similar processes are present in humans. While Kim et al. (2001) could not differentiate learning strategies from memory consolidation, we demonstrate that stress clearly affects the use of learning strategies.

Stress responses include a variety of physiological changes. Previous studies have demonstrated a co-occurrence of endocrine and autonomic responses (Schommer et al. 2003). We observed significant increases in heart rate and decreases in the root mean square successive difference of the interbeat interval ($RMSSD_{ibi}$) in subjects exposed to the TSST, indicative for a strong activation of the autonomic nervous system towards a more dominant sympathetic than parasympathetic control. Moreover, the majority of the participants of the stress group showed an increase in the cortisol level, while most of the control subjects did not. Indeed, the TSST successfully activated the stress system.

Several studies presented evidence for an effect of cortisol and/or autonomic arousal on learning and memory (Buchanan et al. 2006, Cahill and Alkire 2003, Cahill et al. 1994). One strategy to separate these endocrine and sympathetic effects in the present study would

be to compare cortisol responder and cortisol non-responder in the stress and control groups regarding the used learning strategy as responder and non-responder in the two groups did not differ in respect to the considered autonomic parameters (see Buchanan et al. 2006). If an association of cortisol response to the stress manipulation and learning strategy could be found, this would indicate that the used learning strategy is primarily modulated by the glucocorticoid response. However, as the number of subjects is too small in some cells (e.g. there are only 2 spatial learners in the stress group, who were classified as cortisol responder), this strategy is unfortunately not applicable here. An analyses of the cortisol level 20 minutes after the stress manipulation independent of the experimental condition revealed no significant effect of cortisol response on the employed learning strategy. This was also true for heart rate and $RMSSD_{ibi}$.

Dorsal striatum-based and hippocampus-based memory systems have been shown to process information in parallel and simultaneously (White and McDonald 2002). While the relationship between the two memory systems is cooperative in some cases (McIntyre et al. 2003a, Voermans et al. 2004), they compete in others (Matthews and Best 1995, Poldrack et al. 2001, Schroeder et al. 2002). This raises the question how one system comes to dominate behavior, if both systems are intact. It has been shown that the characteristics of the particular task (McDonald and White 1993, White and McDonald 2002) as well as the frequency of task performance (Chang and Gold 2003, Packard 1999) are decisive for the relative importance of learning and memory systems. In line with the results of Kim et al. (2001), the findings of the present study indicate that stress is a further important factor modulating the use of multiple memory systems.

To test and differentiate learning strategies we had designed a navigation task that allows spatial learning as well as more simple stimulus-associated learning. It might be argued that the present paradigm distinguishes not between spatial and stimulus-response learning and memory, but between distal and proximal cue guided learning and memory. The correct card could be identified by a proximal cue (plant). We considered this as being indicative of stimulus-response learning. However, we argue that choosing the card in response to the position of the “distal” cues has to be interpreted as spatial learning. Due to the construction of the room model a simple association of one cue on a wall and one card is not possible. The table is placed exactly in the center of the room and the four cards are placed exactly in the center of the four (imagined) quadrants of the table. Furthermore, the items on the wall are also placed exactly in the center of the walls. Therefore, it is not possible to get the position of the card with the help of *one* of the cues on the walls. Subjects that learn

the position of the "win-card" have to take the relation of at least two cues into account. It has to be emphasized that hippocampal learning and memory functions are not limited to spatial memory (Cohen and Eichenbaum 1991, Eichenbaum 1996, Squire 1994): spatial content is only one particular kind of relational information processed by the hippocampus. Our task shares central characteristics with the Morris water maze, the main spatial navigation task used to test hippocampal functions in rodents. Similarities of the tasks refer to the fixed location of the goal in relation to cues in the environment and varying start positions. In contrast, the strong aversive and life threatening feature (drowning) that motivates the performance of rats is absent. Our task might even be considered as slightly appetitive due to the small monetary reward, while the expectation of good performance might be experienced as social pressure. Advantages of the new test are its feasibility and its relatively high ecological validity. An additional application of the task, namely estimating the stability of the applied strategy, i.e. the memory for the strategy, is under current investigation.

Stimulus-response learning was expressed by 77 percent of the stressed and 52 percent of the control subjects, leaving 11 percent spatial learning in the stressed and 35 percent in controls. Kim and colleagues (2001) report, that half of their stressed and all control rats displayed a spatial response in the memory test. The difference in absolute values is most likely a reflection of test characteristics as described above. Interestingly, other aspects of the learning process like efficacy and speed were not affected by prior stress (Kim et al. 2001). We corroborate these findings as in our study, the number of "non-learners" and the number of trials to the defined learning criterion, i.e. learning speed, were comparable between the non-stressed and stressed groups. Concluding the comparison of the rat and human studies, we suggest that stress enhances the so-called dorsal striatum-dependent "habit" learning at the expense of a flexible, elaborated, "cognitive" way of learning based on medial temporal lobe structures.

Stressed subjects more likely employ less complex stimulus-response learning strategies. We consider this an adaptive mechanism. In stressful, maybe life threatening situations attention has to be diverted and fast reactions are required. Hesitation, delays, might endanger the organism. As our data show, stimulus-response learning needed as many trials as spatial learning. Thus, learning speed per se is not affected. Since stimulus-response memories (habits) do not need an explicit cognitive reflection it is reasonable to assume that they are faster accessible than "cognitive" (e.g. spatial) memories. In other words: stimulus-response learning will allow faster responses in comparable situations. Moreover, while spatial learning leads to the cognitive representation of relations between multiple cues,

stimulus-response learning focuses on single cues only. Hence, it might be argued that stimulus-response learning is cognitively less demanding than spatial learning, leaving more cognitive capacities for coping with the current stress situation. Our finding that stimulus-response learners named the card beside the plant as the only option while spatial learners mentioned both the spatial and the stimulus-response option suggests that stimulus-response learning is also more rigid than spatial learning. This rigidity might be adaptive since it reduces ambiguity and distraction. According to this view one would expect that stimulus-response learners are more certain that they chose the correct card than spatial learners. However, we found no difference between stimulus-response and spatial learners with respect to their reported certainty.

Although we consider stress-related stimulus-response learning as generally adaptive, we are aware of the fact that the reduction of more complex processing of the context has its pitfalls. The lack of cognitive reflection inherent to stimulus-response learning and memory is paralleled by a relative insensitivity to situational changes that require a change in behavior. This idea is in line with the concept of "bounded rationality" (Gigerenzer and Goldstein 1996, Simon 1982) postulating that subjects often use heuristics, i.e. relatively simple rules, which lead to cognitive relief and correct decisions in many situations, -but not in all.

As has been suggested by the exit interview, both spatial and stimulus-response learners were able to memorize the strategies they used in an explicit fashion. This might be seen as an argument against the assumption that the two strategies reflect the use of distinct learning and memory systems. It could be argued that if subjects who choose the card besides the plant are aware of their learning strategy, they can not be classified as stimulus-response learners. In our view, however, making the choice on the basis of the plant is an example of stimulus-response learning irrespective of whether subjects are able to report the used strategy or not. Indeed, there is evidence that caudate-based memory might involve explicit processes. Voermans and colleagues (2004), for instance, demonstrated that the explicit learning of a stimulus-response association led to significant activity of the right caudate nucleus. (Sprengelmeyer et al. 1998) indicated that impairments in declarative memory are associated with the severity of the damage to the caudate loop. Furthermore, Maddox and Ashby (2004) viewed the head of the caudate as part of an explicit category learning system. Thus, although both the stimulus-response and the spatial learners are open for declarative retrieval this does not preclude that the two strategies belong to different memory systems.

Basal and stress levels of cortisol vary across individuals. While the endocrine stress response of the majority of the TSST participants reached peak levels, others kept low cortisol

levels throughout the study (here: 10 out of 36), often called cortisol non-responders. Some participants of the control group (7 out of 36) had elevated cortisol levels throughout the study which might reflect a combination of an anticipatory elevated activity of the stress system and endocrine activation by social demands. In the stress group of the present study, two spatial learners were classified as cortisol responders, while three spatial learners had no cortisol response. Together with the data of spatial learners of the control group, spatial learning strategies are more likely in the face of low cortisol levels. The number of individuals, however, is too small to allow test-statistics related to spatial and stimulus-response strategies.

De Quervain, Roozendaal and McGaugh (1998) demonstrated that footshock stress prior to a retrieval test impairs spatial memory performance. This suggests that our results might also be affected by stress effects on retrieval processes. Further studies are needed to separate such effects from effects on learning strategy use.

There is a bulk of evidence showing that corticosteroids as a major stress correlate impair hippocampus-dependent declarative memory (for a review see Lupien and McEwen 1997), but not hippocampus-independent forms of memory (Kirschbaum et al. 1996, Lupien et al. 1994). This led Lupien and Lepage (2001) to conclude that stress hormones exert a specific and isolated effect on the hippocampus. In the same line, Nadel, Payne and Jacobs (2002) suggested that stress impairs primarily the ability of the hippocampus to bind stimuli together as belonging to a specific context. Under stress “one loses the ability to use critical distinguishing information” (Nadel et al. 2002, p. S8).

Thus, our finding that stressed people employed more often stimulus-response (habit) learning compared with non-stressed controls seems to reflect reduced hippocampal functioning in the presence of stress. As argued above, this is not solely detrimental, but might have some adaptive value.

6 Study II: Modulation of Spatial and Stimulus-response Learning by Exogenous Cortisol

6.1 Research question and hypotheses

Glucocorticoid effects on memory are manifold. While glucocorticoids administered within a certain time window after learning enhance memory performance (Roozendaal 2002, Roozendaal et al. 2006), the administration of glucocorticoids prior to recall impairs memory retrieval (De Quervain et al. 1998, Lupien et al. 2002). Studies which administered glucocorticoids prior to learning show inconsistent findings; both facilitating and impairing effects are reported (Abercrombie et al. 2003, Kirschbaum et al. 1996), for a meta-analysis see Het, Ramlow and Wolf 2005).

In line with earlier animal studies (Kim et al. 2001, Packard and Wingard 2004), we showed recently in humans that stress affects not only memory performance per se but also the way a task is learned (Schwabe et al. 2007, see chapter 5). Memory consists of multiple systems, specialized modules that process particular kinds of information, perform particular operations and are based on a particular neural structure or a network of neural structures (e.g. (Kim and Baxter 2001a, Squire 2004). Two of these modules have been in the spotlight of the multiple memory system literature: a hippocampus dependent “cognitive” memory which has been associated with spatial learning and memory and a caudate nucleus-dependent “habit” memory that was related to stimulus-response learning and memory (Packard and McGaugh 1992, White and McDonald 2002).

We found that subjects who were exposed to a psychosocial stressor (Trier Social Stress Test) prior to training in a learning task that could be solved by spatial and stimulus-response strategies employed significantly more often a stimulus-response strategy in this task than non-stressed controls. Moreover, we suggested that the use of a stimulus-response strategy is more likely in the face of high Cortisol levels (Schwabe et al. 2007). However, since Cortisol levels in the stress group were confounded with autonomic activity and subjective arousal, it remained unclear whether an increase in Cortisol levels, independent of sympathetic and psychological arousal, is sufficient to modulate multiple memory systems in a manner that favours stimulus-response over spatial learning.

In humans and rodents, the effects of glucocorticoids on memory are dose dependent (Abercrombie et al. 2003, Lupien and McEwen 1997). Studies from both populations describe an inversed u-shaped relationship between corticosteroid levels and memory function, such that mild or moderate glucocorticoid levels enhance memory (Buchanan and Lovallo 2001, Lupien et al. 2002), while high levels impair it (Diamond et al. 1999). Comparing the findings of the study by Kim and colleagues (2001) with our results suggests that stress (hormones) might modulate multiple memory systems in a dose-dependent manner as well. While Kim et al. (2001) employed an extremely stressful tailshock paradigm we used a moderate psychosocial stressor consisting mainly of public speech and mental arithmetic. Indeed, Kim et al. (2001) reported an increase in the number of animals that used a stimulus-response strategy from none in the control to 50 percent in the stress group, whereas we observed a 48 percent increase in the use of stimulus-response learning in stressed compared to control subjects.

Consequently, the present study aimed primarily to determine (i) whether an increase in cortisol levels is sufficient to modulate spatial and stimulus-response learning when autonomic activity and psychological arousal are controlled, and (ii) whether a possible modulatory effect of glucocorticoids on multiple memory systems is dose-dependent.

Young females were administered a placebo or Hydrocortison in a moderate (5mg) or high (30mg) dose 60 minutes before training in a recently developed, non-arousing learning and memory task that can be acquired via spatial and stimulus-response strategies (Schwabe et al. 2007). The applied learning strategy was derived from the participants' performance in a test trial and their verbal report. We hypothesized that cortisol will increase the use of a stimulus-response strategy. Saliva Cortisol samples and heart rate measurements were taken at baseline, immediately before and after behavioural testing. Subjective arousal was measured with the help of a multidimensional mood questionnaire at baseline and prior to the learning task. To identify possible effects of the pre training treatment on memory consolidation participants were given a one-trial retention test 24 hours after training.

6.2 Materials and methods

6.2.1 Participants

Eighty-four healthy females, recruited from the University of Trier, were paid for participation in this study (mean age: 22.8 years; SD = 2.7 years). Participation was limited to

non-smoking, oral contraceptives using women with a body mass index (BMI) between 20 and 25 kg/m² and no reported history of psychiatric disorders or drug abuse.

Participants had to refrain from smoking, physical exercise, large meals, coffee and alcohol for at least 2 hours before the start of the experiment, because of the known impact of these variables on the HPA axis. All participants provided written informed consent in accordance with procedures approved by the local ethics committee.

6.2.2 Experimental design

A double-blind, placebo-controlled, between-subject design was used. Participants were randomly assigned to one of three treatments: placebo, 5mg Hydrocortisone or 30mg Hydrocortisone. The time line of the experiment is shown in figure 1.

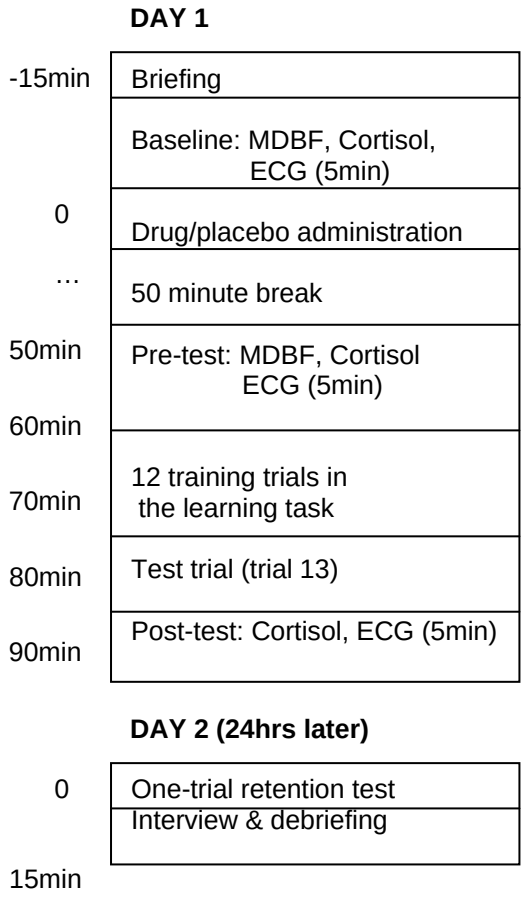


Figure 6.1: *Time line of the experiment.*

6.2.3 Drug administration

Participants received either three pills containing 30mg or three pills containing 5mg Hydrocortison or 3 similar looking placebo pills. The current doses (5 or 30mg) were chosen

to be similar to previous studies reporting mild or severe effects of glucocorticoids on memory (Beckwith et al. 1986, Kuhlmann et al. 2005). Drugs were administered 60 minutes prior to the beginning of the learning task. During the break between the drug administration and the start of the behavioural testing, the participants remained quietly reading in a room adjacent to the testing room.

6.2.4 Learning task

The used apparatus and the procedure of the learning task were same as described in chapter 4.2 (see figures 4.3 a-e). The only difference to the task as used in pilot study I was that the position of the plant had not been varied between individuals during training. Moreover, subjects were presented one retention test trial that was exactly the same as the test trial 24 hrs after training (plant in the same position).

6.2.5 Assessment of psychological arousal

Changes in the psychological arousal of the participants were assessed with the help of the MDBF, a German multidimensional mood scale (Steyer et al. 1994). This questionnaire measures three dimensions of subjective feeling ("elevated vs. depressed mood", "wakefulness vs. sleepiness", "calmness vs. restlessness") on a 5-point rating scale ranging from "not at all" (= 1) to "very much" (= 5). The MDBF was filled out at baseline and about 5 minutes prior to behavioural testing to monitor possible cortisol effects on subjective arousal.

6.2.6 Verbal report

After participants had made the choice for location of the "win-card" on day 2, but before receiving feedback, they were asked (i) to describe the used strategy, (ii) if there might be a reasonable alternative and (iii) to estimate the certainty of the decision on a scale from 0 to 100, where 0 stands for "absolutely uncertain" and 100 for "absolutely certain".

6.2.7 Cardiovascular analyses

Heart rate was derived from a single standard lead II ECG configuration employing telemetric HP 78100A transmitter and HP 78101A receiver system (Hewlett Packard Corp.). ECG was sampled by 1 kHz with 12bit resolution. Beat detection was performed offline by WinCPRS (Absolute Aliens Oy, Turku, Finland) as was artifact control. The following parameters, which have been used successfully in stress research (Buchholz et al. 2003), were

used: mean heart rate and the root mean square successive differences of the interbeat interval ($RMSSD_{ibi}$), the latter being a sensitive index of stress-induced vagal withdrawal.

Heart rate measurements were taken prior to drug administration (baseline), immediately before and after the learning task (pre and post test, respectively).

6.2.8 Collection of saliva and biochemical analyses

Saliva samples were taken with a customary straw, put directly into standard Eppendorf tubes (1,5ml, Eppendorf, Hamburg; Germany), stored at room temperature until completion of the session, and then kept at -20°C until analysis. After thawing for biochemical analysis, the fraction of free cortisol in saliva (salivary cortisol) was determined using a time-resolved immunoassay with fluorometric detection, as described in detail elsewhere (Dressendorfer and Kirschbaum 1992). Due to technical failure 17 baseline, 9 pre and 5 post cortisol values were missing.

6.2.9 Statistical analyses

Data were subjected to χ^2-test, mixed-design or univariate ANOVA, Kaplan-Meier survival analysis, t-test or its non-parametric equivalent the Mann-Whitney-U-test, as appropriate.

To analyze whether the cortisol treatment is predictive of the strategy used in the test trial on day 1 a stepwise regression analysis was computed with the applied strategy as dependent variable and age and body-mass-index (BMI) entered as a first step, heart rate and $RMSSD_{ibi}$ at baseline and pre-test as well as the change in the MDBF scales from baseline to pre-test in a second, and cortisol treatment in a third step.

Reported p-values are two-tailed. $P < .05$ was accepted as significance. All calculations were done with the statistics software SPSS (version 14.0; SPSS Inc.).

6.3 Results

6.3.1 Experimental manipulation

Saliva cortisol: As expected, a mixed design ANOVA with group as between and time as within-factor revealed significant group ($F_{(2,55)} = 194.33$, $p < .001$, partial $\eta^2 = 0.88$), time ($F_{(2,110)} = 85.52$, $p < .001$, partial $\eta^2 = 0.60$) and group × time interaction effects ($F_{(4,110)} = 61.07$, $p < .001$, partial $\eta^2 = 0.69$; see figure 6.2). Bonferroni-adjusted post-hoc tests indicated

that cortisol concentrations were lower in the placebo than in the 5mg Hydrocortison group which in turn had lower cortisol concentrations than the 30mg Hydrocortison group, both pre and post-test (all t-values > 3.35, all p's < .002). At baseline, however, there were no significant group differences ($F_{(2,64)} = 1.45$, $p = .24$, partial $\eta^2 = 0.04$).

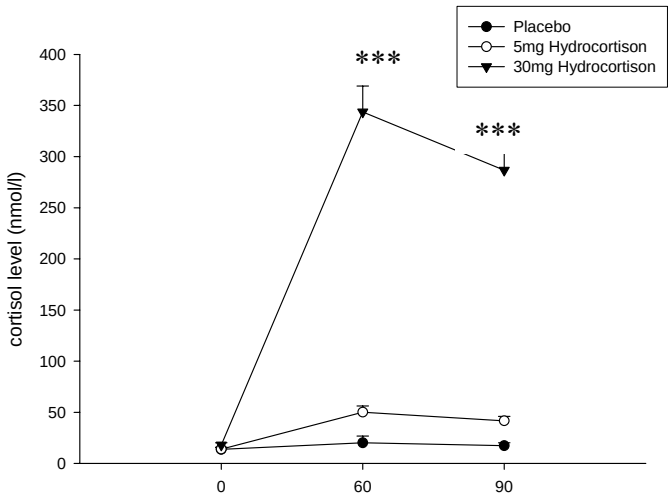


Figure 6.2: *Cortisol concentrations in the 3 groups at baseline, 60 and 90 minutes after drug intake; *** p<0.001.*

Cardiovascular data: Neither heart rate nor $RMSSD_{ibi}$ were affected by the experimental treatment (heart rate: group - $F_{(2,81)} = 0.85$, $p = .43$, partial $\eta^2 = 0.02$; time × group - $F_{(4,162)} = 0.85$, $p = .43$, partial $\eta^2 = 0.01$; $RMSSD_{ibi}$: group - $F_{(2,80)} = 0{,}62$, $p = .54$, partial $\eta^2 = 0.02$, time × group - $F_{(4,160)} = 0.54$, $p = .71$, partial $\eta^2 = 0.01$). Yet, there was a significant time effect for both parameters (heart rate: $F_{(2,162)} = 63.69$, $p < .001$, partial $\eta^2 = 0.44$; $RMSSD_{ibi}$: $F_{(2,160)} = 35.00$, $p < .001$, partial $\eta^2 = 0.30$) indicating lower heart rate and higher $RMSSD_{ibi}$ for pre-test compared to baseline and post-test (all t-values > 5.93, all p's < .001; table 6.1). This is most likely due to the one-hour waiting period between drug administration and the start of the card task.

Subjective arousal: Except a trend indicating higher wakefulness in subjects of the 5mg Hydrocortison group compared to the placebo and 30mg Hydrocortison group ($F_{(2,80)} = 2.72$, $p = .07$; 5mg vs. 30 mg: $t_{(54)} = 2.21$, $p = 0.03$; 5mg vs. placebo: $t_{(53)} = 1.66$, $p < .10$), there was no treatment effect on MDBF scales at baseline or the change in MDBF scales from baseline to pre-test (all F-values < 1.00, all p's > .39; data not shown).

In line with the reported cardiovascular data, higher sleepiness and calmness values were obtained at pre-test, i.e. after the one-hour waiting period, relative to baseline (sleepiness: $F_{(1,80)} = 20.26$, $p < .001$, partial $\eta^2 = 0.20$; calmness: $F_{(1,80)} = 5.20$, $p = .03$, partial $\eta^2 = 0.06$; elevated mood: $F_{(1,80)} = 0.03$, $p = .86$, partial $\eta^2 = 0.01$).

Table 6.1: *Heart rate and RMSSDibi data for the 3 treatments at baseline, pre and post test.*

	Baseline	Pre-test	Post-test
Heart rate (bpm)			
Placebo	76.09 ± 2.17	*68.29 ± 1.76*	73.12 ± 2.25
5mg Hydrocortison	75.25 ± 1.43	*68.72 ± 1.59*	73.55 ± 1.72
30mg Hydrocortison	73.01 ± 1.51	*66.27 ± 1.05*	70.81 ± 1.19
RMSSDibi (msec)			
Placebo	56.29 ± 9.85	**75.36 ± 11.80**	58.64 ± 8.37
5mg Hydrocortison	51.28 ± 5.42	**70.61 ± 8.40**	54.11 ± 5.54
30mg Hydrocortison	44.00 ± 2.89	**61.37 ± 4.67**	51.78 ± 4.28

Data represent means ± SEM. *italics* - significantly lower than at baseline and post-test; **bold** - significantly higher than at baseline and post-test.

6.3.2 Learning strategy and performance on day 1

Groups differed significantly regarding the strategy used in the test trial ($\chi^2(2) = 7.02$, $p < .03$, $C = 0.29$; figure 6.3). While 32 percent of the 30mg Hydrocortison group and 21 percent of the 5mg Hydrocortison group used a spatial strategy, only 4 percent of the placebo group employed the spatial learning strategy. This finding is opposite to the effect of psychosocial stress reported in the previous chapter. A stepwise multiple regression indicated that the cortisol treatment (placebo, 5mg, 30mg Hydrocortison) was the only significant predictor of the applied strategy ($\beta = 0.25$, $p < .04$; table 6.2).

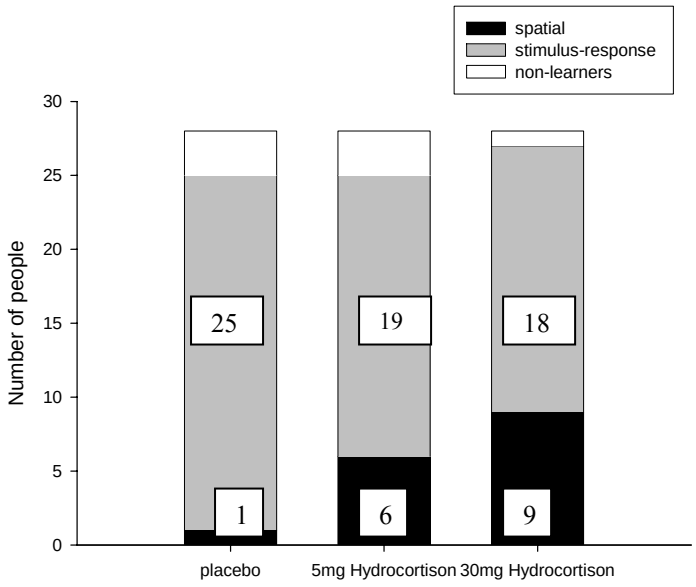


Figure 6.3: *Proportion of spatial, stimulus-response and non-learners in the three treatment groups (boxes show absolute numbers of spatial and stimulus-response learners, respectively).*

Table 6.2: *Stepwise multiple regression on the strategy applied in the test trial on day 1 as a function of age, body-mass-index, heart rate and root mean square successive difference of the interbeat interval at baseline and pre-test, changes in MDBF scales "restlessness vs. calmness", "elevated vs. depressive mood" and "wakefulness vs. sleepiness" from baseline to pre-test and the cortisol treatment (placebo, 5mg, 30 mg Hydrocortison).*

		non-standardized coefficients		standardized coefficients		
Model		B	standard error	Beta	t	p
1	(constant)	,612	,674		,908	,367
	age	,016	,018	,106	,892	,376
	BMI	-,036	,030	-,142	-1,188	,239
2	(constant)	-,985	,940		-1,048	,298
	age	,027	,019	,181	1,438	,155
	BMI	-,030	,031	-,118	-,941	,350
	HR baseline	,003	,012	,078	,301	,764
	HR pre	,014	,015	,252	,909	,367
	RMSSD baseline	-,002	,004	-,161	-,477	,635
	RMSSD pre	,002	,003	,197	,561	,577
	change RC	-,020	,014	-,199	-1,389	,169
	change EDM	,023	,024	,148	,963	,339
	change WS	-,004	,008	-,063	-,514	,609
3	(constant)	-,935	,915		-1,022	,311
	age	,031	,018	,208	1,689	,096
	BMI	-,043	,031	-,170	-1,366	,177
	HR baseline	,006	,011	,136	,539	,592
	HR pre	,011	,015	,200	,740	,462
	RMSSD baseline	-,001	,004	-,108	-,329	,743
	RMSSD pre	,001	,003	,165	,481	,632
	change RC	-,021	,014	-,206	-1,473	,146
	change EDM	,020	,023	,129	,859	,394
	change WS	-,006	,008	-,102	-,842	,403
	Cortisol treatment	,126	,059	,252	2,147	,036

BMI - body mass index; HR - heart rate; RMSSD - root mean square successive difference of the interbeat interval; RC - MDBF scale "restlessness vs. calmness"; EDM - MDBF scale "elevated vs. depressive mood"; WS - MDBF scale "wakefulness vs. sleepiness"

Groups were similar with respect to their learning curves (Kaplan Meier log Rank $\chi^2(2) = 2.02$, $p = .36$; figure 6.4a), learning speed, i.e. the number of trials needed to reach the learning criterion ($F(2,74) = 1.19$, $p = .31$, partial $\eta^2 = 0.02$), and the number of non-learners ($\chi^2(2) = 1.24$, $p = .54$, $C = 0.11$). There was also no difference between spatial and stimulus-response learners regarding their learning curves (Kaplan Meier log Rank $\chi^2(1) = 0.03$, $p = .88$; figure 6.4b) and learning speed ($t(76) = 0.66$, $p = .51$, $d = 0.17$).

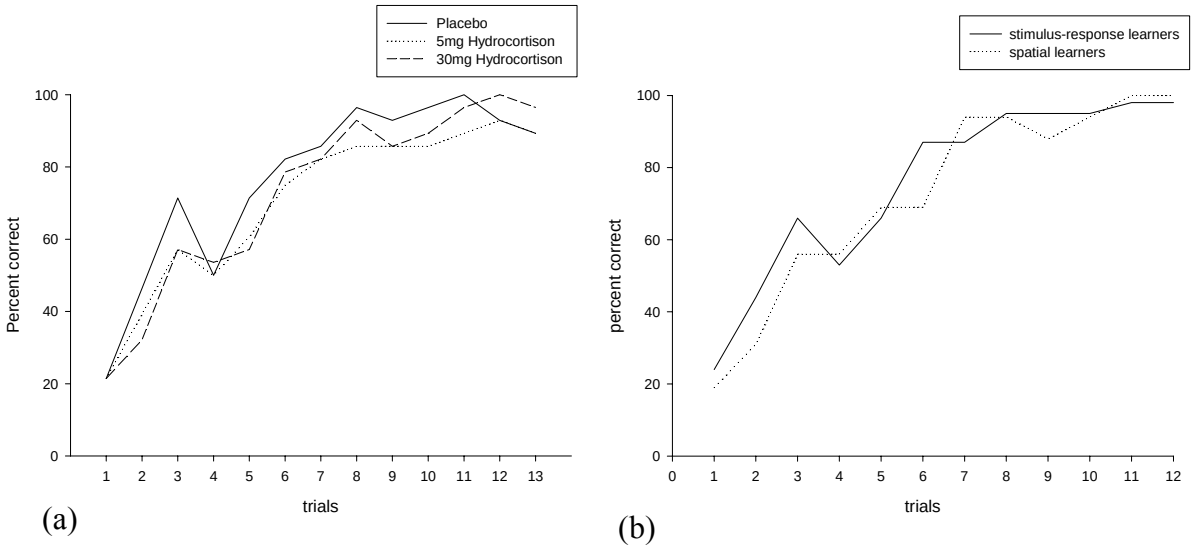


Figure 6.4: *Learning curves of (a) the three treatment groups and (b) spatial and stimulus-response learners.*

6.3.3 Retention test and verbal report on day 2

On the following day, the difference in the used strategy disappeared ($\chi^2(4) = 3.04$, $p = .55$, $C = 0.19$; Figure 6.5). Both groups chose mainly the card next to the plant (stimulus-response strategy). Groups were also similar in the number of participants that chose a different card on day 2 than in the test trial on day 1 (4 in each of the groups).

No strategy- or treatment-related differences in certainty were obtained (spatial vs. stimulus-response: $U = 365.50$, $p = .23$; placebo vs. 5mg vs. 30mg Hydrocortison: $F(2,81) = 0.44$, $p = .64$, partial $\eta^2 = 0.01$). However, reports of spatial and stimulus-response learners (irrespective of treatment) about the possible strategies differed significantly ($\chi^2(3) = 41.38$, $p < .001$, $C = 0.59$). All spatial and all stimulus-response learners were aware of the used spatial and stimulus-response strategy, respectively. However, while 69 percent of the spatial learners reported also the stimulus-response strategy, only 10 percent of the stimulus-response learners were also aware of the spatial strategy.

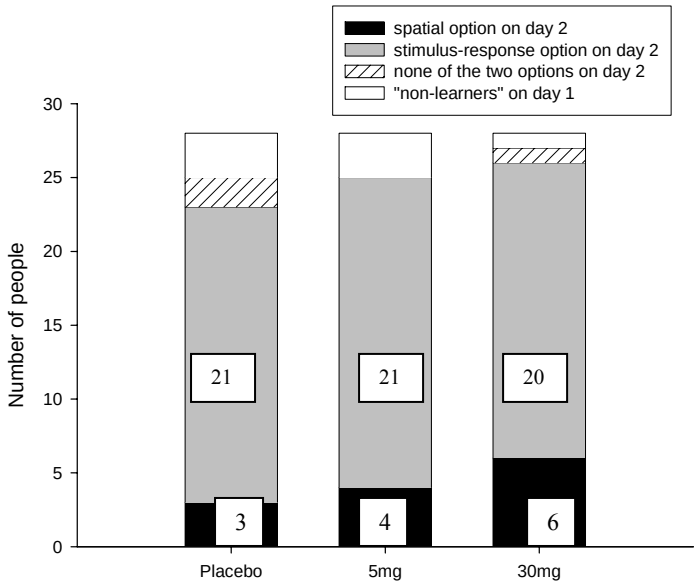


Figure 6.5: *Strategies applied by the three groups on day 2 (boxes show absolute numbers of spatial and stimulus-response learners, respectively).*

6.4 Discussion

Previous studies indicated that behavioural stress modulates multiple memory systems in a fashion that favours caudate-based "habit" over hippocampus-based "cognitive" learning and memory, both in rodents and man (Kim et al. 2001; see chapter 5). In chapter 5, it was reported that stimulus-response learners tended to have higher cortisol concentrations during the card-task compared to spatial learners suggesting a role of the adrenal corticosteroids in memory system modulation. Here, young healthy females were administered 5 or 30mg Hydrocortison or a placebo 60 minutes prior to the card task. Indeed, cortisol influenced the used learning strategy in a dose-dependent manner. However, this effect was opposite to the effect of psychosocial stress reported in chapter 5. Contrary to the hypothesis, the spatial strategy was most often employed by the 30mg group, while the stimulus-response strategy was most often used in the placebo group. Importantly, the effect of cortisol was independent of autonomic and subjective arousal. Explanations for the unexpected cortisol effect include CRF and ACTH, the observed autonomous arousal and the cortisol concentrations observed in this study.

Endocrine stress responses involve a cascade of CRF, ACTH and finally cortisol (see chapter 2.2). Exogenous cortisol administration increases cortisol only. CRF and ACTH are most likely even reduced by Hydrocortison, because of negative feedback of cortisol at the level of the hypothalamus and pituitary. CRF is the strongest activator of the HPA axis. Moreover, it is a neurotransmitter in limbic-autonomic connections. Besides its role in HPA

axis regulation it is amongst others involved in the regulation of reproduction, immune function and most important in cognitive function (Lehnert et al. 1999). Blank and colleagues (2002) characterized the action of CRF on hippocampal synaptic plasticity and found that CRF application facilitated LTP in the hippocampus. Using context- and tone-dependent fear conditioning Radulovic et al. (1999) showed that CRF acts also on memory consolidation. Corroborating these findings Contarino and colleagues (1999) observed spatial recognition memory impairments in mice lacking the CRF receptor 1. In the same line, Behan and colleagues (1995) reported evidence suggesting that CRF deficits contribute to cognitive impairment in Alzheimer's disease. Furthermore, Benno Roozendaal and colleagues (Roozendaal et al. 2002a) antagonized the CRF receptor in the basolateral amygdala and found 48-h retention performance in a inhibitory avoidance task to be impaired. These findings provide strong evidence for a role of CRF in cognition, in particular in memory processes. Similarly, cognitive functions have been ascribed to ACTH and ACTH-like neuropeptides. Pitsikas and colleagues (1990), for instance, showed that an ACTH analog (Org2766) improved the performance of fornix lesioned rats in the Morris maze. And Roman, Han and Baudry (1989) tested the effects of two ACTH analogs on various olfactory learning tasks and found that ACTH analogs facilitated learning performance. Thus, reduced CRF and ACTH might have contributed to the kind of memory system modulation obtained in the present study. However, most of the above cited studies do not preclude that the effects of CRF and ACTH are mediated by cortisol and corticosterone, respectively. Furthermore, most of these studies suggest a facilitating effect of CRF and ACTH on hippocampal memory. Hence, if the observed cortisol effect was due to CRF or ACTH, one would expect impaired hippocampal memory in the 5 and 30mg Hydrocortison groups since ACTH and CRF levels should be rather low in these groups. However, (hippocampus-dependent) spatial learning was most likely in the 30mg group. This could be explained by an even stronger effect on (nucleus caudate-dependent) stimulus-response learning. Though, whether CRF and ACTH have an impact on caudate-based learning and memory has not been shown yet.

An alternative explanation for the finding that spatial learning was more likely the higher the Hydrocortison dose was takes the autonomic arousal during task performance into account. It is well established that stress effects on memory consolidation require both glucocorticoid and noradrenergic activity, converging in the basolateral amygdala. Roozendaal (2002) suggested that this cooccurrence is not only important for stress effects on memory consolidation but also for the effects of pre-learning stress, i.e. stress effects on the acquisition of information, and pre-retrieval stress, i.e. stress effects on memory recall (see

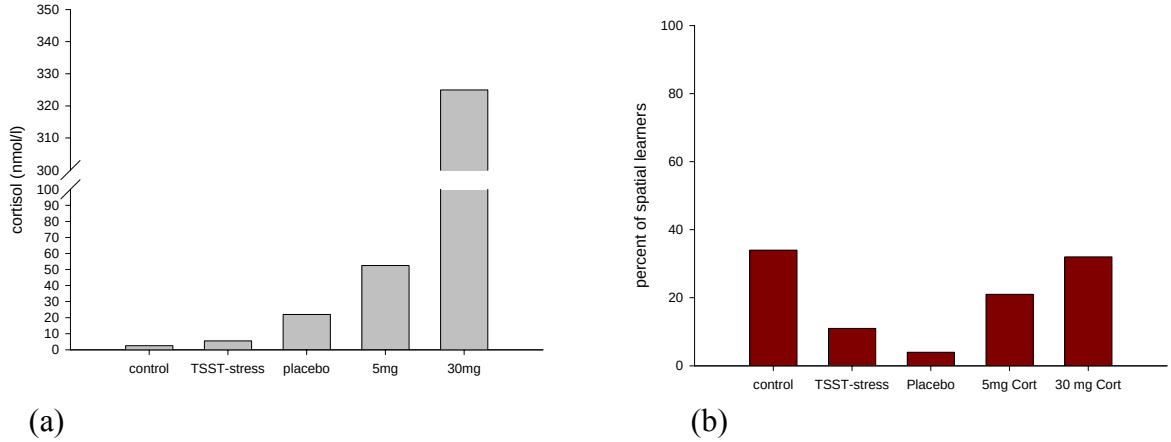
chapter 3.1). It could be argued that the stress-induced modulation of spatial and stimulus-response learning and memory requires both autonomic and glucocorticoid activity as well. As indicated by pre and post test heart rate measurements, the card task did not lead to significant autonomic arousal, at least not to an arousal level comparable to a stress situation such as the TSST (see chapter 5). While the lack of autonomic arousal during the card-task could explain the absence of the modulatory effect observed for psychosocial stress, it cannot account for the fact that the effect of exogenous cortisol is *opposite* to the effect of the TSST.

A third explanation for the finding that cortisol (Hydrocortison) administration modulated memory systems in favour of hippocampus-based spatial learning considers the cortisol concentrations observed here. Despite there were significant differences between the present and the previous study, most important the composition of the sample (30 percent males vs. females only) and the treatment (stress vs. exogenous cortisol administration), a comparison of the two studies is justifiable since the setting (time and place), the time line and the procedure of the card-task were the same in the two studies.

In general, the cortisol concentrations in the present study were significantly higher than those in response to the TSST. This was expected for the 5mg and 30mg Hydrocortison group. Yet, even the placebo group had higher cortisol concentrations than the TSST group. This was only partly due to higher baseline values; there was also an increase in the cortisol levels in the placebo group (from about 12 to 20 nmol/l), which was most likely because of the detailed information about possible adverse effects of cortisol and the uncertainty what would happen next. As displayed in figure 6.6, cortisol levels at the beginning of behavioural testing were lowest in the control group (TSST study) and highest in the 30mg Hydrocortison group. Interestingly, the number of spatial learners was highest in these two groups (about a third in both groups) and the lowest number of spatial learners was observed in the placebo group which was characterized by medium cortisol levels. Thus, the combined findings of the previous and the present study suggest an (inverse) u-shaped relationship between cortisol and learning strategy.

The assumption that spatial learning is most likely when glucocorticoid concentrations are rather low or high and least likely when glucocorticoid concentrations are medium is supported by a recent animal study (Schwabe et al., in prep.). Mice were either restraint stressed, left untreated, injected corticosterone or saline and afterwards tested in a circular hole board task that could be acquired via spatial and stimulus-response strategies. While all untreated mice (lowest corticosterone concentration) and 75 percent of the corticosterone injected mice (highest corticosterone concentration) used a spatial strategy, more than 40

percent of the saline injected mice (medium corticosterone concentration) used the stimulus-response strategy.



(a) (b)

Figure 6.6: (*a) Cortisol concentrations in the groups of the previous (control vs. TSST) and present study (placebo vs. 5mg vs. 30mg Hydrocortison) at the beginning of the card-task, (b) Percentage of spatial learners in the five groups.*

Does the idea of a u-shaped relationship between glucocorticoids and the use of a learning strategy conflict with the bulk of studies suggesting that high cortisol levels impair hippocampus-dependent learning and memory? In the view of the author of this work it does not. Most of the studies that investigated stress effects on (hippocampal) memory focused on quantitative parameters such as the number of words or slides remembered and reported impairments of a stress group *relative* to a control group (Buss et al. 2004, Kim et al. 2001, Kirschbaum et al. 1996, Newcomer et al. 1994, Payne et al. 2006, Tops et al. 2003). They did not show that hippocampus-dependent learning and memory is impossible after stress. Payne and colleagues (2006), for instance, found stressed subjects with a correct recall rate of about 60 percent impaired relative to a control group with a correct recall rate of about 75 percent. Moreover, the present work does not focus on quantitative but qualitative parameters, namely the use of a certain strategy. It does also not focus on stress effects on a single memory system. It aims to investigate the modulation of multiple memory systems by stress. Thus, the finding that spatial learning was more often used in the face of high cortisol levels than in the face of medium cortisol levels does not necessarily implicate that hippocampal learning was not impaired by high cortisol. It could also indicate that caudate-dependent learning was strongly affected by high glucocorticoid concentrations, changing the balance of powers in favour of the hippocampal system. Why should the two memory systems differ with respect to

their stress sensitivity? The answer to this question could lie in the distribution of GR and MR in the brain (see chapter 2.3). Brain areas differ with respect to the density of MRs, the receptors that mediate tonic glucocorticoid actions. While MRs are found in abundance in the hippocampus, there are no MRs in the neostriatum (de Kloet et al. 1999). GRs are widespread in the brain, but show an exceedingly high density in the hippocampus. Consequently, it could be argued that the hippocampal system is already affected by moderate corticosteroid levels, while the caudate nucleus is only affected in the face of high glucocorticoid concentrations. To test this hypothesis the stress effects on hippocampus- and caudate-based systems have to be studied separately. The present data allow of course no final conclusion about the relation between glucocorticoids and learning strategy, but suggest that it is most likely not linear.

In contrast to the previous study, this study tested also retention performance 24 hours after training. Although, groups did not differ regarding the number of subjects that chose another card on day 2 than on day 1, the group difference in the applied strategy observed on day 1 disappeared. This was due to the fact that 2 subjects of the placebo group switched to the spatial option, while at the same time 2 respectively 4 participants of the 5 and 30mg Hydrocortison group changed to the card next to the plant (stimulus-response option). Does this indicate that the effect of glucocorticoids on the modulation of the used learning strategy is transient? This is a tempting speculation as it would fit to the view that the modulatory effects of stress on learning strategies are primarily mediated via MRs (Schwabe et al. 2007). However, this argumentation conflicts with the findings of Kim et al. (2001) who reported a clear effect of stress on the applied strategy 24 hours after training. Moreover, the present study suffers regarding the interpretation of the results on day 2 from the same problem as the Kim et al. study: Glucocorticoid levels were high both during and after the learning task. Consequently, effects on acquisition and consolidation can not be disentangled.

In line with previous studies showing an effect of behavioural stress on the use of hippocampus- and caudate-dependent learning and memory (Kim et al. 2001, Schwabe et al. 2007, see chapter 5), cortisol did not affect participants' learning curve, learning speed and decision certainty. Furthermore, spatial learners were significantly more often aware of the respective alternative strategy than stimulus-response learners demonstrating again the cognitive narrow-mindedness or focusedness of stimulus-response learners (see also 5.4).

Though, the way how cortisol modulates the use of spatial and stimulus-response learning strategies is not fully understood yet, the present findings show clearly that glucocorticoids affect the quality of learning. Importantly, these effects can occur without changing quantitative parameters such as learning speed and latencies (Schwabe et al., in

prep.). Consequently, pure quantitative analyses of behaviour in general and pure quantitative analyses of stress hormone effects on learning and memory in particular are in danger to be deceptive. They might miss stress (hormone) effects that are of the utmost significance.

7 Study III: “Cognitive” versus “Habitual” Learning and Memory as a Person Characteristic?

7.1 Research question and hypotheses

The previous chapters focused on the regulation of multiple memory systems by acute factors, particularly the emotional state and glucocorticoid level of a person. Here, the question is addressed whether stable person characteristics affect the use of different learning strategies as well. Is there a permanent tendency to use "cognitive" (e.g. spatial) or "habitual" (e.g. stimulus-response) strategies?

Indeed, some studies suggest to answer this question in the affirmative. Mizumori, Yeshenko, Gill and Davis (2004) studied hippocampal and striatal neural activity patterns of rats during performance of spatial and response maze tasks. Based on the finding of reward-specific firing patterns in the hippocampus and caudate nucleus the authors suggested that motivation might be one factor that influences the contribution of hippocampal and striatal learning and memory systems to behavior. The motivation of an individual is a function of both environmental factors, such as reinforcement, and personal factors. Person variables that might affect the motivation in a given situation include temporary factors, such as tiredness or nutritional status, as well as more permanent factors like achievement motivation and reward sensitivity. Consequently, the view that motivation modulates the use of multiple memory systems implies an effect of durable person variables.

Evidence supporting the idea that the use of different learning strategies is influenced by rather stable person characteristics is provided by Bohbot, Iaria and Petrides (2004). They tested patients with medial temporal lobe lesions in a radial-maze equivalent computer task that could be acquired by a spatial or stimulus-response strategy. Surprisingly, Bohbot and colleagues (2004) observed that half of the patients with a compromised hippocampus chose spontaneously to use the spatial strategy (and were impaired at doing so). Half of them even continued to use the inefficient spatial strategy in subsequent trials. The authors concluded that there might be a genetic predisposition or an experience-dependent bias to use a certain strategy. A genetic disposition could be translated into an expression of higher receptor density, protein synthesis and blood flow leading to higher oxygen and glucose levels in certain brain areas compared to others. In line with this argumentation, Colombo, Brightwell

and Countryman (2003) reported that rats using a spatial strategy had an increase in phosphorylated CREB in the hippocampus, while rats that used a stimulus-response strategy had an increase in phosphorylated CREB in the caudate nucleus. Hence, through sustained protein synthesis a particular brain region can become more efficient in information processing. Furthermore, Sutherland, McDonald and Savage (2000) investigated the effects of prenatal ethanol administration on learning and memory of adult rats and found that prenatally exposed rats employed in a cue-place competition task, which was very similar to the water maze task used by Kim et al. (2001, see chapter 3), significantly more often a stimulus-response strategy than control rats.

On the basis of these findings it seems justified to hypothesize that the modulation of multiple memory systems is not only affected by transient factors but also by rather stable characteristics of the individual. This study aims to test whether people have a disposition to use “cognitive” (e.g. spatial) or “habit” (e.g. stimulus-response) learning predominantly. For this purpose a new task had to be developed which is different from the learning and memory task already developed (see chapter 4), but allows a differentiation of stimulus-response and spatial learning as well. Thirty subjects performed the two tasks, the new learning and memory task (color/position task) and the previously developed one (card task), one after another on the same day. This was to show that both tasks refer to the same issue. A separate group of twenty-four subjects participated first in the card task and 3 months later in the color/position task.

It was hypothesized that multiple memory systems are not only modulated by acute factors but also by rather stable person variables. Therefore people who choose a spatial strategy in the card task should tend to use a spatial strategy in the color/position task 3 months later as well. Likewise, subjects who employ a stimulus-response strategy in the card task were thought to employ an associative strategy in the subsequent color/position task. Furthermore, subjects who accomplish the two tasks immediately one after the other should also use corresponding strategies in the two tasks. If the latter is not the case, the results of the subjects who worked on the color/position task 3 months after performing the card task can only hardly be interpreted. In addition, it will be investigated whether the response pattern of spatial and stimulus-response learners is affected by the emotional valence of the acquired stimuli.

7.2 Methods

7.2.1 Subjects

Fifty-five healthy volunteers agreed to participate in this study. Thirty participants (25 females, 5 males; age mean: 23.2 years; age range: 19-34 years) performed the card task and the color/position task immediately one after the other. Twenty-five subjects took already part in study I (see chapter 5). All of them were in the control group in study I, i.e. they accomplished the card task without being stressed before. They performed only the color/position task in the present study. One of these 25 subjects could not be included in the analysis because of technical problems.

All subjects were students of the University of Trier or the University of Applied Sciences Trier. They received course credits and/or chocolate for participation.

7.2.2 The color/position task

Subjects were first presented a configuration of 4 two-syllable German words (positive, negative or neutral[4]) and 4 colors (yellow, green, blue, red) for 60 seconds on a common 17" computer screen (see figure 7.1). Each word was associated with a color and each word-color pair was presented in one of the four corners of the screen. Participants were requested to memorize this configuration. Afterwards they performed two tasks: a dot probe and a color naming task.

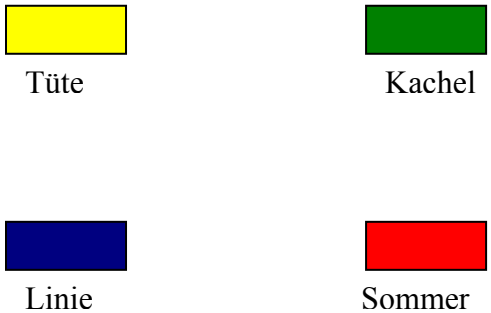


Figure 7.1: *Example of a configuration with three neutral and one positive word that was learned by the subjects.*

The dot probe task. The task used in the present study is a modification of the dot probe task by MacLeod, Mathews and Tata (1986), which was used to assess selective attention. The authors presented stimuli 500 ms prior to presentation of a dot in the location

[4] The valence of the used words was rated by a separate group of 52 persons before.

where one of the stimuli was presented. Participants were instructed to respond on a remote key at which side of the screen the dot appeared.

In the present study, subjects sat in front of a computer screen and were presented a word via headphones; either one of the four previously learned words or a neutral, new one[5]. After 1 second participants were presented an arrow on the screen, which was located in one of the four corners and pointed to the right or to the left. It was the subjects' task to indicate as fast as possible the direction of the arrow by pressing the corresponding key of the mouse (i.e. the right key, if the arrow pointed to the right and the left key, if the arrow pointed to the left). After a 1 second break (white screen) the next word was given via headphones and the next arrow appeared.

Sixteen words were presented in one trial, each followed by an arrow the subject should respond to. Half of these words were neutral, new words. The position of the arrows that followed these new words was randomized. Furthermore, each of the four previously learned words was presented twice, once followed by an arrow that was located in the corner where the word had been during the learning phase (*match*) and once followed by an arrow that was located in a position different from the one where the word had been located during learning (*non-match*).

The direction of the arrows was randomized, as was the order of matching, non-matching sequences and new words.

The color naming task. Same as in the dot probe task subjects were presented a word via headphones; either one of the four learned words or a neutral, new word. Exactly one second after the presentation of the word a colored field (yellow, green, blue or red) was presented in the centre of the screen. Subjects were requested to press as fast as possible the key of the keyboard which color corresponded to the color of the presented field. The next word was presented after a one second break (white screen).

One trial consisted of 16 word-color sequences. Eight of the 16 words were neutral and new; the color that followed these words was randomized. In addition, the four learned words were presented twice, once followed by the color the word was presented with during learning (*match*) and once followed by one of the other three colors (*non-match*). Again, the order of matching, non-matching sequences and new words was randomized.

[5] None of the new words was used twice.

Subjects were given 8 trials, i.e. they had to memorize 8 different configurations of words and colors and performed the dot probe as well as the color naming task eight times. The order of the two subtasks was varied between trials. In trial one the dot probe task was presented first and the color naming task was given subsequently, in the second trial the order was changed and so on.

The reaction times of the individuals were used as the dependent variable. Since it was expected that subjects would differ considerably with respect to their reaction times, comparisons based on raw reaction times were viewed as not reasonable. Instead, the difference between the individual reaction times for matching and non-matching combinations computed as Δ = reaction time matching – reaction time non-matching was used as the central parameter. This parameter was assumed to reflect learning best. If a person learned a word-position or word-color association, he/she should expect which color will follow or in which position the arrow will appear and respond therefore faster in matching trials than in trials in which a new word is presented. On the other hand, if the expectation is not met, i.e. if a learned word is presented with a color or arrow position that was different from the one it had been presented with during learning the person should respond more slowly than if a new word is presented. Thus, the difference between matching and non-matching combinations should be bigger than the matching – new difference, if a person learned the word-color and word-position combination, respectively, and be therefore a better indicator for learning. A faster reaction in the matching than in the non-matching dot probe conditions indicates that the position of the word was learned. A comparable pattern in the color naming task is indicative for associative learning, i.e. stimulus-stimulus learning. Hence, participants who show a faster reaction in the match than in the non-match condition (a negative Δ value) in the dot probe task but not in the color naming task are classified as “spatial” learners, while subjects who show a faster reaction in the match than in the non-match condition in the color naming task, but not in the dot probe task are classified as “associative” learners.

It was hypothesized that individuals who use a spatial strategy in the card task show spatial learning in the color/position task as well, whereas subjects who employed a stimulus-response strategy in the card task were assumed to show associative learning in the color/position task.

7.2.3 The card task

The card task was applied exactly as described in chapter 4.2.1.

7.2.4 Procedure

Subjects performed the color/position task either three months after accomplishing the card task or immediately after the card task. They received a standardized written instruction before each of the two tasks. The processing time for the two tasks was about 70 minutes.

7.2.5 Statistical analyses

All statistical analyses were performed with the help of SPSS-software (version 13.0; SPSS Inc., Chicago, Illinois). P-values smaller than 0.05 were considered significant. If not indicated differently, two-tailed p-values are reported.

7.2.6 Power analysis

To test the specified hypotheses paired t-test and F-test models were applied. Given the sample size of N = 54 and an α-level of 0.05 a paired t-test has a power of 1-β = 0.83 to detect a medium-sized effect. A repeated measures analysis of variance (ANOVA) could detect a medium-sized effect with a power of 1-β = 0.36. Thus, the statistical power of this study is far below the ideal power of 1-β = 0.95 (see Westermann 2000). Consequently, special attention has to be paid to the observed effect sizes.

7.3 Results

7.3.1 Card task and color/position task on the same day

7.3.1.1 Card task

Of the 30 participants, who performed the two tasks on the same day, 27 subjects chose the card besides the plant in the test trial (stimulus-response learners) and 3 subjects chose the card in the position where the “win-card” had been located during training (spatial learners; see table 7.1). Due to this clear imbalance in the number of spatial and stimulus-response learners a mixed design ANOVA which would be appropriate to answer the research question can not be computed. Therefore, the responses of spatial and stimulus-response learners have to be "analyzed" on a descriptive level mainly.

Table 7.1: *Number of spatial and stimulus-response learners in the card task at the two time points.*

		learning strategy		
		stimulus response	spatial	total
interval between card task and color/position task	same day	27	3	30
	3 months	14	10	24
total		41	13	54

7.3.1.2 Color/position task

New, matching and non-matching combinations

A repeated measures ANOVA indicated that reaction times differed between new, matching and non-matching combinations in the *dot probe* (Greenhouse Geisser $F_{(1.66, 88.10)} = 4.90$; $p < .02$; partial $\eta^2 = 0.09$). Post-hoc paired t-tests revealed that reaction times were faster in matching (M = 512ms) than in non-matching (M = 525ms) combinations ($t_{(53)} = 2.18$; $p < .04$; $d = 0.20$), while reaction times in new (M = 508ms) and matching combinations did not differ ($t_{(53)} = 0.84$; $p = .40$; $d = 0.00$).

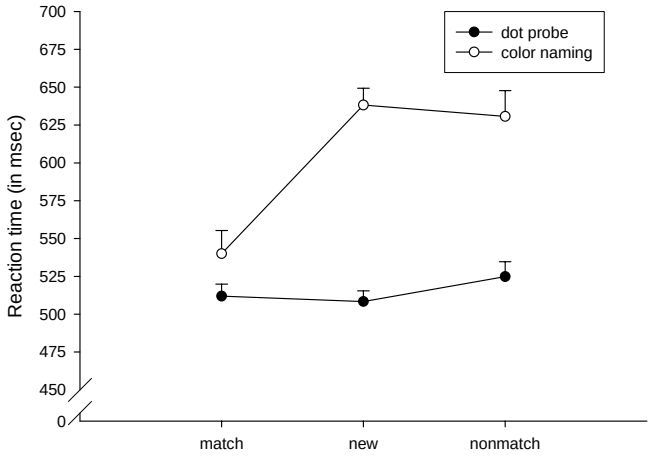


Figure 7.2: *Reaction times in matching, new and non-matching combinations of the dot probe and color naming task. Bars represent Mean ± SEM.*

Similarly, a repeated measures ANOVA showed that reaction times differed in the three combinations in the *color naming task* (Greenhouse Geisser $F(1.62, 85.95) = 30.81$; $p < .001$; partial $\eta^2 = 0.37$). Post-hoc paired t-tests revealed that reaction times were faster in matching (M = 540ms) than in non-matching (M = 631ms) combinations ($t(53) = 5.36$; $p < .01$; $d = 0.76$), whereas new (M = 638ms) and non-matching combinations did not differ ($t(53) = 0.59$; $p = .56$; $d = 0.07$). The reaction times for the two tasks and the three types of combinations are summarized in figure 7.2.

Learning strategy and matching versus non-matching differences in the two tasks

The difference in reaction times in matching versus non-matching trials was significantly smaller in the dot probe (M = -8ms) than in the color naming task (M = -83ms; paired t-test; $t(26) = 3.39$; $p < .002$; $d = 0.97$) for *stimulus-response learners*. *Spatial learners*, on the other hand, showed a smaller matching versus non-matching reaction time difference in the color naming task (M = -43ms) than in the dot probe task (M = -70ms). As shown in figure 7.3 this suggests an interaction between tasks and learning strategy applied in the card task.

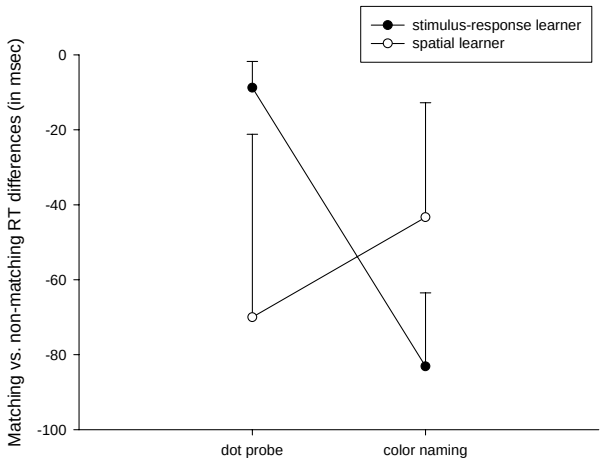


Figure 7.3: *Interaction effect between task and learning strategy on matching versus non-matching reaction time differences. Bars represent Mean ± SEM.*

7.3.2 Card task and color/position task with an interval of 3 months

7.3.2.1 Card task

Based on the strategy employed in the test trial of the card task, 14 of the participants were classified as stimulus-response learners, while 10 were classified as spatial learners (see

table 1). Though the sample size is rather small, this ratio of spatial and stimulus-response learners allows inference statistical methods.

7.3.2.2 Color/position task

New, matching and non-matching combinations

The reaction times in the two tasks and three combinations are displayed in figure 7.4. Differences in the reaction times in new, matching and non-matching *dot probe* combinations were indicated by a repeated measures ANOVA ($F_{(2,46)} = 3.14$; $p = .05$; partial $\eta^2 = 0.12$). Post-hoc paired t-tests revealed faster reaction times in matching (M = 514ms) than in non-matching combinations (M = 525ms), however, this difference did not reach significance ($t_{(23)} = 1.21$; $p = .24$; $d = 0.16$). The reactions to new words (M = 502ms) were significantly faster than those in non-matching ($t_{(23)} = 2.19$; $p < .04$; $d = 0.34$), but not than those in matching combinations ($t_{(23)} = 1.56$; $p = .14$; $d = 0.19$).

In the *color naming task* reaction times differed in the three combinations, too (Greenhouse Geisser $F_{(1.47, 38.87)} = 10.36$; $p < .001$; partial $\eta^2 = 0.31$). Post-hoc paired t-tests indicated significantly faster reaction times in matching combinations (M = 544 ms) than in new (M = 629ms; $t_{(23)} = 4.47$; $p < .01$; $d = 0.72$) and non-matching combinations (M = 649ms; $t_{(23)} = 3.39$; $p < .01$; $d = 0.73$); there was no significant difference between the latter two kinds of combinations ($t_{(23)} = 0.88$; $p = .58$; $d = 0.16$).

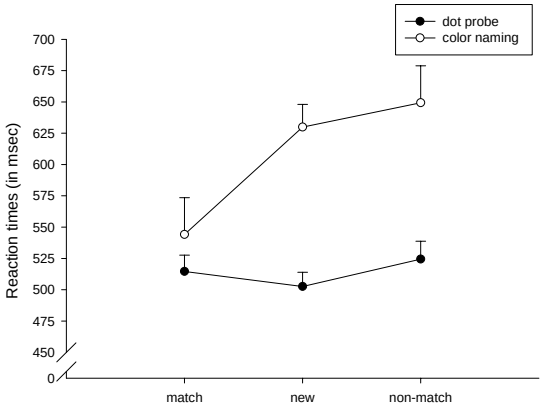


Figure 7.4: *Reaction times in the matching, new and non-matching combinations for the dot probe and color naming task. Bars represent Mean±SEM.*

Learning strategy and matching versus non-matching differences in the two tasks

A mixed-design ANOVA with task (dot probe versus color naming) as within-subjects factor and learning strategy in the card task (spatial versus stimulus-response learner) as between-subjects factor revealed a significant main effect of the task ($F_{(1,22)} = 13.65$; $p <$

.001; partial $\eta^2 = 0.38$). Matching versus non-matching reaction time differences in the dot probe (M = -10ms) were significantly smaller than in the color naming task (M = -105ms; $t(23) = 3.43$; $p < .02$; $d = 0.85$). Neither a main effect of learning strategy ($F(1,22) = 0.89$; $p = .36$; partial $\eta^2 = 0.04$) nor a significant interaction between task and learning strategy ($F(1,22) = 2.02$; $p = .17$; partial $\eta^2 = 0.08$) appeared. As displayed in figure 7.5 the matching versus non-matching reaction time difference in the color naming task tended to be smaller in stimulus-response (M = -75ms) than in spatial learners (M = -148ms). This effect, however, did not reach significance ($t(22) = 1.18$; $p = .25$; $d = 0.49$). In the dot probe task there was no comparable effect (spatial: M = -8ms; stimulus response: M = -12ms; $t(22) = 0.24$; $p = .81$; $d = 0.10$).

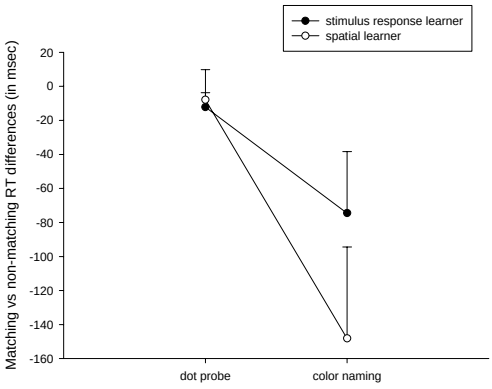


Figure 7.5: *Interaction effect between task and learning strategy on matching versus non-matching reaction time differences. Bars represent Means±SEM.*

7.3.3 Effects of emotional valence

7.3.3.1 Dot probe task

A mixed-design ANOVA with emotional valence as within-subjects factor and learning strategy in the card task and time (immediately versus 3 month interval) as between-subjects factors indicated a significant main effect of emotional valence on matching versus non-matching reaction time differences ($F(1.58,79.07) = 4.65$; $p < .02$; partial $\eta^2 = 0.09$; figure 7.6). Post-hoc paired t-tests revealed a significantly larger matching versus non-matching reaction time difference for positive words (M = -39ms) than when neutral words were learned (M = -0.8ms; $t(53) = 2.56$; $p < .01$; $d = 0.47$). Although matching versus non-matching differences were larger for positive words than for negative words (M = -16ms), this difference was not significant ($t(53) = 1.53$; $p = .13$; $d = 0.26$). Similarly, matching versus non-

matching differences associated with negative words were larger than those associated with neutral words, but this difference did not reach significance ($t_{(53)} = 1.4$; $p = .17$; $d = 0.25$).

Significant main effects of learning strategy ($F_{(1,50)} = 1.23$; $p = .23$; partial $\eta^2 = 0.02$) or time ($F_{(1,50)} = 0.02$; $p = .90$; partial $\eta^2 = 0.00$) were not found.

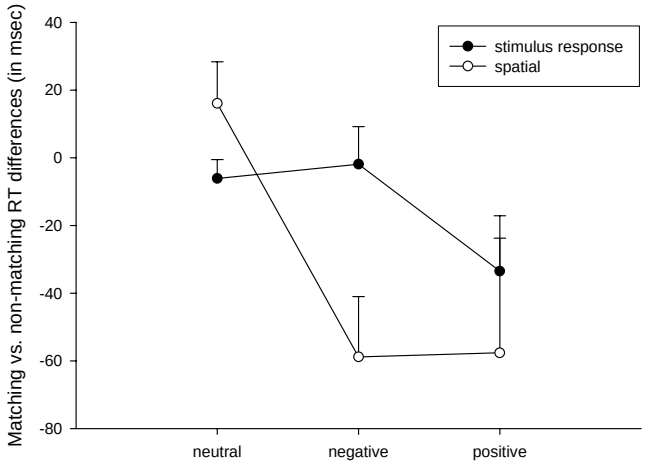


Figure 7.6: *Differences in reaction times in matching and non-matching dot probe combinations dependent on emotional valence of the learned words and used learning strategy in the card task.*
Bars represent Mean ±SEM.

Furthermore, a significant emotional valence × learning strategy interaction was found (greenhouse geisser $F_{(1.58,79.07)} = 3.33$; $p = .05$; partial $\eta^2 = 0.06$; figure 7.6). Spatial learners responded faster in matching than in non-matching combinations when the learned word was positive or negative but not when the learned word was neutral ($F_{(2,24)} = 3.48$, $p < .05$, partial $\eta^2 = 0.23$; positive vs. neutral: $p < .06$, negative vs. neutral: $p < .01$, positive vs. negative: $p = .98$). Stimulus-response learners, on the other hand, responded faster to matching than to non-matching combinations only when positive words were presented ($F(2,80) = 2.74$, $p = .07$, partial $\eta^2 = .06$; positive vs. negative: $p < .07$, positive vs. neutral: $p < .10$, negative vs. neutral: $p < .70$). Thus, spatial and stimulus-response learners differed mainly in their reaction times to negative words with the spatial learners showing higher matching versus non-matching differences. None of the other interactions was significant (all p-values > .50; all partial η^2-values < 0.03).

7.3.3.2 Color naming task

Table 7.2 presents the matching versus non-matching reaction time differences for the color naming task. In contrast to the dot probe task, none of the main effects and none of the interactions reached significance (all p-values > .29; all $\eta^2 < 0.02$).

Table 7.2: *Matching versus non-matching reaction time differences in the color naming task depending on learning strategy, the interval between the card and color/position task and the emotional valence of the learned words.*

Valence	Learning strategy	Interval between tasks	Mean (in ms)	SEM	N
positive	stimulus response	same day	-106,9630	178,66029	27
		3 months	-27,4286	182,34402	14
		total	-79,8049	181,69125	41
	spatial	same day	-65,0000	23,30236	3
		3 months	-106,4000	92,22340	10
		total	-96,8462	82,45589	13
	total	same day	-102,7667	169,76123	30
		3 months	-60,3333	153,95755	24
		total	-83,9074	162,81269	54
negative	stimulus response	same day	-103,6296	152,46542	27
		3 months	-138,2143	301,61544	14
		total	-115,4390	212,01710	41
	spatial	same day	-44,0000	159,79987	3
		3 months	-143,6000	123,54414	10
		total	-120,6154	132,70678	13
	total	same day	-97,6667	151,43687	30
		3 months	-140,4583	239,58043	24
		total	-116,6852	194,72514	54
neutral	stimulus response	same day	-61,7037	61,05030	27
		3 months	-45,7857	102,75825	14
		total	-56,2683	76,89474	41
	spatial	same day	-40,6667	52,53887	3
		3 months	-97,6000	102,12215	10
		total	-84,4615	94,36685	13
	total	same day	-59,6000	59,77579	30
		3 months	-67,3750	103,58605	24
		total	-63,0556	81,40498	54

7.4 Discussion

This study aimed to investigate the stability of the learning strategy used by an individual, i.e. the effect of stable person variables on memory system use. To address this issue subjects' learning strategies in the card task were compared with the strategy used in a

reaction time based paradigm (color/position task), either with both tasks accomplished on the same day or with an interval of three months between the two tasks. The obtained results suggest that the stability of learning strategies is low.

Participants' reaction times showed clear effects of learning. In both subtasks (dot probe and color naming task) reaction times in matching combinations were always faster than those in non-matching combinations. This difference was smaller in the dot probe than in the color naming task. While there were four response options in the color naming task, there were only two in the dot probe. Hence, reaction times were generally faster in the dot probe than in the color naming task. Thus, the reason for the smaller matching versus non-matching difference in the dot probe is probably a "ceiling effect" in subjects' reaction times.

Those participants who used a spatial strategy in the card task and accomplished the color/position task on the same day showed a larger matching versus non-matching difference in the dot probe compared to the color naming task. In other words: they used a spatial (or place) strategy in the color/position task as well. By contrast, those subjects who employed a stimulus-response strategy in the card task and performed both tasks immediately one after the other showed a larger matching versus non-matching difference in the color naming task than in the dot probe, i.e. they used a stimulus-associated learning strategy (see 7.2.2). Thus, when card task and color/position task were given shortly one after the other subjects seem to use corresponding strategies in the two tasks. However, since there were only three spatial learners in the card task when both tasks were presented on the same day, these results have to be interpreted very carefully, at best.

Interestingly, those who were classified as spatial learners in the color/position task showed a clear learning effect in the dot probe *and* the color naming task, whereas those who were classified as stimulus-response learners showed a clear learning effect in the color naming task only. This finding corresponds to the outcome of study I that spatial learners were aware of the spatial and stimulus-response option, while stimulus-response learners mentioned the stimulus-response strategy as the only option. Thus, the results of this and the first study point to a reduced cognitive openness in stimulus-response learners. The issue how adaptive this rigidity is has been discussed in chapter 5 already.

When there was an interval of 3 months between the performance of the two tasks, the association between the learning strategy used in the card task and the strategy employed in the color/position task disappeared. Both, those who were classified as spatial learners based on the strategy used in the card task and those who were classified as stimulus-response learners showed a very small learning effect in the dot probe, but a significant matching

versus non-matching reaction time difference in the color naming task. That is, both groups used a stimulus-associated strategy in the color/position task.

Thus, the obtained results suggest – although, again, they have to be interpreted very carefully – that memory system use is barely affected by stable characteristics of a person, at least when there are no pre-, peri- or postnatal impairments such as prenatal ethanol exposure (Sutherland et al. 2000). Though, the present findings suggest that the use of multiple memory systems is primarily determined by situational factors, it is likely that if a person experiences a situation very frequently, he/she might habitually use a certain learning strategy. Supporting Bohbot and colleagues' (2004, see above) assumption that a bias for spatial or stimulus-response learning might be due to experience-based changes in the efficiency of certain brain areas Maguire et al. (2000) found structural changes in the hippocampi of humans with extensive navigational experience (London Taxi drivers). The same group (Maguire et al. 2006) reported recently that these changes in hippocampal gray matter volume are associated with improved spatial memory and an altered ability to acquire new visual-spatial information. Thus, it is tempting to speculate that such alterations in brain morphology are also accompanied by a proneness to use spatial over stimulus-response strategies.

The pattern of reaction time differences in matching versus non-matching combinations was only moderately affected by the emotional valence of the stimuli used. In the color naming task there was no effect of the valence of the learned words. In the dot probe task, matching versus non-matching differences were bigger when emotional – especially positive valent – words were presented. Those subjects who were classified as spatial learners as well as those who were classified as stimulus-response learners based on the strategy used in the card task showed a learning effect for positive words, but no learning effect for neutral words (spatial learners were even faster in non-matching than in matching combinations when neutral words were presented). When negative words were presented spatial learners showed a learning effect, while stimulus- response learners did not. Therefore, the different matching versus non-matching differences in spatial and stimulus-response learners in the dot probe are primarily due to the fact that stimulus-response learners showed no sign of learning when the learned words that were presented were negative. This is surprising since other studies suggested that learning and memory is especially strong for negative stimuli (Cahill et al. 1996a, Kern et al. 2005). One possible explanation for the finding is that learning was also enhanced in stimulus-response learners. However, since they focus on single stimuli the facilitating effect of negative valence might enhance especially the stimulus-stimulus learning and further reduce the attention paid to the position of the word which is reflected in the dot

probe matching versus non-matching reaction time difference. Indeed, stimulus-response learners responded much faster in the color naming task when negative words were presented than when positive or neutral words were learned and later on presented (because of a high standard error of means this difference remained insignificant; see table 7.2).

The guiding hypothesis of this work is that stress enhances stimulus-response ("habit") learning at the expense of spatial ("cognitive") learning. Kim and colleagues (2001) reported that half of the tail-shocked rats used a stimulus-response strategy, whereas none of the non-stressed rats used this strategy. In study I, however, the majority of both TSST-stressed and non-stressed subjects employed stimulus-response strategy. In the same line, both spatial and stimulus-response learners employed in the present study a stimulus-associated strategy in the color/position task 3 months after the card task. These results suggest that people do *not* use spatial ("cognitive") learning mainly and stimulus-response ("habit") learning in case of stress only, rather individuals tend to employ stimulus-associated learning when both spatial as well as stimulus-response learning could be applied. Following this argumentation stress does not change the learning strategy of an individual, but strengthens the predominance of stimulus-response learning. If people have a general tendency to use simple stimulus-related learning, the question is which factors enable individuals to learn spatially (cognitively). It could be speculated that variables such as relaxation or intrinsic motivation might be of importance, but this has to be addressed by future research.

In addition to the small number of people who employed a strategy that could be interpreted as spatial or place-associated the present study suffers from two conceptual problems. First, the association of the color/position task and the card task and the stability or change in the used strategy was tested in different people. It is concluded that if there is an association between the two tasks in one group of people, there will be an association in others as well. This conclusion is – although probable – uncertain. A better way would be to present people first both tasks immediately one after the other and give them the color/position task three months later again. In contrast to the card task the color/position task could be presented repeatedly as its intention is less transparent than the intention of the card task. A second problem relates to the already in chapter 4 discussed issue, whether a task that is presented on a computer screen, a task that is two-dimensional, can be spatially learned. Is it possible to apply a spatial strategy in the color/position task? Same as in the computer-based task which was described in chapter 4 vantage points were not changed and no cues allowing spatial orientation were presented. Thus, it seems not reasonable to declare the strategy identified by a larger matching versus non-matching difference in the dot probe than

in the color/naming task as spatial, rather it is a place-associated strategy. However, evidence was presented that the strategies used in the card task and the color/position task correspond to each other. Therefore, a change in the strategy used in the color/position task is a sign of changes in the strategy employed in the card task.

Despite these shortcomings, the present study provides an important contribution to the research on multiple memory systems. This study is the first that addressed the stability of the learning strategy used by an individual explicitly. It is suggested that the use of learning strategies is not stable and thus the effect of stable person variables on multiple memory systems use rather low. This, however, does not preclude that there is a significant interaction between personal and situational factors on learning and memory systems use.

8 Summary and Concluding Remarks

Evidence from human and animal studies has shown that there are multiple **memory** systems defined by distinct neural substrates and functional demands (Iaria et al. 2003, Packard et al. 1989, White and McDonald 2002). Earlier animal studies suggested that **stress** modulates multiple memory systems in favor of caudate nucleus-based stimulus-response ("habit") and at the expense of hippocampus-based spatial ("cognitive") learning and memory (Kim et al. 2001, Packard and Wingard 2004). The present work aimed to test whether this holds true for humans as well. Thus, the main question of this work was: Does stress modulate modulate multiple memory systems in favor of "habit" learning and memory in humans? To answer this question a paradigm was developed that allows to distinguish spatial and stimulus-response learning and memory in humans. Using this newly developed task (the "card-task") it was shown for the first time that (psychosocial) stress affects the learning strategies applied by humans. Subjects that were exposed to the Trier Social Stress Test (TSST) prior to training in the card-task employed significantly more often a stimulus-response strategy than non-stressed controls. As stimulus-response learners tended to have higher saliva cortisol concentrations compared to spatial learners, the glucocorticoid stress hormones were hypothesized to be the mechanism underlying memory system modulation. To test this hypothesis young healthy humans were administered cortisol one hour before being tested in the card-task. Cortisol, indeed, modulated the used learning strategy, independent of autonomic and subjective arousal. However, the modulatory effect of cortisol was opposite to the effect of psychosocial stress. The use of a spatial strategy was the more likely the higher the cortisol dose was. The explanation for this discrepancy favored here takes the cortisol concentrations in the two studies into account and postulates an u-shaped relationship between glucocorticoids and the applied learning strategy. A third study addressed the question whether there is a long-lasting proneness to prefer spatial over stimulus-response learning and vice versa. If there is a tendency to use a certain learning strategy, individual characteristics and traits should be identified that predict the kind of learning. Future studies would have to consider these characteristics to assess the effects of stress and stress hormones on learning and memory adequately. The present findings suggest that there is no such long-lasting strategy preference.

Overall, this work highlights an aspect that has often been neglected in memory research - the quality of learning, i.e. the way a task is acquired.

8.1 Implications and future directions

The starting point of this work was a rodent study showing that behavioral stress affects the way a subsequent task is learned (Kim et al. 2001). Here, these findings were translated to humans. In a next step, the present findings could be re-translated to animals. To further illuminate the role of glucocorticoids in the modulation of multiple memory systems, it would be extremely helpful to study adrenalectomized rodents in a corticosteroid substitution paradigm. Following such a translational approach provides the opportunity to combine the advantages of animal and human experiments. In animal studies, manipulations (e.g. lesions of certain brain areas) are possible that are not feasible in humans but yield valuable information regarding mechanisms underlying a certain phenomenon. Furthermore, the experimental situation is a real life situation for an animal, there is no awareness of being part of a scientific study. Thus, animal studies might be considered more objective, i.e. less biased by the subjects, than human experiments. Human participants, on the other hand, can be asked about their thoughts and feelings. And most important, researchers are primarily interested in the human situation, animals are mostly "only" a model for the human situation. So far, the translational approach has been used scarcely. For the progress of science - not only in the field of learning and memory - this should be changed in the future.

The premise of this work is that memory is composed of several different abilities depending on different brain areas. Two memory systems were at the centre of interest: (i) a hippocampal (better: medial temporal lobe) system dealing with spatial (more general: declarative) learning and memory and (ii) a caudate nucleus system engaged in stimulus-response learning and memory. A third memory system that was of relevance here is the amygdala. The amygdala, however, was not viewed as a place of permanent storage. It was rather seen as a modulator of memory processes in other brain areas. It is to be noted that spatial and stimulus-response learning were not directly but indirectly - via other studies using similar tasks - related to the hippocampus and caudate nucleus, respectively. The use of neuroimaging techniques such as functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) or the study of brain damaged subjects, in particular patients suffering from temporal lobe lesion, Huntington's or Parkinson's disease, would be required to provide direct evidence of an involvement of the hippocampus and caudate nucleus in the two kinds of learning. This was not feasible within this work.

Though, the present work focused on hippocampus, caudate nucleus and amygdala, numerous other brain areas have been associated with memory functions, e.g. the prefrontal cortex or the cerebellum (Gabrieli 1998, Squire 2004). Whether stress influences other memory systems than the hippocampus-dependent declarative one, is largely unknown. Similarly, it is not known whether stress exerts a modulatory impact on other memory systems as well. Is there a general principle in the modulation of memory systems by stress? Does stress always modulate memory systems in favor of the system being cognitively least demanding? Future studies are clearly requested to address these questions.

This work focused on the modulation of spatial and stimulus-response learning. However, it is important to note that these two kinds of learning are merely examples of two broader categories of learning and memory. "Cognitive" learning, for which spatial learning is an example, refers to a conscious and flexible way of learning that allows transfer to new situations. "Habit" (e.g. stimulus-response) learning, on the other hand, is less flexible, it is rigid and not necessarily conscious. Here, it is suggested that these two kinds of learning are modulated by stress. This finding could be highly relevant for both the understanding of certain psychiatric disorders and social interactions in everyday life.

Post traumatic stress disorder (PTSD) can evolve in consequence of the experience of extremely stressful events such as war, torture or domestic violence. It is accompanied by altered glucocorticoid levels (Yehuda 2006). The most prominent symptom of PTSD is the re-experiencing of the traumatic event when exposed to trauma-related stimuli (e.g. odours). It is tempting to speculate that these intrusions are the result of strong stimulus-response associations formed under severe stress. Hypercortisolemia is often found in severe forms of depression (Gillespie and Nemeroff 2005). While emotional disturbances are in the centre of depressive disorders, patients exhibit cognitive problems as well. Depressive patients are impaired in mental flexibility and cognitive-set shifting tasks (Airaksinen et al. 2004, Harvey et al. 2004) suggesting an impairment in "cognitive" learning. PTSD and depression are only two examples of mental disorders characterized by dysregulations of the HPA axis and cognitive disturbances, which often complicate therapy. Knowledge about factors underlying these stress – and most likely glucocorticoid - mediated deficits is a first step to prevention, early intervention and successful treatment.

Stereotypes are oversimplified generalizations about an entire group of subjects without regard for individual differences. They share several features with stimulus-response associations. Both, stereotypes and stimulus-response associations, allow fast reactions and decisions and are quite persistent once they are established. Both lead to "habitual" thinking

and behavior. Both have the advantage of cognitive relief but might lead to erroneous judgments. Is "habit" learning a basis for stereotypes? If "habit" learning is favored by stress, are stereotypes more likely in individuals who are frequently exposed to stress? Are, for instance, people who are threatened by unemployment or live in a highly stressful environment more susceptible to racism, sexism and other kinds of discrimination? Indeed, there is first evidence that psychological stress encourages stereotyping (Friedland et al. 1999). Using socially relevant stimuli in studies testing the modulatory effect of stress on "cognitive" and "habit" learning could help to further illuminate these issues.

The present work started out to study a field largely neglected in stress and memory research, the effects of stress and stress hormones on the quality of learning. It is not an excursus, it should rather be a starting point for future research since it links two "hot topics" of modern societies - stress and the acquisition of flexible knowledge structures.

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Erklärung

Hiermit erkläre ich, dass ich die vorliegende Arbeit selbst verfasst und keine anderen als die angegebenen Hilfsmittel verwendet habe. Zudem wurde die Arbeit an keiner anderen Universität zur Erlangung eines wissenschaftlichen Grades eingereicht.

Trier, den 10. Oktober 2007

Lars Schwabe