Principles of Learning and Memory

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Short List of Contents

Contents

Preface

"How the brain enables the mind is the question to be answered in the twenty-first century…" (Gazzaniga, 1998, p. xii). This question is at the core of research on human learning and memory. Whereas previous attempts at addressing Gazzaniga's "grand question" have focused solely on psychological processes, researchers are now calling for interdisciplinary work that bridges the areas cognitive psychology, cognitive neuroscience, cognitive neuropsychology, neuroanatomy, physiology and biology. This volume reviews the recent research on human learning and memory. Our goal is to provide an overview of the exciting incites provided by research investigations that meld multiple research methodologies and domains.

Research on learning and memory is performed at different levels of analysis ranging from the cell to observable behavior. The breadth of research methodologies raises the challenge of integrating the different approaches. In order to answer questions about the brain structures and systems that enable human cognitive activity, it is necessary to relate approaches and results from experimental psychology to those provided by biology, neuroanatomy, or neuroscience. The former are concerned with the systems level of behavior, the latter with more elementary levels of neurons and neuronal networks. It is only through a synthesis of the disciplines that cover the whole hierarchy of analysis, that researchers can develop a better understanding of the system, its components, its constituting elements, and, last but not least, its interaction with the environment

The emphasis of the chapters in this volume is on the interconnections between the level of behavior and the level of neural activities and structures. The goal is to overcome the traditional borders separating different fields of research in order to present an integrated pattern of results that enables a broader, interdisciplinary view and a deeper understanding of human learning and memory. The volume thus presents an interdisciplinary synthesis of current research connecting cognitive science and neuroscience.

The large amount of research and the broad range of phenomena require us to focus on selected topics. We selected phenomena that are central to human learning and memory, and that are studied from different perspectives in cognitive psychology, in neuroscience, and in biology. By analyzing the literature fifteen principles were delineated which seem to be most central for research on learning and memory and which are currently being investigated through an interdisciplinary approach. These principles can be subsumed under five main themes: (A) Formation of memories; (B) Organization of memories during encoding, storage and retrieval; (C) Consolidation of memories; (D) Control of memories during information processing; and (E) Adaptive specialization of memories.

A. Formation of memories: The human cognitive system is able to learn and to change, to improve and to adapt performance based on experience and changes in the environment. How does the brain enable learning and memory? The first four chapters by *Lachnit,* by *Kress and Daum,* by *Röder and Rösler,* and by *Roth* focus on the mechanisms and underlying brain structures that participate in the formation of new memories, i.e. on the processes that lead to the acquisition of knowledge. The chapters discuss results from animal and human research that point to four basic principles: spatio-temporal contiguity, multiple brain structures underlying experience-related changes, brain plasticity, and emotional learning.

B. Organization of memories: How are processes of encoding, storage and retrieval related to brain structures and neural processes? Probably one of the most important insights gained through recent research is that these processes are based on highly organized and specialized structures of the brain (e.g., Damasio, 1989; Squire, Knowlton, & Musen, 1993). Functional modularity of the brain is now one of the key concepts of neuroscience. Data obtained from experimental analyses of human cognitive performance as well as a theoretical analysis of memory phenomena suggest that specialized subsystems perform specific tasks like encoding, storage, retrieval, and modification of information. These systems are defined by structural and functional criteria, in particular by the type of information representation that is available to them. The goal of research is to identify such specialized subsystems and to understand their functional intricacies. This is the central issue addressed by *Rösler and Heil*, by *Buchner and Brandt,* and by *Jonides, Sylvester, Lacey, Wager, Nichols and Awh*. These chapters cover the principles of coding specific storage and retrieval, of multiple memory systems, and of separate systems of working memory.

C. Consolidation of memories: The flexible acquisition of new information is essential for systems that have to interact with a changing world. Equally important is the ability of the system to transform this new information into stable memories that can reliably guide behavior later. Chapters by *Schwarting*, by *Paller*, and by *Brand and Markowitsch* focus on the mechanisms and processes that support the consolidation of newly acquired knowledge and provide for enduring memories. These authors cover the principle of memory consolidation and its pharmacological modulation, the principle of cross-cortical consolidation of episodic memories, and the principle of bottleneck structures necessary for consolidation and retrieval.

D. Control of memories: The chapters in this section all deal with the basic mechanisms of how information is represented and how information transfer is controlled in the nervous system. The chapter of *Munk* discusses the principle of transient binding in the CNS, which is a powerful, empirically based hypothesis that explains how the brain can find its equilibrium between two seemingly antagonistic processing modes: cortical adaptivity versus consolidation, or rapid reorganization versus the generation of stabilized representations. The principle of inhibition is another basic mechanism, which regulates activation processes on both the neuronal and behavioral levels of memory representations. *Dagenbach & Kubat-Silman* review several inhibitory mechanisms, derived from cognitive psychology, that are relevant to working memory and long-term memory control. They relate these mechanisms to possible neural correlates. *Mayr's* chapter draws on recent evidence from behavioral, brain imaging, and single-cell recording work to sketch out an integrated view of the neurocognitive basis of executive control.

E. Adaptive specialization of memories: Pinker (1997), referring to Darwin's claim that future psychological research will be performed on new foundations, stated that the process of relating psychological and biological research has been slow except for the important development of evolutionary psychology, as initiated by Cosmides and colleagues (e.g. Barkow, Cosmides, & Tooby, 1992). Evolutionary psychology has engendered an unusually strong combination of approaches that includes cognitive psychology's analysis of information processing and evolutionary biology's analysis of complex, adaptive behavior of species. *Güntürkün and Durstewitz* and of *Gallistel* continue this fruitful collaboration in their chapters, which cover the principle of species independent learning phenomena and the principle of adaptive specialization.

The fifteen chapters of this volume are based on the International Symposium on Human Learning and Memory held in March 7-10, 2001. Speakers from the USA and Germany contributed to the conference and agreed also to write chapters for this textbook. These scientists, leaders in their fields, were asked to discuss principles from an interdisciplinary point of view. Due to the scope of the chapters, the volume is intended as an advanced textbook for students of the disciplines of neuroscience and cognitive science.

The editors acknowledge the financial support provided by the German Research Society (DFG, Bonn) and the State of Lower Saxony (Hannover), which supported the international conference held at the Hanse Institute for Advanced Study (Delmenhorst). The hospitality of the Hanse Institute is gratefully acknowledged. We are especially grateful for the generous support of the Academy of Sciences, Göttingen, who made this volume possible. We thank the speakers and the other participating young and senior scientists for joining the conference and for shaping the project by their lively discussions, and we thank the authors for their readiness to contribute to the volume. Special thanks go to Gale Pearce (Eugene, Oregon, USA) for examining chapters written by German authors as a native speaker, and finally to Adjuta Bertsch and Renate Kalk (Marburg, Germany) for accomplishing most of the work that was necessary to prepare a camera ready manuscript.

Hamburg, Göttingen, Marburg, September 2002   Rainer H. Kluwe
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Section A

FORMATION OF MEMORIES

1

The Principle of Contiguity

Harald Lachnit

The Law of Contiguity is considered a keystone of most scientific theories of learning, memory, and knowledge. In general, the Law of Contiguity states that after events occur together (in spatio-temporal proximity), the reoccurrence of only one event evokes the 'memory' of the others.

The present chapter is an attempt to outline how this principle stimulated theorizing as well as empirical research in the area of learning and memory, with special emphasis on the former. In part, I will follow the course of arguments put forth in the excellent review of "Classical conditioning and the Law of Contiguity" by Gormezano & Kehoe (1981).

We will start with a brief look at the historical antecedents in philosophy and early psychology from Aristotle, across British Empiricism and reflexology to behaviorism, culminating in the most unconstrained contiguity theory proposed by Guthrie (1935). From its zenith we will accompany the Principle of Contiguity while it is riding a roller coaster through a landscape of empirical attacks and theoretical rescue operations back to the significance of contiguity for learning (but not behavior). We will close with a recent attempt to renounce contiguity in favor of time and rate.

Historical Antecedents: Philosophical Roots and Early Psychology

The roots of the Law of Contiguity can be traced back to Greek philosophy. Aristotle is generally credited with originating the concepts of association and contiguity. In his discussion of memory, he stated that knowledge and mind are built from basic *sensations* which themselves are hooked together through associations. Similarity, contrast, and previous spatial or temporal contiguity of events determine which events will be recalled together.

The British Empiricists (about 1650 – 1850) were the actual predecessors to psychological theories of association. Thomas Hobbes, John Locke, Thomas Hartley, James Mill, and John Stuart Mill were opposed to the Cartesian tenet of innate ideas. Instead, they favored the idea that humans are born with a mind that is a blank slate (tabula rasa) and that all information enters the mind via simple sensory perception. These philosophers proposed the existence of a connective force – association – that enabled complex mental entities composed of simple (sensory) events. They outlined one primary and some secondary laws of association. The primary law of association was the Law of Contiguity: An association between two events will be formed only if they occur in spatio-temporal proximity. The most important secondary law of association, the Law of Frequency, states that the number of repetitions of contiguous pairings determines their subsequent associative strength. By assuming physiological vibrations as counterparts of mental events, Hartley opened a window for the evaluation of this philosophical principle by empirical sciences. Furthermore, he laid the foundation of the concept of the stimulus trace, which became very important in later days.

The crucial step in the conversion of the Law of Contiguity into a fundamental principle of learning and memory took place in the dawn of the 20th century, when Pavlov worked on the method of the conditioned reflex as a tool for the physiological study of the neural mechanisms by which animals adjust to their environments. It was Bekhterev (1913), however, who first asserted the parallels of the conditioned reflex and the associative doctrine. Lashley (1916) stated that the conditioned reflex method enables the investigator to precisely control stimuli and measure responding. Thus, Pavlovian conditioning may be considered an almost ideal example of associative learning. At about the same time, Thorndike (1913) studied animal intelligence. In his Law of Effect he stated that the connection between situation and response is strengthened when the response is closely followed by satisfaction. Hence, Thorndike's Law of Effect is a principle of association through contiguity, too. In the rise of Behaviorism, the conditioned reflex (now called conditioned response) changed from an example of association through contiguity to the substitute for the Law of Contiguity (Guthrie, 1930). Ultimately, Guthrie (1935) assumed that nothing but contiguity – one mere pairing of a stimulus and a response – is sufficient for learning. Guthrie's theory and its successor, the statistical learning theory of Estes (1950), are the most rigorous variants of an unconstrained Law of Contiguity.

Empirical Departures from the Omnipotent Law of Contiguity

One of the most important variables in the empirical evaluation of the Law of Contiguity has been the interstimulus interval (ISI), the time elapsing from the onset of the conditioned stimulus (CS) until the onset of the unconditioned stimulus (US). The Law of Contiguity predicts that conditioning should take place when CS and US are presented in close temporal proximity. Empirically, however, reliable occurrence of conditioning has repeatedly been observed even when CS and US are separated in time such as in trace conditioning (Pavlov, 1927) or taste aversion learning (Garcia, Ervin, & Koelling, 1966). These observations put a heavy burden on the omnipotent Law of Contiguity.

To go from bad to worse, research suggests that little or no conditioning occurs at ISIs close to zero (e.g., Bernstein, 1934) and that conditioning does not occur equally well at all ISIs. The optimal ISI is the interval at which conditioned responding is at a maximum, whereas longer and especially shorter intervals lead to lower levels of conditioned responding (reversed u-shape). The duration of the optimal ISI is influenced by several factors (for an overview see Gormezano & Kehoe, 1981), for example the response system being conditioned, gradients of inhibitory and excitatory strength along the time axis, and the proportion of reinforced and non-reinforced trials. But even if these factors are kept constant, the optimal ISI varies with the difficulty of the conditioning task. In addition, the optimal ISI is considerably smaller in reinforcement schedules with only one CS than in schedules that require discrimination between two CSs, one being paired with a US and the other one being unpaired (Gormezano & Moore, 1979; Hartman & Grant, 1962).
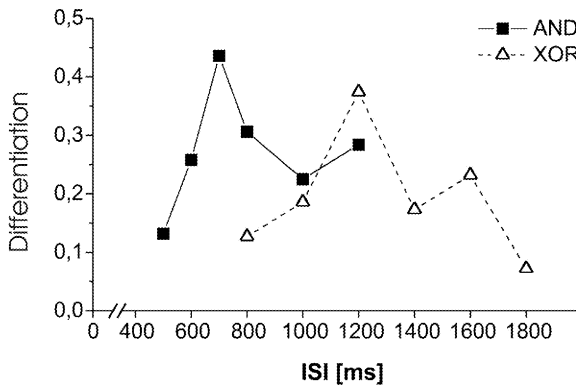
Figure 1. Asymptotic eyelid response differentiation for conjunction (AND) and exclusive disjunction (XOR) in the experiments of Kinder and Lachnit (2002). Each data point resembles response differentiation averaged across the second half of trials. (Adapted from Kinder & Lachnit, 2002).

Even more, in a differential eyelid conditioning study with humans (Kinder & Lachnit, 2002), where all the variables just mentioned where kept constant across groups, we nevertheless observed quite different optimal ISIs. There were 96 trials (48 followed by an airpuff: +; 48 without an airpuff: -) of four different CSs (combinations of dark blue letters on a white screen, e.g., A and B, being either present or absent). Two groups of participants had to solve one of two discrimination problems each, based on the logical rule of conjunction (AND: AB+, AnonB-, nonAB-, nonAnonB-) or exclusive disjunction (XOR: AB-, AnonB+, nonAB+, nonAnonB-). Although this was the only difference between groups, the optimal ISI differed by 500 ms (see Figure 1). Furthermore, even at optimal ISIs the amount of differentiation differed.

Theoretical Attempts to Retain the Law of Contiguity

One possibility to redeem the Law of Contiguity in the face of successful trace conditioning and ISI effects is to assume that a stimulus trace bridges the empty interval between the offset of the

CS and the onset of the US. From this point of view, the effective stimulus is not the distal but the proximal stimulus. In a more modern language, the contiguity principle can be saved by assuming that the mental representations of the CS and US overlap.

Along these lines, Guthrie (1935) postulated that the effective CS consists of kinesthetic and proprioceptive feedback stimuli arising from responses to the nominal CS. Due to their latency, a forward stimulus onset asynchrony is the best condition for contiguity of the feedback stimulus and the unconditioned response (UR). With this assumption, he was able to explain the superiority of a forward asynchrony compared to an IS of zero. However, he could not explain the reversed u-shape of the IS function.

Hull's (1937) suggestion was able to overcome this problem. He assumed that the onset of the CS initiates a stimulus trace that first rises in strength and then decays back to zero. He further assumed that the increment in associative strength is proportional to the trace intensity at the point of contiguity between the CS trace and initiation of the US/UR. Under this assumption the reversed u-shape is easily explained. Furthermore, the form of the ISI function may serve as an indicator of the intensity of the CS trace. As we will see later, Hull's idea is very much related to some aspects of the much younger theory of Wagner (1981).

Further Empirical Challenges to the Law of Contiguity

The modern era of conditioning started with observations that conditioning to one CS is not independent of conditioning to other CSs. Instead, what is learned about one CS strongly affects what is learned about the others. During the late sixties and early seventies of the last century, accruing empirical evidence from two lines of research – stimulus competition and contingency effects – challenged the idea that contiguity is sufficient for the establishment of associations. In a brilliant overview, Rudy & Wagner (1975) summarized findings from the first line of research with compound stimuli dealing with phenomena of stimulus selection or selective association. In the following two paragraphs we will briefly look at two of these stimulus selection phenomena, blocking and relative validity.

A typical blocking design (Kamin, 1968, 1969) consists of three phases. In Phase 1, one group of subjects is trained with a CS A followed by a US (A+) until asymptote is reached. A second group experiences no training in Phase 1. In Phase 2, both groups are trained with a compound of A and B followed by the US (AB+). In Phase 3, tests with B alone show considerable responding in the group without prior A+ training, but less or no responding in the group with A+ training. Thus, A+ training prior to AB+ training blocked conditioned responding to B alone, although B was presented in temporal contiguity with the US. The most radical conclusion from this kind of observation was to totally dismiss contiguity as a neither necessary nor sufficient condition for the development of associations and to favor informational or predictive value instead.

In a relative validity design (Lober, Lachnit, & Shanks, 2002a; Wagner, Logan, Haberlandt, & Price, 1968), two compound stimuli, AX and BX, are used. For one group of

subjects, AX is consistently reinforced whereas BX is never reinforced (AX+, BX-) so that A and B have a perfect relationship with reinforcement. For another group of subjects both compounds are reinforced on half of their respective presentations (AX+/-, BX+/-) so that A and B are uncorrelated with reinforcement. Although the schedule for X is identical in both groups, X triggers a much smaller response in the correlated group as compared to the uncorrelated group (Wagner et al., 1968). Thus, although the contiguity between X and the US was the same in both groups, conditioned responding to X varies with the relative predictive value of X compared to A and B. In the correlated group, X is a poor predictor of reinforcement compared to A or B while in the uncorrelated group all three cues are of equal predictive power.

In the second line of research, the challenge of contiguity by contingency, the relative probability of a US occurrence in the presence and absence of a CS is manipulated. This may best be illustrated by a study by Rescorla (1968) with rats in a conditioned emotional response paradigm. In this study, four groups of rats experienced a 40 percent partial reinforcement schedule: the conditional probability for US in the presence of the CS was .40, and the conditional probability for the nonoccurrence of the US in the presence of the CS was .60. Thus, CS-US contiguity was the same for all four groups. The four groups, however, differed with respect to the frequency of USs interspersed in the inter-trial interval. The conditional probability for a US when no CS was present was 0 (Group 0), .10 (Group .10), .20 (Group .20) or .40 (Group .40). Hence, contingency was varied across groups. Rescorla observed strong conditioning in Group 0, intermediate conditioning in Group .10, even weaker conditioning in Group .20, and no conditioning at all in Group .40. Taken together, the amount of conditioning clearly varied with contingency, independent of contiguity. In spite of contiguity there was no conditioning observed when the contingency was zero. Thus, Rescorla viewed the CS-US contingency but not contiguity as the critical determinant for the occurrence of conditioning.

Competition Protects the Principle of Contiguity

With these empirical departures from a strict Law of Contiguity in mind, one may assume that adequate theories of learning have to get rid of the Law of Contiguity. However, as I will illustrate with two examples, the most influential theories of learning, – so called competitional accounts – published in the seventies, retained contiguity as a necessary principle.

Despite differences in many respects, competitional theories such as the modified contiguity theory (Rescorla & Wagner, 1972; Wagner & Rescorla, 1972) and attentional theories (e.g., Sutherland & Mackintosh, 1971) assume that contiguity is necessary for the formation of associations. Both further assume that stimulus selection results from a competition between the CSs of a compound. In case of the modified contiguity theory, the CSs compete for associative strength while in case of attentional theories the CSs compete for attention.

Let us start with an outline of the theory of Sutherland & Mackintosh (1971), one example of attentional theories. First, this theory assumes that attention is a positive function not only of CS-intensity, but also of the number of previous co-occurrences of the CS and the US (i.e., contiguity). Second, attention to the CS is necessary in order to establish associative

strength, because attention allows the perceiver to learn about the CS–US relationship. Third, at any time there is a limited amount of attention. Hence, in case of a compound AB, the elements A and B compete for this limited amount of attention.

The attentional explanation of blocking, for example, is as follows. Due to the repeated pairing of A and US in Phase 1, A captures all of the attention and none is left over for B in Phase 2. When no attention is left for B, it cannot be conditioned. Therefore, the empirical observation of blocking no longer is a challenge for the Principle of Contiguity.

The modified contiguity theory (Rescorla & Wagner, 1972; Wagner & Rescorla, 1972) assumes that a change in the associative strength of a CS A is proportional to the discrepancy between reality and expectancy, where expectancy equals the algebraic sum of the associative strengths of all CSs present at the trial under consideration. It further assumes that a US can support a fixed amount of associative strength. Thus, in case of a repeatedly presented compound AB+ the associative strength accruing to A becomes unavailable for B and vice versa. The Rescorla-Wagner theory has proven to be the dominant theory of associative learning for the last three decades (see Miller, Barnet, & Grahame, 1995; Siegel & Allan, 1996).

The explanation of blocking is straightforward again. Although there is contiguity of B and the US in Phase 2, B will not be able to attain any associative strength, when A already has caught all of it in Phase 1. In such a case, A alone is able to perfectly predict the occurrence of the US.

The relative validity effect is explained as follows. Because of the fact that in the correlated group (AX+, BX- training)X is a poor predictor of the US compared to A or B, A catches most of the associative strength supported by the US and little or nothing is left for X. In contrast, in the uncorrelated group (AX+/-, BX+/- training)X has comparable predictiveness with regard to A and B, so X does not loose its potential to accrue associative strength at the expense of A and B.

In addition, the modifed contiguity theory can explain the contingency results. When USs are interspersed among CS presentations, the context itself acquires excitatory associative strength. This is due to the fact that the so-called US alone presentation is, according to the theory, a pairing of the context and the US. On CS presentations, the context and the CS form a compound and both parts of this compound compete for associative strength. In the case of Group 0, no USs are interspersed. When the compound of CS and context is paired with the US, excitatory associative strength accrues to both the CS and the context. When the context is (repeatedly) presented alone it now predicts a US, but no US occurs. Therefore, the associative strength of the context will be reduced to zero to match expectancy with reality. In case of Group .40, context presentations are paired with the US in 40 percent of all cases. Hence the context itself develops the amount of excitatory associative strength that is necessary for a correct prediction. Because reality does not change when the CS is presented together with the context (the US occurs in 40 percent, too), the CS contributes nothing beyond the prediction already made by the context alone. As a consequence, the associative strength of the CS will not be modified, i.e., it is blocked by the context.

Taken together, the empirical observations sketched in the last section do not pose a challenge to the necessity but only the sufficiency of contiguity.

Contiguity of Memory Traces

Let us now turn from theories of learning to a theory of learning and performance, which connects to the idea of stimulus traces and describes 'Standard Operating Procedures' (SOP) in memory (Wagner, 1981). As Wagner put it, SOP is a theory of automatic processing (in contrast to more flexible routines of controlled processing).

This model assumes that nodes, which consist of a number of elements, mentally represent each stimulus. Each element is in one of the following three distinct states of activation: inactivity (I), primary activity (A1), and secondary activity (A2). Furthermore, it is assumed that elements can only reside in an active state for a limited amount of time. This is due to competition with other stimuli with respect to a limited capacity of overall nodal activity. More specifically, elements in the A1 state rapidly decay to the A2 state (so called self-generated A2 representation) and then more slowly decay back to the state of inactivity. In addition to this, it is assumed that elements can only be activated directly from state I to state A1, but not from state A2 to state A1.

Conditioning is possible only when a CS is represented in the A1 state. When the CS and the US are rehearsed simultaneously (both are concurrently activated in the A1 state), a CS – US association develops. For that reason, future CS presentations will be able to excite a representation of the US from the I state directly into the A2 state (so called retrieval-generated A2 representation). In other words, contiguity of the A1 states of CS and US leads to excitatory learning. In contrast to this, inhibitory learning will take place if the US representation is in the A2 state simultaneously with the CS being in A1.

This model, too, is able to deal with the empirical challenges of the Law of Contiguity. Blocking, for example, occurs because after pretraining of A with US, the compound AB activates A and B nodes to A1 plus US nodes (directly activated by A) to A2. Hence, A1 of B and A1 of the US will not be rehearsed together. Thus, excitatory conditioning of B cannot take place. SOP also can explain the inverted u-shape of the ISI function. When the CS is presented to briefly, conditioning will be poor because there is not sufficient time for a CS representation to be activated to A1. On the other hand, when the CS is too long, A1 of the CS will already have decayed to A2, while the US is activated to A1.

In addition, SOP is able to deal with trial spacing effects. Trial spacing experiments regularly find that training trials that are spaced in time are more effective than massed trials, a phenomenon that is well known in memory research (distributed versus massed training). The contiguity of the CS and the US, however, is the same in spaced and massed training. A typical trial spacing experiment includes only one CS that is repeatedly and consistently reinforced (CS+). If the interval between CS+ presentations is short, learning usually proceeds more slowly compared to conditions where the interval is longer. According to SOP this occurs due to two

reasons. First, if the interval between successive CS+ presentations is short, it is more probable that the US representation is still in the A2 state from the previous trial. Therefore, only very few elements will be activated to the A1 state. As a consequence less excitatory learning can take place. Second, this amount of increased A2 activity of the US overlaps with A1 activation of the CS+ such that there is a considerable increase in inhibitory learning. This increase in inhibitory learning will reduce the net effect of excitatory learning or even have the consequence that the CS becomes an inhibitor (Ewing, Larew, & Wagner, 1985). Along the same line, SOP is able to explain related findings in differential conditioning with more complex discrimination problems such as positive and negative patterning. In both kinds of patterning problems, participants demonstrated better learning about reinforced stimuli when the relative amount of CS–US pairings was smaller (Lachnit, Lober, Reinhard, & Giurfa, 2002).

Back to the Significance of Contiguity for Learning

The acquisition deficit accounts of cue competition such as the Rescorla-Wagner theory have been challenged by expression deficit accounts, especially the comparator hypothesis (Miller & Matzel, 1988; Miller & Schachtman, 1985). This hypothesis can be viewed as a derivative of Rescorla's (1968) contingency model and Gibbon & Balsam's (1981) scalar expectancy theory (upon which we will touch later). The comparator hypothesis differs from its precursors in that it assumes that associations are formed according to the salience of the CS and the US as well as according to the contiguity between them. Thus, with respect to learning of associations, the comparator hypothesis clearly is a turn back to the initial Law of Contiguity. There is no competition between cues and hence no deficit in acquiring associative strength during training. Instead, there is cue competition at the time of testing. Response deficits observed at test are a failure to express an acquired association. The comparator hypothesis (for an extended comparator hypothesis see Denniston, Miller, & Matute, 1996) therefore is not a theory of learning but a theory of performance (i.e., a response rule for Pavlovian conditioned behavior).

According to the comparator hypothesis, responding to a CS does not only depend on the current CS-US association but also on the association of its comparator stimulus with the US (e.g., the training context in which the CS is learned). Excitatory behavior is predicted if the CS-US association is significantly stronger than the context-US association and inhibitory behavior is predicted if the CS-US association is significantly weaker than the context-US association. For the development of these associations it is assumed that contiguity is the only necessary requirement for strengthening associations.

The comparator hypothesis can account for the empirical observations that challenged the Law of Contiguity and led to modern associative theories of learning. And yet, learning primarily is conceptualized as a matter of contiguity. Furthermore, for several years the comparator hypothesis was unique in being supported by studies of posttraining deflation and inflation of competing cues that yielded retrospective revaluation effects. In such studies, after initial training of a compound (e.g., AB+) one element (e.g., A) is trained further (e.g., A+) while the other is not. Nevertheless, when this other element (B in our example) is tested thereafter, conditioned

responding is different from responding to B at the end of initial acquisition (weaker in our example). This advantage of the comparator hypothesis dwindled away, however, when modified acquisition-deficit accounts of cue competition (Dickinson & Burke, 1996; van Hamme & Wasserman, 1994) were also able to predict those effects. Even worse, in causal learning we (Lober, Lachnit, & Shanks, 2002b) just observed results that are at variance with the comparator hypothesis but are in agreement with the modified associative learning theories. On the other hand, the comparator hypothesis clearly is able to explain our trial spacing effects (Lachnit et al., 2002).

The Behavioral Expression of an Association Needs More Than Contiguity

Miller's comparator hypothesis clearly was a turn back to the Law of Contiguity. With the temporal encoding hypothesis (Miller & Barnet, 1993), he emphasized the importance of another aspect of time. The temporal encoding hypothesis assumes that CS – US associations are composed of more than simple links between representations of events: it suggests that the temporal relationships that exist among events are encoded as important attributes of the association, too. Thus, associations are composed of more than simple links between events.

This idea might best be illustrated by a brilliant experiment of Cole, Barnet, & Miller (1995). The authors used a conditioned emotional response paradigm in which a CS_1 lasting for 5 s signaled an aversive US (0.5 s). They hypothesized that the fear induced by the US would suppress licking of a water tube (with licking latency as the measure of the conditioned response strength). Rats either received delay conditioning with US onset exactly at offset of CS_1 (see first row of Figure 2), or they received trace conditioning with US onset 5 s after CS_1 offset (see second row of Figure 2). Half of the subjects were tested with CS_1 for suppression immediately after acquisition. Because trace conditioning is less effective than delay conditioning, the trace conditioning group should show weaker suppression than the delay group, which is exactly what was observed. The other half of the subjects, which were not tested immediately, received brief and nonreinforced backward secondary conditioning (CS_1 was immediately followed by a CS_2 that lasted for 5 s, too; see third row of Figure 2) after the initial acquisition and were tested afterwards with CS_2.

Associative learning theories – assuming only a simple link between events – predict that the group that received primary trace conditioning followed by backward secondary conditioning should show no conditioned responding to CS_2. First, this should be the case because the primary conditioning in this trace conditioning group was weaker than in the delayed conditioning group and second, because the secondary conditioning was backward conditioning, which is normally assumed to produce little or no conditioning.

The temporal encoding view is that temporal information of Phase 1 (e.g., CS_1 duration, ISI, CS_1 - US order) is encoded, and superimposed or integrated with the order and interval information of Phase 2 (e.g., CS_2 duration, CS_1 - CS_2 order), resulting in a memory representation or temporal map as illustrated in Rows 4 and 5 of Figure 2. This idea of memory blending across different phases of an experiment is consistent with theorizing about episodic memory in humans

(e.g., Metcalfe, 1990). Thus, the trace conditioning group (Figure 2, Row 5) should show strong conditioned responding to CS_2, because the offset of CS_2 exactly matches the potential onset of the US. CS_2, therefore should be a good predictor of the US. In the delay conditioning group (Figure 2, Row 4) the onsets of US and CS_2 coincide. Here, CS_2 is not a good predictor of the US and therefore should elicit much less conditioned responding.

The results of Cole et al. (1995) were clearly in contradiction to associative learning theories and in support of the temporal encoding hypothesis. They suggest that the theoretical analysis of elementary associations should incorporate timing as an important attribute of the association and not only as a determinant of associative strength. Taken together, according to the temporal encoding hypothesis, temporal contiguity between a CS and a US is sufficient for the formation of an association, but the predictive relationship between CS and US is necessary for the behavioral expression of the association.
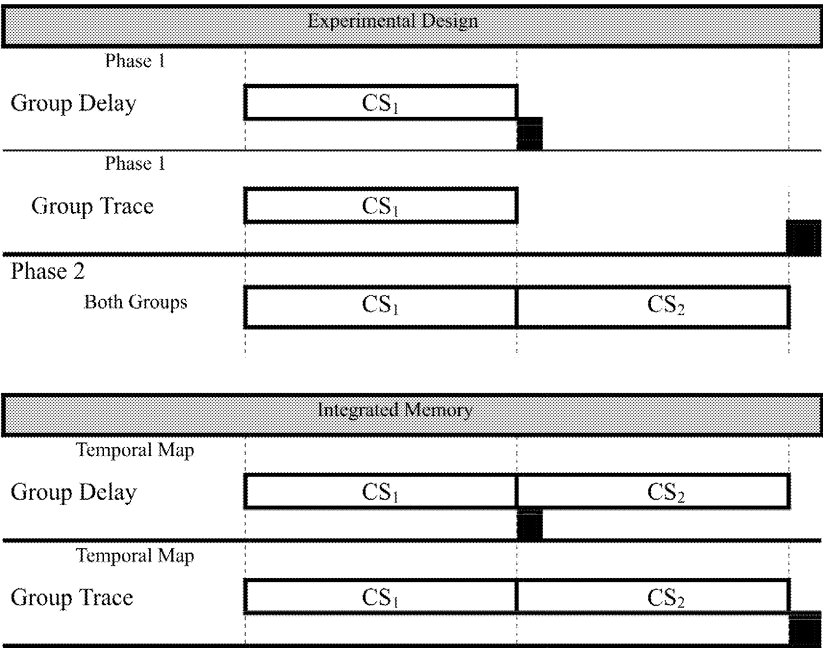
Figure 2: Diagram of the temporal arrangement (Rows 1, 2, and 3) of the experiment by Cole, Barnet, & Miller (1995) as well as of the hypothesized integrated temporal map (Rows 4 and 5). Black rectangle symbolizes the US (adapted from Cole et al., 1995).

Renouncing Contiguity in Favor of Time and Rate?

Based on an extensive literature on timed behavior (for review, see e.g., Gibbon, Malapani, Dale, & Gallistel, 1997), Gallistel & Gibbon (2000) also hypothesized that subjects in conditioning experiments store the durations of inter-event intervals in memory and subsequently recall those remembered durations (see also Gallistel, Chap.15 in this book). Gallistel and Gibbon, however, departed from the temporal encoding hypothesis in at least two fundamental ways. First, while Miller (Miller & Barnet, 1993) assumed that the formation of associations is the core process mediating conditioned behavior, Gallistel and Gibbon get along without association at all. Instead, they propose that the learning of temporal intervals (Gibbon & Balsam, 1981) and event rates is the core process in conditioning. There is no associative bond, no strengthening of connections through repetition, and no need for contiguity anymore. Second, in the temporal encoding hypothesis, expression of behavior depends on predictive relationships, whereas in the timing model remembered intervals and rates translate into behavior through decision processes. With the exception of the comparator hypothesis, associative models lack such an explicit decision mechanism. Thus, the conceptual framework of the timing model is much more similar to psychophysical frameworks of sensory processing and perception than to theories of learning (and behavior).

Gallistel and Gibbon showed that the timing theory is able to explain cue competition effects such as blocking and relative validity as well as contingency effects. Furthermore, it is compatible with the observations of Cole et al. (1995).

Future empirical and theoretical attempts will determine whether it is reasonable to declare the principle of contiguity dead in this new look at conditioning. My personal guess is that the Principle of Contiguity will rise from the dead again.

2

The Principle of Learning Based on

Multiple Brain Structures

Thomas Kress and Irene Daum

Learning in higher species is unlikely to reside in a single brain area and unlikely to be based on a single unitary mechanism. Even simple forms of experience-related changes in the brain are associated with parallel changes in multiple structures. To elucidate this principle, we will focus on a simple and well researched example of learning, namely eyeblink classical conditioning (EBCC). Since the days of Pavlov, scientists have been interested in a - superficially - simple form of learning, and it might seem surprising that only recently the complexity of EBCC in humans and other higher species has been unraveled. An emerging concept is that even the association of only two stimuli demands a range of different brain areas. Eyeblink classical conditioning is often referred to as a "model system" of the neurobiology of learning, and it is especially suitable for the illustration of the diversity of brain structures concerned with learning. The empirical evidence reported here focuses on studies in humans, but the rich data base that stems from animal work is also considered.

Classical conditioning as a Model System in the Neurobiology of Learning

Classical conditioning is one of the most fundamental types of associative learning, and conditioning procedures are the most common methods in animal research on the neuronal basis of learning (Thompson & Krupa, 1994). The most frequently investigated learning paradigm is classical conditioning of the eyelid response. The most basic form has been termed "single cue"

or "delay" conditioning. A neutral stimulus, often a tone lasting 400 to 800 milliseconds, serves as a conditioned stimulus (CS) and is paired with a brief (50 - 80 ms) corneal air-puff unconditioned stimulus (US). The air puff is delivered several hundred milliseconds after tone onset and elicits a reflexive closure of the eye. Both stimuli overlap in time and co terminate.

Repeated simultaneous presentation of CS and US leads to associative learning: the organism learns that the CS predicts the US. As the number of pairings increases, eyelid closure occurs during the CS-US interval and therefore precedes US presentation, representing a conditioned response (CR). During early acquisition, eyelid CRs observed in the CS-US interval are followed by a separate UR. Later during the course of acquisition, both responses merge into a single CR (see figure 1).
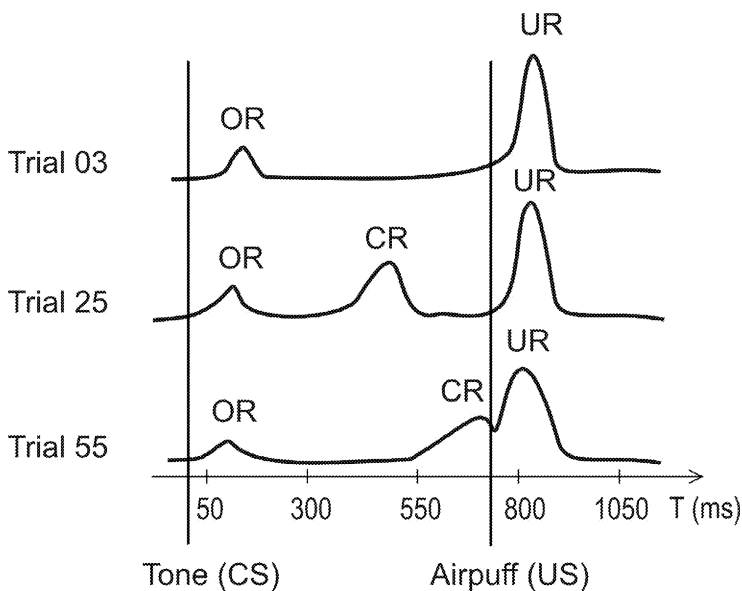
Figure 1. Typical alterations of eyeblink conditioned responses during the course of learning.

Eyeblink classical conditioning can be investigated in a very similar way in humans and laboratory animals by simple pairings of a tone and corneal air puff. During acquisition, comparable changes related to learning can be observed with respect to latency and form of the eyelid movement (Levey & Martin, 1968). During the last 15 years, an increasing number of studies has confirmed the usefulness of this paradigm for comparative neuroscience research. EBCC has been described as a "model systems to memory disorders" (Solomon, Beal, & Pendlebury, 1988) or as "model system demonstrating parallels in animal and human aging" (Woodruff-Pak, Finkbiner, & Katz, 1989). Classical conditioning is referred to as a component of non-declarative learning in the model of multiple memory systems by Squire (1987). Non-declarative learning is characterized as a slowly developing modification of behavior by

experience. It does not depend on conscious processing of the learning episode or the ability to verbalize the experience (Squire, Knowlton, & Musen, 1993). Classical conditioning fulfils the criteria for non-declarative learning better than other components as e.g., priming (see Daum & Schugens, 1995).

Further advantages of classical conditioning as a research tool in neuroscience are the high degree of experimental control over stimulus presentation, the very specific nature of the target response and the close temporal relation of responses to the eliciting stimuli. Growing evidence suggests that the rules which specify CR acquisition are comparable across species and that mechanisms of classical conditioning bear significance to more complex forms of learning (Hawkins & Kandel, 1984). Conditioning procedures normally do not place high demands on attentional control or memory systems for the retention of instructions, which permits analysis of associative learning even in patients with severe cognitive deficits.

Neuronal circuits that mediate classical conditioning have been studied extensively within the context of animal models (see Thompson & Krupa, 1994). On the basis of this large database, it is possible to derive specific hypothesis concerning the neuropsychological correlates of associative learning in humans, or as Woodruff-Pak & Steinmetz (2000) have pointed out: "The knowledge base on neural substrates and mechanisms involved in classical eyeblink conditioning make it an ideal paradigm for testing theories and brain mechanisms of memory and learning".

Neuroanatomical Basis of Delay Conditioning

The Role of the Hippocampus

Electrophysiological recordings in rabbits have consistently shown that the firing rate of hippocampal neurons is highly correlated with the occurrence and topography of eyeblink CRs (see Thompson, 1991). These findings have provided clear evidence for a hippocampal contribution to associative learning. Lesion studies, on the other hand, revealed that bilateral hippocampal damage had no detrimental effect on CR acquisition in delay or two tone discrimination procedures (Berger & Orr, 1983; Schmaltz & Theios, 1972). Interestingly, hippocampal activity was found to vanish after lesions to the interpositus nucleus of the cerebellum (Sears & Steinmetz, 1990).

In an attempt to reconcile the above reported inconsistent findings, it has been argued that plastic changes do occur in the hippocampus during the course of learning ("correlated activity"), but these changes are not necessary for the behavioural manifestation of the CR (Squire, 1987). Hippocampal activity does not seem to reflect the CS-US association per se, but may be related to the processing of other aspects of the learning situation, such as the context (Thompson, 1991). Depending on the complexity of the association to be learned, hippocampal activity may become more important for adequate CR expression, and interactions with other areas of the brain may become involved (McIntosh & Schreurs, 2000).

In accordance with animal studies, neuropsychological investigations of patients with bilateral temporal lobe damage (including the hippocampus) indicated sparing of delay

conditioning in spite of severe amnesia (Clark & Squire, 1998; Daum, Channon, & Canavan, 1989; Gabrieli et al., 1995; Weiskrantz & Warrington, 1979; Woodruff-Pak, 1993). Moreover, Schugens & Daum (1999) reported that patients with hippocampal dysfunction were not only able to acquire CRs normally, but were also able to retain CRs at a normal rate over periods of days and weeks. The functional integrity of the hippocampal system which is mandatory for the formation of new declarative memories is thus not necessary for the long-term retention of EBCC.

The Role of the Cerebellum

Cerebellar-Brain Stem circuitry. Electrophysiological recordings as well as lesion studies have indicated an essential role of the cerebellum for delay conditioning. Changes in the rate of cerebellar neuronal firing were found to predict the occurrence and topography of eyeblink CRs. Even within a conditioning trial, the behavioral eyeblink CR is preceded by an increase in neuronal activity by approximately 60 ms (McCormick & Thompson, 1984). After lesions to the cerebellar cortex, the deep nuclei or their afferents, previously learned CRs were no longer present and untrained animals showed severe acquisition deficits (see Thompson & Krupa, 1994; Yeo, 1991, for reviews). By contrast, CR acquisition was intact with US application contralateral to the lesioned side in unilaterally damaged animals. Conditioning of heart rate responses was also spared after cerebellar lesions (Lavond, Kim, & Thompson, 1993). The UR was generally found to be unaffected, suggesting that the acquisition deficit cannot simply be explained in terms of motor dysfunction (Thompson, 1991).

On the basis of experimental evidence in animals, Thompson (1991) described a model of the essential neuronal circuitry involved in EBCC. According to this model, somatosensory information on the US is projected via the inferior olive and climbing fibres to the cerebellum. Auditory projections which convey information about the CS tone are also projected via pontine nuclei and mossy fibres to the cerebellum. Information about CS and US thus merge in the cerebellar nuclei and possibly also in the cerebellar cortex. An efferent projection from cerebellar nuclei to the red nucleus and to the brainstem motor nuclei which control eye closure forms the basis of the experience-related modification of the reflex (see fig. 2).

Neuropsychological Studies in Patients with Cerebellar Lesions. In spite of the ongoing debate on the exact mechanism of the cerebellar contribution to EBCC (see (Bloedel, 1987), it is generally agreed that cerebellar damage results in pronounced acquisition deficits. The same conclusion can be drawn from a number of studies in patients with cerebellar dysfunction.

Following two single case studies of EBCC acquisition deficits of patients with ischemic damage to the cerebellum or cerebellar afferents (Lye, O'Boyle, Ramsden, & Schady, 1988; Solomon, Stowe, & Pendlebury, 1989), controlled group studies also confirmed the necessity of the functional integrity of the cerebellum for delay conditioning. Topka and colleagues (Topka, Valls-Sole, Massaquoi, & Hallett, 1993) investigated eyelid conditioning in patients with cerebellar atrophy, patients with combined damage to cerebellum and brainstem and control subjects, using a tone CS and a periorbital shock US. Both patient groups revealed a substantial acquisition deficit, whereas reflexive eyelid closure URs were intact. Daum and colleagues

(Daum et al., 1993) reported a pronounced EBCC acquisition impairment in patients with selective cerebellar lesions in a tone-air puff delay conditioning procedure. Reflex URs were spared, concomitant autonomic conditioning and electrocortical measures of associative learning were also intact in cerebellar lesion patients. This general pattern indicates that the cerebellar mediation may be specific for sensorimotor conditioning (Daum et al., 1993).
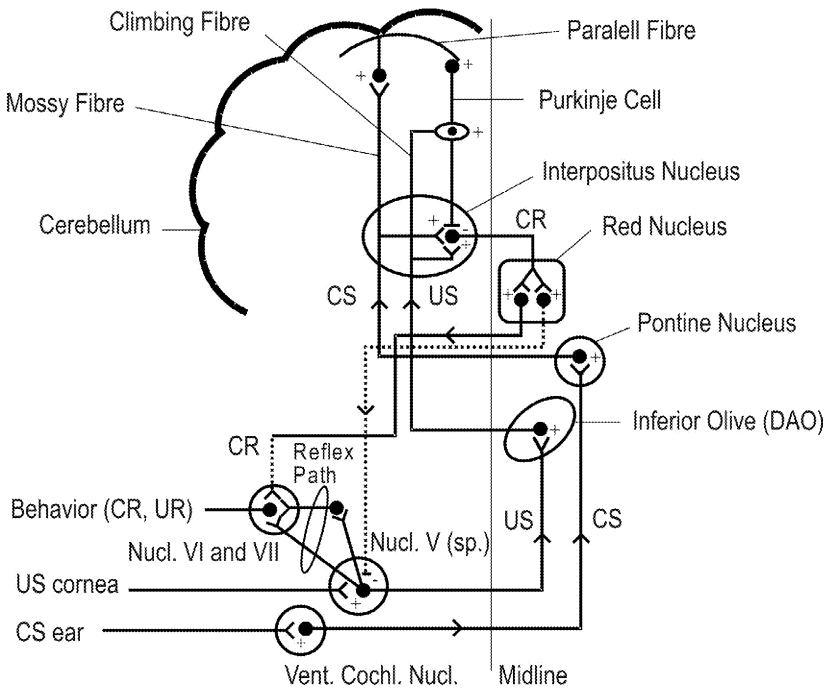
Figure 2. Circuits involved in classical conditioning of eyeblink responses. Somatosensory projections reach the dorsal accessory portion of the inferior olive (DAO) and climbing fibre projections pass on the information to the cerebellum. The tone CS pathway involves auditory projections to pontine nuclei and their mossy fibre projections to the cerebellum. The efferent pathway originates in the cerebellum and projects to the red nucleus. The descending rubral pathway acts on motor neurons in the sixth and seventh cranial nucleus (nuclei VI and VII). Additional abbreviations: Nucleus V (sp). spinal fifth cranial nucleus; Vent. coch nucleus, ventral cochlear nucleus (adapted from Thompson, 1986, 1991).

Replicating both studies described above, Woodruff-Pak, Papka, & Ivry (1996) investigated EBCC in patients with unilateral as well as bilateral lesions and normal control subjects in a tone-air puff delay procedure. Both patient groups showed a pronounced acquisition deficit; the unilateral lesion group was, however, only impaired when the eye ipsilateral to the damaged cerebellar hemisphere was conditioned.

Taken together, all neuropsychological studies in cerebellar lesion patients have yielded evidence for the hypothesis that the functional integrity of the cerebellum is necessary for EBCC. This finding has been documented across different patient samples, different types of USs, different durations of the CS-US interval and different methods of response registration techniques and therefore appears to be a very reliable observation.

In human studies the exact locus and the extent of critical lesions within the cerebellum remains to be determined. Many patients with cerebellar dysfunction are able to learn a small number of CRs. Conventional neuroradiologic data do not allow a sufficiently precise determination of lesions to permit conclusions about the differential role of nuclei vs. cortex. A general preliminary finding is that damage to the lateral cerebral hemisphere produces a milder deficit than damage to the deep cerebellar nuclei. Furthermore, the functional integrity of deep nuclei seems to be sufficient to produce a small number of eyeblink CRs (Daum, 2001; Daum et al., 1993; Woodruff-Pak, Papka, & Ivry, 1996).

Deficient Timing as the Basis for Acquisition Impairments? The cerebellar contribution to timing is frequently discussed as a potential mechanism which may underlie the EBCC acquisition impairments of cerebellar patients. Topka, Valls-Sole, Massaquoi, & Hallett (1993) proposed that poor timing of the CR prevented their patients from establishing efficient reactions to the tone; i.e. the blinks occurred too late. Woodruff-Pak, Papka, & Ivry (1996) reported that CR frequency correlated with a performance in a tapping task which was designed to assess subjects` ability to rhythmically express voluntary movements. A detailed psychophysiological analysis of CR characteristics did, however, not confirm the hypothesis that poor timing alone accounts for the acquisition deficit. When ill-timed or delayed CRs were added to those in the conventional CR time interval (about 200 ms preceding the US), a substantial conditioning deficit remained in patients with cerebellar dysfunction (Daum et al., 1993).

A recent study did, however, offer evidence that mild cerebellar dysfunction can affect CR parameters during delay conditioning. Dyslexic children with clinical evidence of cerebellar dysfunction as a group acquired CRs normally, but showed abnormal tuning of CR timing during acquisition (Nicoloson, Daum, Schugens, Fawcett, & Schulz, 2002). In the control group, CR latencies moved closer to US impact during the course of acquisition to achieve optimal air puff avoidance, CR parameters remained unchanged in the group of dyslexics. This result suggests a mild deficit in efficient CR timing associated with cerebellar dysfunction.

Studies in Healthy Subjects. Studies in healthy subjects are an important further source of evidence for the cerebellar contribution to EBCC. Temporary pharmacological manipulation of cerebellar function in humans can be achieved by the application of the non-competitive NMDA-antagonist Memantine. Memantine has a high receptor binding affinity in the cerebellum, together with a relative low affinity in the hippocampus and forebrain structures (Porter & Greenamyre, 1995). In a double-blind placebo-controlled study, a single dose of Memantine led to a significant delay in learning with lower overall CR frequency, without affecting UR characteristics or attention and memory performance (Schugens et al., 1997). The NMDA antagonist Memantine thus produces a selective deficit in associative learning in the presence of intact cognitive abilities which are not dependent on the cerebellum.

Additional evidence for the cerebellar involvement in EBCC comes from imaging studies which have consistently demonstrated cerebellar activations during acquisition (Logan & Grafton, 1995; Molchan, Sunderland, McIntosh, Herscovitch, & Schreurs, 1994; Schreurs et al., 1997). All PET-studies yielded, however, additional activations in other brain regions, e.g., the hippocampus, basal ganglia and cortical regions. These findings have been interpreted in terms of multiple representations of learned associations. Extracerebellar activations vary, however, to a great degree between studies, and their functional implications are thus unclear. Since lesions in regions activated in imaging studies do not produce a significant conditioning deficit, it is likely that the activations reflect non-essential changes. Such changes may be related to processing of the learning context or characteristics of the experimental protocol. Activation might also reflect conscious processing of stimulus and response contingencies. Schreurs et al. (1997) concluded in this regard that "learning .. may involve the interactions among a number of neural systems and … any region has the potential to play a role depending on the requirements of the task".

Another technique employed to delineate the underlying EBCC mechanisms is derived from experimental psychology and involves dual task procedures. Dual task procedures are based on the idea that a task performed in parallel to conditioning which also relies on cerebellar processing may interfere with EBCC acquisition of CR because of the recruitment of partially overlapping cerebellar structures. Tasks which are mediated by brain structures other than the cerebellum should have no detrimental effects on conditioning (Papka, Ivry, & Woodruff-Pak, 1995). This hypothesis has received confirmation in a number of recent studies. EBCC in healthy subjects was found to be compromised by parallel rhythmic tapping which depends on cerebellar function as a timing device. Other cognitive tasks such as simple reaction time tasks or recognition judgements do not interfere with conditioning (Papka, Ivry, & Woodruff-Pak, 1995). Moreover, non-declarative learning and memory task mediated by the neostriatum or the posterior neocortex have no influence on EBCC (Green & Woodruff-Pak, 1997).

The Cerebellum and Other Forms of Motor Conditioning. The EBCC model proposed by Thompson (1991) is also thought to be relevant for other forms of motor conditioning. Animal studies of impaired conditioning of the leg flexion response or avoidance learning have offered some support for this hypothesis (see Lalonde & Botez, 1990; Thompson & Krupa, 1994).

Along similar lines, Timmann and colleagues reported deficits in acquisition of conditioned leg flexion responses in cerebellar lesion patients, using a tone CS and an electric shock US (Timmann, Baier, Diener, & Kolb, 2000). In a PET study, cerebellar activation was observed during conditioning of the jaw opening reflex in humans (Maschke et al., 2000). These recently published studies thus imply a more general role of the cerebellum in motor conditioning.

The Role of the Basal Ganglia

Neuroimaging studies in humans have revealed learning-related activation changes not only in the cerebellum but also in the striatum (Logan & Grafton, 1995; Molchan, Sunderland, McIntosh, Herscovitch, & Schreurs, 1994). In animal studies, lesions to substantia nigra were found to delay

EBCC acquisition (Kao & Powell, 1986). Detailed analysis of neuronal activity in the caudate nucleus and the putamen, however, indicated a modulatory rather than a necessary involvement: the striatum is thought to influence latency and shape of eyeblink CRs via projections to brainstem and cerebellar circuits and to integrate eyeblink CRs with other simultaneously proceeding motor activities (White et al., 1994).

Parkinson's disease (PD) is associated with dysfunction of the substantia nigra and the striatum, and the study of PD patients could thus yield insights into the role of the basal ganglia in associative learning. Medicated and non-medicated PD patients were unimpaired in a learning procedure which was identical to the procedure which revealed severe deficits in patients with cerebellar disorders (Daum, Schugens, Breitenstein, Topka, & Spieker, 1996). The functional integrity of nigrostriatal circuits is not necessary for EBCC acquisition, and damage to central motor systems not including the cerebellum has no detrimental effect on EBCC.

Further evidence concerning the role of the striatum in associative learning stems from studies with patients suffering from Huntington's disease (HD). HD is a neurodegenerative disorder associated with neuropathologic changes in the caudate nucleus and cerebral cortex but also in the putamen and the globus pallidus (Grafton et al., 1990). Learning curves and CR frequency of HD patients were found to be unimpaired (Woodruff-Pak & Papka, 1996). Detailed analysis CR topographies, however, indicated shorter peak latencies in HD patients which was interpreted in terms of inefficient timing since optimal CR expression requires a response close to air puff impact on the cornea. This pattern indicates that the striatum is implicated in the modulation of CR response characteristics via projections to the brainstem and the cerebellum (see White et al., 1994). The basal ganglia may thus contribute to the exact temporal implementation of the CR.

Brain Substrates of Complex Conditioning

Cerebellar-Hippocampal Interactions

Animal studies on EBCC have yielded evidence for a significant role of the hippocampus in tasks that require the formation of more complex associations. "Complex" in this regard means that the association to be learned goes beyond simple CS-US associations as in delay conditioning (Berger, 1984; Lavond, Kim, & Thompson, 1993). Hippocampal lesions were found to result in deficits in trace conditioning, a procedure where CS and US are temporally separated by intervals of 500 to 1000 ms (Moyer, Deyo, & Disterhoft, 1990). EBCC impairments after hippocampal lesions have also been observed for reversal learning of a previously learned two tone discrimination (Berger & Orr, 1983), latent inhibition (Solomon & Moore, 1975) and sensory preconditioning (Port, Beggs, & Patterson, 1987). Kim, Clark, & Thompson (1995) and Kim and colleagues (1995) concluded that "It appears that with increasing difficulty of eyeblink tasks, the hippocampus and the cerebellum may interact, possibly via the retrosplenial cortex and the pontine nuclei… to support conditioning". The hippocampal system may influence the brainstem nuclei which mediate the CS via a multi-synaptic tract (Berger, Berry, & Thompson, 1986).
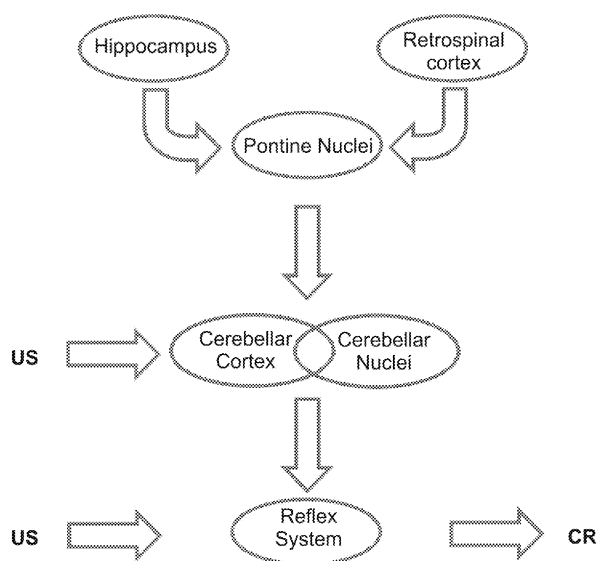
Figure 3. Hippocampal-cerebellar Interaction (adapted from Berger et al, 1986).

        The exact mechanisms of interaction between hippocampus and brainstem/cerebellum remain to be explored. Moore & Solomon (1984) have argued that the hippocampal system participates in "preventing irrelevant stimuli from acquiring control over behavior" (S. 467). A deficient reversal learning mechanism may thus be due to difficulties in ignoring a CS previously paired with the US after reversal of contingencies. Impairments in negative patterning which requires learning that two single stimuli (say A and B) are followed by an US while a combination of these two (AB) is not, have been explained along similar lines. Simulations using network models predict a pronounced deficit in EBCC negative patterning after lesions of the hippocampal system. The deficit is attributed to a lack of inhibition of CRs in trials containing the compound (AB) stimulus (Buhusi & Schmajuk, 1996; Schmajuk & DiCarlo, 1992).

Neuropsychological Studies in Patients with Damage to the Hippocampal System

Trace conditioning. As described above, trace conditioning is characterized by a temporal separation of CS and US and requires the formation of an abstract association or "trace" between these two (Pavlov, 1927). Since the hippocampus is thought to bind single elements of an information into a coherent ensemble during memory processes (Eichenbaum, Otto, & Cohen, 1992), hippocampal lesions should interfere with trace conditioning. CS-US associations in the cerebellum are formed in the range of a few hundred milliseconds; for longer gaps as in trace conditioning, additional hippocampal processing is required (Manns, Clark, & Squire, 2000).

In single case studies, two patients with bilateral damage to the medial temporal lobe region needed more trials to reach a learning criterion in a trace conditioning task than healthy controls did (Woodruff-Pak, 1993). In a controlled group study using CS-US trace intervals of 500, 750 and 1000 ms, patients with hippocampal lesions showed a severe learning deficit (McGlinchey-Berroth, Carrillo, Gabrieli, Brawn, & Disterhoft, 1997). These results would support the idea of an hippocampal involvement in trace conditioning.

Discrimination learning. The role of the hippocampus in discrimination learning was examined in a number of studies with different levels of complexity. The most simple form is two tone discrimination where tones of a certain frequency are paired with an air puff (CS+) while tones of a different frequency are always presented alone (CS-). This type of discrimination learning is unaffected by hippocampal damage (Daum, Breitenstein, Ackermann, & Schugens, 1997; Daum, Channon, & Gray, 1992). Patients with hippocampal lesions did, however, show pronounced deficits in two tone discrimination learning, when CS and US were separated by an interval of 500 to 1000 ms (Clark & Squire, 1998).

Since two tone discriminations can be learned by simply associating CS+ with US, such tasks may be relatively insensitive to hippocampal dysfunction. More complex discrimination tasks involving the formation of conditional discrimination may tap hippocampal mediation more strongly. Consistent with this idea, patients with hippocampal lesion were severely impaired in a conditional discrimination task in which a colored light was followed by tone and US combination while a differently colored light appeared with a tone without US (Daum, Channon, & Canavan, 1989; Daum, Channon, Polkey, & Gray, 1991). Patients showed CRs to the tone, irrespective of the color of the preceding light which predicted whether or not a US would follow. This deficit was accounted for as impaired learning of if-then rules or as a deficit in configural cue learning (Rudy & Sutherland, 1989).

Damage to the hippocampal region was also found to impair reversal learning of two tone discrimination (Daum, Breitenstein, Ackermann, & Schugens, 1997). After acquiring the initial discrimination in a normal way, patients learned to acquire CRs to the new CS+, but were unable to inhibit blinking to the new CS- (i.e. the old CS+). Taken together, the results described so far are in accordance with the hypothesis of hippocampal modulation of cerebellar circuits via a descending inhibitory projection (Thompson, 1991). The exact mechanisms of this modulation are still unknown. It seems likely that "the hippocampal system in humans may only modulate the expression of CRs that are generated by the cerebellum" (McGlinchey-Berroth, 2000). Alternatively it could be argued that the hippocampal system serves to inhibit the expression of a CR depending on specific task demands, e.g., the context of the CS.

Cerebellar – Prefrontal Interactions

In spite of a large number of studies on the neuronal correlates of EBCC, relatively little is known about the basis of extinction processes. It is not yet known, e.g., if extinction implies the active inhibition of a CS-US association as proposed by Pavlov (1927), if it involves loss of all, or part, of the original memory (Napier, Macrae, & Kehoe, 1992) or if it relies on formation of

an entirely new CS-noUS association that competes with the existing CS-US association (Myers et al., 1996).

Animal studies on extinction processes indicated that CRs were not shown when the cerebellum was inactivated during extinction. After the pharmacological effect had worn off, CRs reappeared. The subsequent extinction process was entirely normal (Hardiman, Ramnani, & Yeo, 1996). This pattern suggested that extinction produces plastic changes in the same cerebellar circuits that are also responsible for acquisition. This hypothesis was at least partly supported by data from a PET study in which healthy control subjects showed a correlation between cerebellar activation and CRs during acquisition and extinction. While cerebellar activation increased during acquisition, it decreased during extinction, i.e. activation changes followed CS-US contingencies (Schreurs et al., 1997). Comparable activation changes were, however, also observed in the prefrontal and the superior temporal cortex.

Alternative views suggest that acquisition and extinction depend upon different neuronal structures. According to these views, the representation of the learned response is preserved and the behavioral phenomenon of extinction is accomplished through cortical structures taking control over the subcortical structures responsible for acquisition (see Hugdahl, 1998). An important structure that exerts modulatory influence on the CR circuits of cerebellum and brainstem is the hippocampal system (see above). However, it seems unlikely that this structure plays a major role in extinction since hippocampal lesions did not lead to extinction impairments, neither in clinical nor in animal studies (Berger & Orr, 1983; Daum, Channon, & Gray, 1992; Schugens & Daum, 1999).

Apart from the hippocampus the prefrontal cortex (PFC) has been discussed as a structure which may control subcortical CR circuits. As described above, Schreurs et al. (1997) reported inverse activation changes in acquisition and extinction in the PFC. Along similar lines, a PET-study by the same research group (Molchan, Sunderland, McIntosh, Herscovitch, & Schreurs, 1994) yielded significantly enhanced activations in the PFC during extinction. This activation is sought to reflect the alteration of the of the associative meaning of the CS tone during extinction. Similar conclusions were drawn by Hugdahl and colleagues (1995) in a PET-study on classical conditioning of electrodermal responses. The exact loci within the PFC vary among studies, most frequently inferior frontal regions are implicated, and less consistently dorsolateral regions.

As described above, PET-studies have yielded activation changes of different brain regions, while their specific role in learning processes remains unclear. A suitable tool to distinguish between "essential" and "correlated" activity (Thompson, 1991) are lesion studies (see Daum & Schugens, 1995). CR circuits in cerebellum and brainstem are not only connected with motor cortex by a multisynaptic pathway but also via reciprocal connections with the PFC (Schmahmann, 1991) which might therefore be a possible substrate for a cortical modulation of subcortical circuits. Selective lesions of motor and prefrontal cortex had no detrimental effects on extinction in the rabbit (Ivkovich & Thompson, 1997), there are as yet no clinical data on the effect of PFC lesions in humans on extinction.

In a study by Kress & Daum (2002), extinction processes were examined using dual task procedures. After a delay conditioning acquisition phase which was identical in both groups,

subjects either had to carry out a verbal fluency task or to read aloud words appearing on a screen. The verbal fluency task is known to depend upon the functional integrity of the PFC. Subjects of the verbal fluency group showed more CRs and a reduced extinction speed relative to the control group. These findings support the hypothesis of a putative role of the PFC in extinction.

Recent Developments

One of the most promising developments of neuroscience research is the application of network models to associative learning in the field of eyelid conditioning. These models are especially useful in explaining empirical data and making predictions for learning under varying circumstances as well as to elucidate dynamic interactions between different brain areas during learning (see Schmajuk, 2000). A further direction is the investigation of EBCC in patients with neurogenetic disorders which preferentially affect cerebellar nuclei or the cerebellar cortex; findings from such studies should offer important insights into the differential contribution of different cerebellar structures to associative learning.

Conclusion

In conclusion, findings of neuropsychological EBCC research have made an important contribution to the understanding of the mechanisms of simple associative learning. An important recent development is the investigation of dynamic interactions between different brain areas during tasks of different complexity in preference to research strategies which focus on the potential involvement of a single brain area. It is to be expected that taken together, the results from the converging research methods of neuropsychology (lesion studies, functional imaging, pharmacological studies) will lead to a better understanding of the functioning of the brain as a system during associative learning.

3

The Principles of Brain Plasticity

Brigitte Röder & Frank Rösler

The capability of the central nervous system (CNS) to adapt its functional and structural organization to current requirements is known as neural plasticity. Such changes can be examined at different organizational levels of the CNS; changes at the molecular-, synaptic-, neural-, system-, and behavioral level are mutually dependent (Shaw & McEachern, 2001). Plastic changes are triggered by learning, e.g., perceptual and motor training and by injuries, e.g., a deafferentation of parts or of all afferents of a sensory system. Moreover, the capacity to change is a characteristic feature of the CNS throughout life although there are qualitative and quantitative differences between developmental and adult plasticity. This chapter reports major findings on training- and lesion-induced plasticity. Results from animal and human research in the somatosensory, auditory, visual and motor system are reviewed and the possibly mechanisms underlying brain plasticity are discussed. Moreover, possible differences between developmental and adult plasticity are considered.

Training-Induced Plasticity

The first cortical processing stages of sensory systems are arranged in topographically organized maps. For example, the somatosensory cortex has a somatotopically organized representation of the body surface known as the "homunculus", i.e., adjacent skin areas are represented in vicinity in the postcentral gyrus (the site of the primary somatosensory cortex). There are characteristic distortions within this map, e.g., the representation of the hands and the lips are magnified. These protuberances within the sensory representations go together with smaller receptive fields and

result in a higher spatial resolution. Similar topographically organized maps exist for the motor system (in the precentral gyrus), the visual system (retinotopically organized maps in the occipital lobe) and the auditory system (cochleatopically or tontopically organized maps in the superior temporal gyrus). Although the rough structure of these maps is genetically determined, their final organization is shaped by experience (Zhang, Bao, & Merzenich, 2001). The general organization of sensory maps can be understood as an evolutionary grown adaptation to the average requirements associated with the most probable environment. As is shown in the following, the CNS keeps the ability to adapt the functional organization of sensory representations to new demand profiles throughout life.

Somatosensory System

For example, in a study of Jenkins, Merzenich, Ochs, Allard, and Guíc-Robles (1990), monkeys had to keep contact with a rotating grooved disc, most often with finger two but sometimes with the adjacent fingers as well. The authors found an exaggerated neural representation of the stimulated skin areas (see figure 1) and receptive fields were unusually small, reflecting a finer grain spatial resolution.
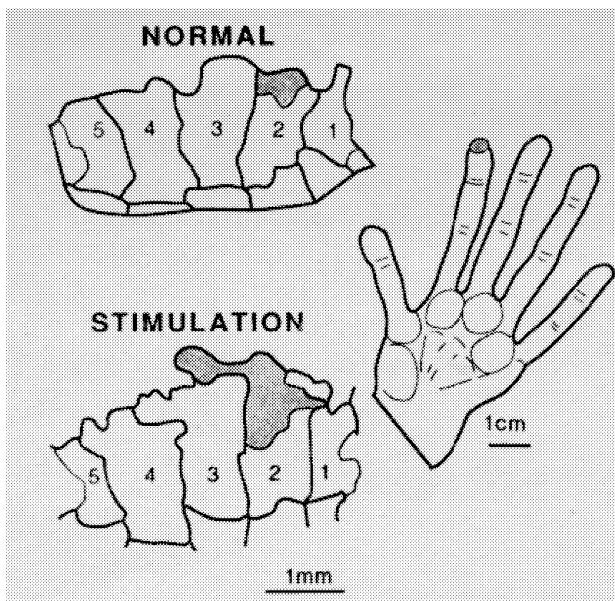
Figure 1. Somatosensory representations of a monkey's digits in primary sensory cortex before and after training. The representation of the most often used finger (digit 2) enlarged most. (From: Jenkins et al., 1990).

        A prerequisite for adult plasticity to occur seems to be the behavioral relevance of the triggering input. This is impressively demonstrated by a series of tactile training studies in monkeys (Recanzone, Jenkins, Hradek, & Merzenich, 1992; Recanzone, Merzenich, & Dinse,

1992; Recanzone, Merzenich, Jenkins, Grajski, & Dinse, 1992). Vibrotactile stimuli were applied to a particular skin area. The monkey was rewarded for the detection of stimuli that had a frequency higher than a 20 Hz standard stimulus (Recanzone, Jenkins, Hradek, & Merzenich, 1992). Behaviorally, the authors observed a decrease of the discrimination threshold from 6-8 Hz to 2-3 Hz. After several weeks of training the cortical representation of the trained skin segment was enlarged by a factor of 1.5 to 3 (Recanzone, Merzenich, Jenkins, Grajski, & Dinse, 1992) (note that the absolute size of the representational area of the trained fingers did not change). Since the size and the overlap of receptive fields increased, other or additional mechanisms must have contributed to behavioral improvements. The authors suggested that the relevant stimulus feature (the frequency of the involved vibrotactile stimuli) became more and more distinctly represented in the somatosensory cortex. Indeed, they found an increased synchronized activity across a larger number of cell assemblies (Recanzone, Merzenich, & Schreiner, 1992). Importantly, comparable changes were not observed in animals that received the same tactile stimulation but were engaged in an auditory discrimination task (i.e., during passive stimulation).

A natural analog of these findings is the observation that the sensory representation of the trunk surface containing the nibbles of nursing female rats is exaggerated in comparison to non-nursing rats and, moreover, the RF-size is reduced by up to 70 percent (Xerri, Stern, & Merzenich, 1994).

The increasing availability of more sophisticated electrophysiological and brain imaging techniques has made it possible to investigate training-dependent plasticity in humans as well. There are two main approaches to this issue: (1) The retrospective approach investigates people who have a history of specific perceptual training, e.g., blind people (Röder & Rösler, 2002) or musicians (Münte, Altenmüller, & Jäncke, 2002). (2) In longitudinal studies people are repeatedly examined while they are engaged in a perceptual training program.

An example of the retrospective approach is the investigation of tactile skills in the blind: It has been hypothesized that blind people should display enhanced tactile skills, because they rely more than sighted people on the use of their haptic sense. In particular, reading Braille, the tactile writing system of the blind, requires a very finely grained tactile resolution. Indeed blind professional Braille readers, when compared to sighted non-Braille readers, show lower tactile two-point discrimination thresholds (Röder & Neville, 2002, see Figure 2) and elevated tactile hyperacuity (Grant, Thiagarajah, & Sathian, 2000; Van Boven, Hamilton, Kauffman, Keenan, & Pascual-Leone, 2000). By contrast, there are hardly any reports on absolute sensitivity differences between blind and sighted adults (Axelrod, 1959; Röder & Neville, 2002). That the blinds' superiority is in fact due to the intense use of their tactile sense is suggested by the findings of van Boven et al. demonstrating that after some practice their sighted participants were able to catch up with the blind participants. Nevertheless, a particular advantage for tactile learning due to visual deprivation can not be excluded (Kauffman, Théoret, & Pascual-Leone, 2002). Using somatosensory evoked potentials (SEPs) and transcranial magnetic stimulation (Pascual-Leone et al., 1993) provided evidence for an enlargement of the representational area of the Braille reading finger, which, moreover, depended on recent experience (Pascual-Leone, Wassermann, Sadato, & Hallett, 1995). For example, Pascual-Leone et al. (1993) applied electric stimuli to reading and non-reading fingers of professional Braille readers. The N20 and P22 of

the somatosensory evoked potentials (i.e., deflections indicating the first cortical processing stage of tactile input) were recorded with a close to maximum amplitude from a larger scalp area after stimulating the reading finger, as compared to the non-reading finger or after applying electric pulses to any finger in non-Braille-reading controls. Correspondingly, transcranial magnetic stimulation (TMS) at a larger number of scalp sites suppressed the detection of tactile stimuli at the reading finger as compared to the non-reading fingers (Pascual-Leone et al., 1993). Moreover, in simple tactile discrimination tasks shorter reaction times were found for blind people which were accompanied by shorter latencies of early event-related potentials (Röder, Rösler, Hennighausen, & Näcker, 1996), indicating that the sensory cortex of the blind may change its processing efficiency due to perceptual training (for example, Braille reading).

Two-point Thresholds
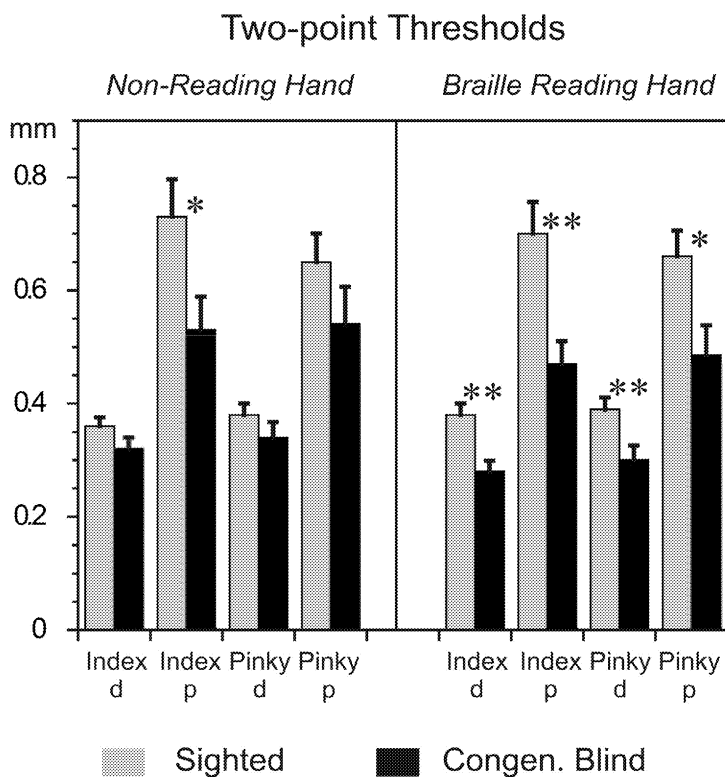
Figure 2. Tactile two-point thresholds for the index and little finger (both the distal (d) and proximal (p) part) of the non-reading and reading hand of congenitally blind professional Braille readers (black bars) ad the non-dominant and dominant hand of matched sighted controls. Braille readers have lower two-point thresholds at their reading hand. (From: Röder & Neville, 2002).

Similarly, research suggests that the cortical representations associated with a string player's (left) fingering hand, change (Elbert, Pantev, Wienbruch, Rockstroh, & Taub, 1995). Interestingly, these changes (increased dipole strength) were the larger the earlier the string players had started to play their instrument, pointing towards differences in the amount of cortical map plasticity during development and adulthood periods (see below section: Differences between developmental and adult plasticity).

Compared to the retrospective approach, a longitudinal approach to studying the neural correlates of perceptual learning has several advantages. First, participants can be selected randomly. Second, it is possible to exactly control the amount of practice. Finally, it is possible to study the time course of learning and the accompanying neural changes. The major disadvantages of longitudinal studies are the immense effort required for investigation, and the fact that the amount of perceptual training that is experienced by blind people or musicians is hard to match. An improvement of tactual acuity due to practice has, similar as in Van Boven, Hamilton, Kauffman, Keenan, & Pascual-Leone (2000), been demonstrated for tactile hyperacuity tasks (Sathian & Zangaladze, 1998) and texture discrimination tasks (Sathian & Zangaladze, 1998). Braun, Schweizer, Elbert, Birbaumer, & Taub (2000) presented horizontally arranged dot patterns to the index and little finger of one hand. The middle of three dots either was displaced to the left or to the right. The task of the participants was to indicate the direction of the middle dot. Using high density electroencephalographic recordings Braun et al. provided evidence for an increasing distance between the cortical representations of the participants' index and little finger when active discrimination was required. By contrast, under passive stimulation the reverse was observed. Interestingly, the latter was accompanied by the participants having increasing difficulty in localizing near threshold tactile stimuli with their hands. Similar mislocalizations were reported in Braille readers who used more than just one finger to read Braille (Sterr et al., 1998) suggesting that similar changes of perceptual learning induced plasticity are investigated with the retrospective and longitudinal approach.

Auditory System

In order to extract general principles of training-induced plasticity more than one modality system has to be investigated. Recanzone, Schreiner, and Merzenich (1993) ran similar studies in monkeys with auditory stimuli as they had done with tactile stimuli (see previous section). Monkeys were rewarded for detecting frequency differences between two successively presented tones. Continuous behavioral improvements were accompanied by an enlargement of the primary auditory cortex representation that corresponded to the trained frequencies. Moreover, these neurons displayed steeper frequency tuning curves. Again, these changes were neither seen in untrained controls nor in animals that had received the same auditory stimulation as the experimental group but who had been engaged in a tactile discrimination task. Corresponding neural changes have been reported in guinea pigs using a conditioning procedure (Weinberger, Javid, & Lepan, 1993; Weinberger et al., 1990).

To study auditory map plasticity in humans, both the retrospective and longitudional approaches have been employed. For example, magnetoencephalographic recordings in blind humans have revealed an enlarged tonotopic representation (personal communication, Thomas

Elbert, April 2002), which may be related to the higher reliance of blind people upon hearing in general and superior speech perception skills in particular (Röder, Demuth, Streb, & Rösler, 2002; Röder, Rösler, & Neville, 2000). Moreover, shorter latencies (Röder, Rösler, Hennighausen, & Näcker, 1996) and shorter refractory periods for the auditory vertex potential were observed for congenitally blind participants as compared to matched sighted adults (Röder, Rösler, & Neville, 1999). Since refractory periods are most likely related to the excitability of sensory cortices, the latter finding was interpreted as evidence for an enhanced excitability of the auditory cortex in the blind. At the behavioral level, the blind participants displayed superior auditory discrimination times in both studies. These findings are consistent with those for musicians who, compared to non-musicians, displayed enhanced responsiveness (larger dipole moments fitted for the magnetic N1 equivalent) to piano tones (Pantev et al., 1998). Consecutive studies confirmed these results and extended them by showing that the enhancement is specific to the primary instrument played by a musician (Pantev, Roberts, Schulz, Engelien, & Ross, 2001). Importantly, it is possible to elicit similar changes by auditory perceptual training: Menning, Roberts, and Pantev (2000) employed a 15 day training distributed over three weeks. Participants had to compare tones with a 1000 Hz standard stimulus. Discrimination thresholds decreased over the time course of training and MEG recordings revealed an accompanying increase in the source strength of the N1 wave and the so called mismatch negativity, which has been associated with a pre-attentive deviant detection. Analogous results due to training have been reported for speech stimuli (Kraus et al., 1995).

Visual System

In animals, training-induced plasticity has less often been studied in the visual than in the remaining sensory systems. Results are, however, consistent with the principles guiding reorganizations as unraveled in the somatosensory and auditory systems. For example, by artificially manipulating the depolarization level of visual neurons during visual stimulation (Fréganc, Shulz, Thorpe, & Bienenstock, 1992; Shulz & Fréganc, 1992), researchers were able to change the orientation selectivity and ocular preference of neurons in V1. Schoups, Vogels, Qian, & Orban (2001) made use of the fact that visual perceptual learning is locally highly specific. They presented small oblique gratings of a particular orientation to one retina location. The monkeys had to discriminate these gratings. A second retina location was passively stimulated with a different grating in the same animals. Over the time course of several weeks the authors report marked behavior improvements that were accompanied by a sharpening of the corresponding orientation tuning curves for the trained (but not passively stimulated) V1 neurons. In contrast to perceptual training experiments with auditory stimuli (see previous section), neither a peak shift nor an expansion of the number of cells encoding the trained orientation were observed. The lack of cortical map expansion of a trained retinal location was confirmed using a three line bisection task (Crist, Li, & Gilbert, 2001). Surprisingly, in the latter study orientation selectivity and receptive field properties of V1 cells did not change either. Rather the authors observed that the presence of additional lines modulated the firing rates of deafferented neurons during learning. Therefore, the firing pattern of a larger number of cells (cell ensembles), rather than the response properties of single neurons, change as a function of perceptual learning.

Research suggests that deaf people display enhanced visual processing skills in order to compensate for the lack of auditory input, much as blind people display augmented auditory and somatosensory skills. While there is (corresponding to the findings in the blind) hardly any evidence for absolute visual threshold differences between deaf and hearing people (e.g., Bross, 1979; Bross & Sauerwein, 1980; Finney & Dobkins, 2001), deaf people do demonstrate processing differences. They show faster processing of peripherally presented visual stimuli (Bosworth & Dobkins, 2002; Neville & Lawson, 1987) and faster recovery of early visual potential shifts (Neville, Schmidt, & Kutas, 1983). The latter finding mirrors the shorter refractory periods of early auditory event-related potentials in the blind.

In contrast to the few animal studies on the neural correlates of visual perceptual learning, the human behavior literature on this issue is quite extensive. Visual search tasks (Ahissar, Laiwand, Kozminsky, & Hochstein, 1998; Karni, 1996; Karni & Sagi, 1993), hyperacuity paradigms (Fahle, 1997; Fahle, Edelman, & Poggio, 1995; Poggio, Edelman, & Fahle, 1992), and gating and movement discrimination tasks (Wijers et al., 1987), have been employed. For example, people are able to learn an offset between two lines that is no larger than 0.1 degrees of visual angle. This is by far smaller than the resolution of the retinal photoreceptors and has been termed hyperacuity. Visual perceptual learning is very specific and improvements of venier acuity does not generalize to other tasks such as curvature or orientation discrimination (Fahle, 1997), nor to other retinal locations, nor to the other eye, although the latter result was not always confirmed (Schoups, Vogels, & Orban, 1995). The degree of learning specificity in the visual system seems to be a function of task difficulty and attention (Ahissar & Hochstein, 1997); Ahissar & Hochstein, 2000): The more difficult a task, the narrower the focus of spatial attention and the more locally specific the training effects.

Motor System

As sensory representations change as a function of use, cortical representations of muscles engaged in training expand as well (Nudo, Milliken, Jenkins, & Merzenich, 1996). This is nicely demonstrated by the observation that the cortical representation of the dominant hand is larger and more complex than that of the non-dominant hand (Nudo, Jenkins, Merzenich, Prejean, & Grenda, 1992). In humans, an enlargement of the motor representations of muscles involved in moving the hand when reading Braille has been detected in blind Braille readers (Pascual-Leone et al., 1993) and a higher excitability of the motor cortex was reported for musicians (for a review see Münte, Altenmüller, & Jäncke, 2002). These results were drawn from preexisting populations. Karni et al. (1995) used a finger-opposing task to investigate the time course and neural basis of motor learning in humans. Over three weeks of training, participants learned to tap the training sequence faster and more accurately. These improvements were restricted to the trained hand and sequence. Correspondingly, functional magnetic resonance imaging (fMRI) revealed an enlarged cortical representation of the learned sequence only (Karni et al., 1995).

Effects of enriched environments

Structural changes of the CNS due to environmental alterations have been investigated with enriched vs. impoverished environments. "Enriched" means that animals are exposed to different kinds of stimulation that provide ample opportunities for learning. Such environments (as compared to impoverished ones) are related to thicker and heavier cortices, a more extensive branching of dendrites, a larger number of dendritic spines, the latter two facts indicating a denser wiring (Black, Jones, Nelson, & Greenough, 1998; Turner & Greenough, 1985; (Rosenzweig & Leiman, 1982). Anatomical plasticity is not restricted to the developing system; enriched environments elicit similar though smaller (Black, Jones, Nelson, & Greenough, 1998) and qualitatively somewhat different anatomic changes (Kolb & Gibb, 2001), in adult animals (Green, Greenough, & Schlumpf, 1983). At the behavioral level these changes correlate with faster learning, particularly in more complex tasks (Black, Jones, Nelson, & Greenough, 1998).

Mechanisms

In sum, perceptual and motor learning are accompanied by a change of sensory maps associated with the trained sensory epitheliae. The reorganization consists of a strengthening and enlargement of cortical representation as well as a change in the processing efficiency. Gilbert, Sigman, and Crist (2001) discuss several mechanisms through which learned information is represented in the brain, i.e. principles of brain plasticity accompanying perceptual learning. The population code idea assumes that a given neuron participates in the encoding of different attributes. The conjoined activity of many neurons (i.e., cell ensembles) and the relative firing strength of each neuron encodes a particular stimulus feature. If it is possible to recruit more neurons, the ensemble will encode these stimulus attributes in finer grain. Alternatively, the same goal is achieved by sharpening the tuning of cells. The latter results in a relatively larger firing rate change when a stimulus attribute shifts. Therefore, steeper tuning curves of neurons are able to encode a given stimulus feature (e.g., orientation, spatial position) with the same resolution but with relatively fewer neurons or to represent the attribute with a higher precision using the same number of (or even more) neurons (Fitzpatrick, Batra, Stanford, & Kuwada, 1997). Accordingly, motor sequence learning has been shown to lead to an enlarged cortical representation only during an initial learning phase (Pascual-Leone et al., 1999).

Furthermore, it is possible to enhance the efficiency of encoding by changing the temporal firing patterns both among neurons and with respect to the stimulus. As an additional possibility Gilbert, Sigman, and Crist (2001) discuss a change of the locus that represents the trained stimulus. For example, in visual search stimuli defined by a combination of two features have to be searched in serial rather than in parallel (Treisman & Gelade, 1980). Transcranial magnetic stimulation studies have shown that serial visual search depends on an intact right parietal lobe (Walsh, Ashbridge, & Cowey, 1998). After considerable training, the serial search mode turns into a parallel one and a deactivation of the right parietal cortex no longer disrupts task performance (Walsh, Ashbridge, & Cowey, 1998), indicating that structures other than the right parietal cortex mediate (parallel) visual search now.

The Hebb rule has been suggested as the overall guiding principle of sensory map plasticity and learning in general: If activity of a pre- and postsynaptic neuron is correlated, the connection will be strengthened, while if it is uncorrelated the connection will be weakened. Hebbian plasticity has been associated with long-term potentiation (LTP) and long-term depression (LTD) (Cain, 2001; Teyler, 2001; see Schwarting in this volume for details). For the case of a restricted number of channels, Gilbert, Sigman, and Crist (2001) and Stemmler (1987) propose the activity of a so called anti-Hebbian rule (Barlow & Foldiak, 1989, in Gilbert, Sigman, & Crist, 2001). This principle expresses the idea that neurons within an ensemble try to decorrelate their activity by removing information that is shared by different stimuli and enhancing their response to features unique for a given stimulus ("orthogonalization of representations", see sharpening of the tuning of a cell). Such an effect is impressively demonstrated by patients whose webbed fingers were surgically separated (Mogilner et al., 1993). After the operation, the fused, i.e., non-somatotopic cortical representation segregated.

In addition to these *physiological* changes *anatomical plasticity* (changes in the number and form of synapses, size of cell somata and dendritic trees) finally contributes to a stabilization of changes, provided the new requirements exist for a longer time epoch (Kolb & Wishaw, 1990).

Moreover, the fact that behavioral relevance and attention modulates or exaggerates cortical map plasticity points towards a modulating influence of additional brain regions. For example, a stimulation of the cholinergic nucleus basalis can alter cortical map reorganizations, including RF-reorganizations in A1 (e.g., refined or degraded responsiveness; Kilgard & Merzenich, 1998a, b). It has been hypothesized that the activity of basal forebrain structures marks behavior relevant stimulation. Similarly, a simultaneous electric stimulation of the mesencephalic reticular formation (MRF) enhances the response synchronization of the visual cortex cells, which have been considered to be important to increase stimulus salience (Munk, Roelfsema, König, Engel & Singer, 1996). Finally, feed-forward/feedback loops running through the thalamic reticular nucleus may mediate attention effects upon use-dependent reorganizations (see below, Guillery, Feig, & Lozsádi, 1998; Kaas, 1999; Yingling & Skinner, 1976).

Although some use-dependent reorganizations seem to be maladaptive (see mislocalizations of tactile stimuli in Braille readers or acquired focal dystonia in musicians) most of the changes observed in the time course of perceptual training correlate with behavioral improvements and seem therefore to be functionally adaptive. Intramodal plasticity accompanying perceptual learning guarantees a continuous adaptation of the nervous system to environmental changes.

Lesion-Induced Plasticity

The central nervous system can suffer either direct or indirect injuries. While in the first case CNS tissue itself is damaged, in the second case CNS structures remain intact, but are deprived of input either by deafferentation or deprivation. A deafferentation may be partial, e.g., a limb is amputated or a local part of the retinal is damaged, or it may be complete as in totally blind or profound deaf individuals. First, intramodal plasticity after partial deafferention is reviewed, i.e.,

changes taking place in the brain structures primarily linked to the deafferented inputs. Second, cross-modal plasticity after the total loss of input from one sensory modality will be discussed.

Intramodal Plasticity after Partial Deafferentiation

Sensory representations and their variations across different individuals of a species may be understood as an evolutionarily grown average that represents the optimum adaptation to the expected environment. In this context, perceptual learning is thought to change the emphases in neural networks, i.e. behavioral relevant stimuli gain salience. These changes may be considered to be the natural scatter around a mean representation. A much more profound disruption of the sensory map balance is caused by deafferentation because parts of a neural network are suddenly separated from their input. Such instances raise the question of how the unused neurons are integrated in the remaining system and what the behavioral consequences of such reorganizations are.

Somatosensory and Motor System. Many different types of deafferentations have been investigated in the somatosensory and motor systems (Kaas, 2001; Merzenich & Jenkins, 1993). For example, cutting the median nerve, which serves the glabrous skin of the thumb, index finger, half of the middle finger and parts of the palm, removes the input of a large cortical region of the hand representation. The deafferented neurons start to develop RFs for rear hand regions. The initially large and overlapping RFs continuously shrink and organize topographically, that is, after several weeks the cortical territory that had formally represented the innervation zone of the medial nerve now responds to stimuli of the rear side of the thumb, index and middle finger as well as to the rear hand and new regions of the palm (Merzenich et al., 1983). Similarly, after amputating digit 3, the cortical region formally associated with this digit becomes occupied by the adjacent digits. Interestingly, the new representational area has smaller RFs indicating a finer grained representation of digit 2 and 4 (Merzenich & Jenkins, 1993). Such lesion-induced cortical map changes can be extensive. Pons et al. (1991) observed that S1 neurons normally associated with the monkey's arm responded to stimuli at the face 12 years after the deaffentation of the arm; this corresponds to a change spanning a distance within the cortex as far as 10 to 14 mm.

Corresponding results have been reported for the motor system, e.g., cutting the motorneurons that control the movements of the vibrissae in rats results in a take over of the associated motor cortex units by adjacently represented muscles, i.e., those controlling eye and forelimb movements. As a consequence, a stimulation of the former vibrissae area triggered movements of the eyes and forelimb (Sanes, Suner, & Donoghe, 1990, in Kaas et al., 1990).

While it is difficult or even impossible to study the subjective correlates of lesion induced plasticity in animals, behavioral reports are easy to obtain in humans. Approximately 70 percent of all amputees report permanent phantom sensations (Katz, 1992). Non-painful phantom limbs (e.g, tingling, temperature, movement sensations etc.) have been distinguished from painful phantom sensations (e.g., cramps). This categorization has been suggested by different neural changes observed in the two patient groups (Grüsser et al., 2001, see below). First, neurophysiological investigations in amputees have demonstrated similar massive re-

organizations as have been found in primates with deafferented limbs (Elbert et al., 1994; Yang et al., 1994). These reorganizations did not necessary correlate with the presence of double sensations (when the face is touched the participant experiences an additional sensation at the amputated limb, called "referred sensation"). Rather, the amount of reorganization was correlated with the degree of experienced phantom pain (Flor et al., 1995). These initial findings have recently been replicated and extended to the motor cortex (Karl, Birbaumer, Lutzenberger, Cohen, & Flor, 2001; Lotze, Flor, Grodd, Larbig, & Birbaumer, 2001). For example, Lotze et al. (2001) had upper limb amputees execute movements with their intact arm and their lips and found (using fMRI) that lip movements activated regions in the somatosensory and motor cortex that are normally associated with the arm. However, this was true only for patients with painful phantom limbs. Interestingly, when these patients imagined moving their lost limb, they did not only show higher activity within the contralateral somatosensory and motor cortex but also in the adjacent face area. If phantom-pain is indeed linked to cortical reorganizations, (a) treatments that attenuate phantom limb pain should also influence the extent of cortical reorganizations and (b) counteracting lesion-induced reorganizations should reduce phantom-limb pain. Evidence for both assumptions have indeed been reported. Opiate medication reduced subjectively perceived pain intensity in patients with a painful unilateral upper or lower limb amputation and, moreover, using magnetoencephalographic recordings, a reduced extent of cortical reorganization was found (Huse, Larbig, Flor, & Birbaumer, 2001). Flor, Denke, Schaefer, and Grüsser (2001) employed a somatosensory discrimination training in patients with intractale phantom limb pain at the amputation stump and compared those with a control group receiving a 'standard' treatment including medication, transcutaneous nerve stimulation and physiotherapy. Results showed a reduction of both discrimination thresholds and pain intensity in the first group, which were accompanied by a reduction of lesion-induced cortical reorganizations. These results fit well with the observation that using a myoelectric rather than a cosmetic prosthesis can prevent both, the development of phantom limb pain and lesion induced cortical reorganizations (Lotze et al., 1999).

   Auditory system. Robertson & Irvine (1989) lesioned part of the cochlea in guinea pigs. Immediately after the lesion they observed that neurons in A1 formally associated with the lesioned cochlea area became responsive to lesion edge frequencies. Although firing thresholds were initially higher they decreased to normal during the consecutive months (for a review see Irvine, 2000).

   In humans direct evidence for injury-related reorganizations in the auditory cortex is sparse. Pantev, Wollbrink, Roberts, Engelien, and Lütkenhöner (1999) functionally deprived a cochlea region by exposing participants for three hours on three days to music in which the frequencies centered around 1 kHz were cut out. Using magnetoecephalographic recordings the authors observed a reduced responsiveness to band pass noise bursts centered at the deprived notched frequencies. Pantev et al. interpreted their results as evidence for short-term plasticity in the human auditory cortex corresponding to changes reported in animals (Irvine, 2000; Robertson & Irvine, 1989).

   Tinnitus, i.e., ear ringing or auditory sensations without a corresponding external triggering sound, is very likely the auditory equivalent to phantom-limb sensations (Jastreboff, 1990). It has been assumed that tinnitus originates in a local damage of the cochlea which in turn

results in reorganizations of the auditory cortex. Indeed, Mühlnickel, Elbert, Taub, and Flor (1998) reported in a subgroup of tinnitus patients an expansion of the tinnitus frequency into adjacent representational zones. Moreover, analogously to the studies in phantom-limb pain (see above), they found a high positive correlation between the subjective magnitude of tinnitus and the extent of the cortical reorganization (as measured by MEG recordings). The change observed in the auditory cortex organization of humans differed from that observed in animals (Irvine, 2000). While an invasion of perilesional frequencies into the deafferented cortical zone was reported in guinea pigs, Mühlnickel et al. found an invasion of the tinnitus frequency into the adjacent auditory cortex zone in humans. Using positron emission tomography (PET) Giraud et al., (1999) studied a group of patients who were able to elicit tinnitus sensation by moving their eyes. Therefore, they were able to investigate the neural correlates of the tinnitus sensation proper. The main tinnitus related activity was found in the auditory association cortex (temporo-parietal region) rather than in the primary auditory cortex (in the superior temporal gyrus). The latter result does not necessary contradict the reported findings in animals and humans (see above) because PET, unlike neurophysiological recordings, does not differentiate between parts of the auditory cortex, e.g., regions representing the tinnitus frequency vs. "healthy" zones. Moreover, the patients of Giraud et al. belonged to a very specific group; they had developed tinnitus after a resection of an acoustic neuroma that had been located in the cerebello-pontine region. More research is needed to clarify the influence of the etiology, extent and duration of deafferentation upon the kind and extent of auditory cortex reorganization and their behavioral correlates.

Finally, it is interesting to note that patients with high frequency loss display reduced low frequency discrimination thresholds at the border of the lost part of the spectrum. It could be speculated that their superior performance is related to a take-over of synaptic space formally representing the lost high-frequency spectrum by lower-frequency input (McDermott, Lech, Kornblum, & Irvine, 1998, in Irvine, 2000). This result is an analogy to the lower two-point thresholds at the stumps after upper limb amputation (Teuber, Krieger, & Bender, 1949, in Merzenich & Jenkins, 1993).

Visual system. If the retina is partially lesioned, visual cortex neurons with RFs in the damaged zone develop RFs in the area surrounding the peripheral scotoma (Chino, Kaas, Smith, Langston, & Cheng, 1992; Kaas et al., 1990). Although first reorganizations are seen immediately, they expand and consolidate within the next months and neurons with new RFs finally develop normal selectivity for spatial frequency and orientation, although RF size remains larger and response rate lower than normal. Interestingly, these plastic changes are suppressed unless the second eye is enucleated or unless a matching lesion is performed in the other eye.

Deteriorating eyesight in humans often results in phantom sensations as has been described for the somatosensory and auditory system. Complex visual hallucinations in patients with visual impairments, but without any history of psychopathological disorders or loss of consciousness, are known as Charles-Bonnet syndrome (Schultz & Melzack, 1991). As is true for other phantom sensations, these patients are fully aware that their visual images do not correspond to an event in external space. Phantom visual images, also called pseudo-hallucinations, can consist of ink-blots, lighted bars, textures, and complex images such as humans, animals or landscapes. They occur with eyes open and eyes closed, in stressful and relaxed

situations. Unlike phantom sensations in the somatosensory and auditory systems, they generally do not cause distress. Phantom visual images can be distinguished from other visual images in that they are perceived as originating in external space rather than in the head. Moreover, they are as vividly experienced as normal visual sensations and are usually not under voluntary control. The neural bases of these sensations are not known yet. ffytche et al. (1998) used fMRI to investigate both the brain activity correlated with phantom visual images and the excitability of striate and extrastriate brain regions during visual stimulation in patients with visual phantom sensations. They found that the hallucinations of color, faces, objects and textures activated posterior fusiform gyrus, left middle fusiform gyrus, right middle fusiform gyrus and collateral sulcus, respectively. Therefore, the hallucination-induced brain activity roughly corresponded to the functional anatomy of the occipital lobe. Moreover, ffytche et al. reported evidence that the ventral occipital cortex activity is generally increased in patients with Charles-Bonnet syndrome, even in epochs without hallucinations. The latter result may be related to findings from animal studies suggesting that a down-regulation GABAeric inhibition accompanies sensory deafferentation (Eysel et al., 1999; Jacobs & Donoghue, 1991).

Kapadia, Gilbert, and Westheimer (1994) created artificial scotomas in healthy people by covering a small rectangular area of a moving display. They found that localization of short line segments is biased towards the center of the artificial scotoma. This shift was already detected after one second and was interpreted as a consequence of RF plasticity. Indeed, a fivefold enlargement of RFs within the unstimulated area has been shown with neurophysiological recordings (Prettet & Gilbert, 1992, in Gilbert, 1995).

Mechanisms of Lesion-Induced Intramodal Changes. It has been assumed that the neural mechanisms underlying lesion-induced plasticity include those mediating training-induced plasticity. In particular, besides physiological changes, i.e., modifications of the synaptic weights of existing connections, anatomical plasticity, such as synaptogenesis and collateral sprouting have been assigned a more important contribution.

Modifications taking place within minutes or hours after the deafferentation cannot be due to anatomical changes since growing processes take much longer. By contrast, immediate changes are thought to indicate a "rebalancing of excitatory and inhibitory factors within a dynamically maintained system" (Kaas, 1999, p. 7622). It is assumed that rapid changes are due to an "unmasking" of previously "silent" synapses. For example, thalamocortical connections do not only terminate at cortical neurons to which they provide suprathreshold input but also at surrounding neurons to which they send subthreshold input. In addition, they activate inhibitory neurons with lateral connections that suppress input from surrounding weaker excitatory afferents. If the most effective or dominating excitatory input of a neuron is deafferented the surrounding, normally ineffective input gains the ability to elicit action potentials of that neuron. Similarly, according to the cascade model put forward by Eysel et al. (1999) deafferentation is immediately followed by a down regulation of GABA mediated inhibition and an up-regulation of NMDA-mediated excitation. This initiates LTP-effects resulting in the turnover of subliminar edge input into effective input for the deafferented neuron. The emergence of LTP is possibly an initial step to consolidate and organize initial changes. Further steps of consolidation may consecutively involve anatomical changes including changes in the form (see perceptual learning above) and number of synapses (synaptogenesis), and the sprouting of new connections (axon

and collateral sprouting). Particular importance has been assigned to the sprouting of cortical long-ranging horizontal connections (Darlan-Smith & Gilbert, 1994). That reorganizations after deafferentation can originate, to some extent, at the cortical level, is illustrated here with three examples: (1) After focal retina lesions the scotoma in the visual cortex has been shown to vanish although the one in the lateral geniculate body still remained (Gilbert & Wiesel, 1992). (2) The secondary somatosensory cortex (SII) is nearly exclusively innervated by SI, i.e., there are hardly any direct connections from the ventroposterior thalamus to SII. After completely destroying the hand region in SI of primates, SII neurons formally representing the hand were initially silenced. After several weeks these neurons became responsive to stimuli of other limbs. (3) After intracortical microstimulation neurons adjacent to the stimulated region developed RFs that overlapped with those of the activated neurons. By contrast, the size and thresholds of RFs did not change for the stimulated neurons. These changes are equivalent to reorganizations elicited by deafferentation (Dinse, Recanzone, & Merzenich, 1993). Nevertheless, recent evidence has confirmed early findings (Wall & Egger, 1971) that similar changes as in the cortex take place at the subcortical level including the spinal cord, brain stem and thalamus as well (Florence & Kaas, 1995; Jones & Pons, 1998; Nicolelis, Lin, Woodward, & Chapin, 1993). It is easy to imagine how plasticity at each higher processing level is potentiated following changes at earlier processing stages.

Nevertheless, neural plasticity seems to be even more complex than previously described. Up to now, we have presented an exclusive bottom-up system, however, recent work suggests that feedback projections from the cortex to the thalamus play a role in neural plasticity as well. Ergenzinger, Glasier, Hahm, and Pons (1998) deactivated parts of the primary somatosensory cortex by administrating a NMDA-antagonist and found an enlargement of the RFs in the ventroposterior nucleus (VP), thus demonstrating a top-down modulation from the cortex to sensory thalamic relay nuclei. These results were extended by demonstrating direct effects of cortifugal connections upon deafferentation-induced reorganizations in the thalamus. Krupa, Ghazanfar, and Nicolelis (1999) used a GABA agonist to anesthetize a small set of facial whiskers in rats either with or without deactivating the primary somatosensory cortex. With S1 intact, they found a reactivation of the deafferented zones by the surrounding input, both at the level of the cortex and thalamus. In contrast, when S1 activity was suppressed, the percentage of neurons in ventroposterior medial thalamus (VPM) that displayed new sensory responses was considerably reduced. These results demonstrate that cortical feedback projections modulate thalamic plasticity. In addition, they also suggest that thalamic reorganization is possible without cortical mediation, even though the cortex may potentiate or partly create plastic changes in the thalamus.

Thalamic reorganizations after deafferentation have been demonstrated in human amputees as well (Davis et al., 1998). All participant amputees had an enlarged thalamic representation of the stump. Stimulating the thalamus elicited phantom sensations in patients who had reported such sensations earlier. These findings as a whole suggest that lesion-induced plasticity and its subjective correlates arise from more complex bottom-up and top-down circuits than has originally been assumed. Moreover, both training-induced and lesion-induced plasticity is modulated by behavioral relevance and attention. Buchner et al. (1999) anaesthetized digit two, three and four in healthy human volunteers and electrically stimulated digit one and five. When

participants had to orient attention to the dorsal surface of the hand, the authors found a decrease of the distance between the somatosensory representations of digit one and five (as accessed by electrophysiological source localization). By contrast, this distance increased when subjects reported that they had attended to the anaesthetized fingers. These results are in agreement with findings demonstrating increased blood-flow changes in the contralateral motor cortex when amputees imagined that they were moving their lost limb (Lotze, Flor, Grodd, Larbig, & Birbaumer, 2001). It may be speculated that the reticular nucleus of the thalamus (TRN) contributes to attention-dependent plasticity. This nucleus is located like a shield between the thalamus and cortex (Guillery, Feig, & Lozsádi, 1998; Yingling & Skinner, 1976). It consists of distinct (e.g., visual, auditory, somatosensory and motor) sectors that have topographically organized representations. TRN receives and sends connections to the thalamus and cortex. In addition, TRN has afferents from the basal forebrain and the brain stem. Activating a section of TRN, such as through cortifugal connections, results in an inhibition of a circumscribed zone of the connected relay nucleus. Because deactivation of the cortex removes the activation of TRN and therefore inhibitory influences upon thalamic sensory representations, it is conceivable that TRN partially mediates the enlargement of thalamic RFs after cortical deactivation (Ergenzinger, Glasier, Hahm, & Pons, 1998; Krupa, Ghazanfar, & Nicolelis, 1999). Thus, considering the connectivity of TRN, including afferents from the frontal attention system, makes this brain structure an important candidate for modulating training- and lesion-induced brain plasticity (Kaas, 1999; Kaas & Ebner, 1998).

In sum, lesion-induced reorganizations disrupt an existing or developmentally emerged balance in sensory representations, much as perceptual training does. While the latter is mainly characterized by "more intense" use, deafferentation means "less intense or no" use. Although the disturbance created by deafferentation is greater than in perceptual learning, the neural changes observed may largely be due to non-use rather than injury per se (at least if the injury is exclusively peripheral rather than spinal; Florence, Taub, & Kaas, 1998; Merzenich, 1998). The total loss of activity of some afferents causes a much larger disturbance than the weakening caused by the training of different inputs. It could be speculated that the smaller extent of training-induced plasticity may be one reason why phantom-sensations are observed after deafferentation but not after perceptual learning. There is, however, one exception reported in the literature: extensive stimulation of the upper arm of healthy volunteers over a long time was followed by the experience of phantom-like sensations (telescoping; Craig, 1993).

Finally, it has to be noted that training- and lesion-induced changes are not necessarily independent. For example, Elbert et al. (1997) found that the cortical representation of the intact arm changes after upper-limb amputation, most likely due to amputees' increased use of the former.

Merzenich, Recanzone, Jenkins, Allard, and Nudo (1988, p. 62) noted that "In general, the greater the number of sources of correlated inputs and the greater the divergence and convergence of their afferent distributions, the greater the possible representational plasticity." Given the complex feed-forward and feedback connectivity between cortical and subcortical regions of the neural information processing pathway, extensive and mutually dependent reorganizations are conceivable. Whether these reorganizations can cross modality borders is the topic of the next section.

Intermodal Plasticity after Totally Deafferenting One Sensory System

Gilbert, Sigman, and Crist (2001) hypothesized that the availability of an increased number of neurons to code a particular stimulus feature could improve processing precision. Therefore, it is possible that the neural structures separated from their visual or auditory input in blind and deaf individuals may contribute to a finer grained representation of auditory/somatosensory and visual/somatosensory functions respectively. That is, if traditionally visual or auditory brain structures are recruited in the blind or in the deaf for the processing of stimuli of their intact senses, these cross-modal reorganizations may contribute to compensatory behavior in these individuals. The term intermodal plasticity is used here to describe anatomical and physiological changes in neural systems usually dominated by the deprived system. In the following section reorganizations of polymodal brain areas and the concept of functional reallocation are discussed.

Reorganization of Multimodal Brain Regions. Different sensory systems interact in order to integrate input of different modality systems to a unique percept (for a review see Calvert, Spence, & Stein, 2003). Some multimodal areas contain unimodal neural clusters separated by neurons responsive to the inputs of more than one sensory modality. Many multimodal brain structures have been identified. The midbrain superior colliculus and cortical regions such as the temporo-parietal junction and the parietal lobe are the most often investigated ones.

For example, the anterior ectosylvian cortex in the cat is comprised of unimodal sections with neurons at the borders between these regions receiving afferents from different sensory systems. In visually deprived cats, the visual section of the anterior ectosylvian cortex is recruited by the auditory, and to a lesser extent, by the somatosensory system (Rauschecker & Korte, 1993). Moreover, auditory neurons displayed a sharper spatial tuning for lateral and rear positions. In addition, research suggests that visually deprived cats demonstrate superior localization skills for lateral and rear sound sources (Rauschecker, 1995; Rauschecker & Kniepert, 1994).

Corresponding evidence has been obtained in humans. Röder, Rösler, and Neville (1999) conducted an experiment with congenitally blind adults that closely modeled the studies of Rauschecker et al. Two arrays of loudspeakers were arranged in frontal (central) and lateral (peripheral) positions around the participants. Short noise bursts were presented randomly from each speaker. Participants had to detect rare deviant noise bursts from either the central or the most lateral speaker. Congenitally blind participants committed less false alarms when locating sounds from the lateral-peripheral speaker, indicating superior auditory localization skills in congenitally blind humans. Moreover, event-related potentials suggested that early auditory spatial filter mechanisms for lateral sound sources are finer tuned in the blind. In addition, the scalp topography of this activity pointed towards a reorganization of multimodal brain regions in the blind. Therefore, the human findings and those obtained in visually deprived cats impressively match. Both visually deprived cats and humans showed more precise auditory-spatial tuning, a reorganization of polymodal brain structures and superior localization skills.

Additional studies on cross-modal plasticity have investigated the N2 wave, which is partially generated in the parietal cortex (Knight, 1990). When rare deviant stimuli have to be detected in a stream of auditory or somatosensory stimuli, they elicit an additional negativity around 200 ms after stimulus onset. Research has repeatedly found with both auditory and

somatosensory stimuli, that this component is more pronounced in the blind than in the sighted over posterior brain regions (see figure 3) suggesting that multimodal brain structures may indeed reorganize in the blind (Kujala et al., 1995a; Röder, Rösler, Hennighausen, & Näcker, 1996; Röder, Rösler, & Neville, 1999). These findings have been confirmed by imaging data showing that parieto-occipital association areas display elevated activity in blind as compared to sighted people (De Volder et al., 1997; Weeks et al., 2000).

Blind minus Sighted
Difference in N2 amplitude (Targets minus Standards)
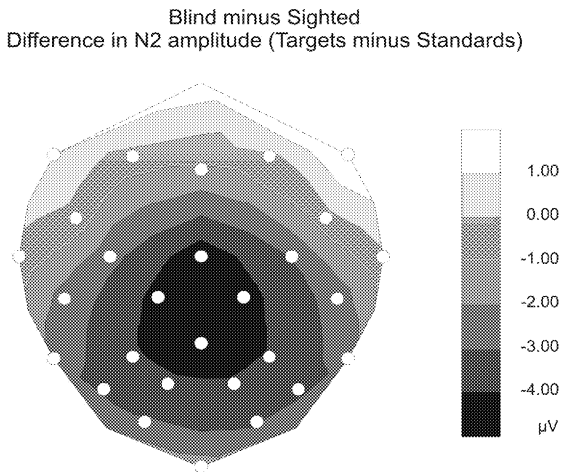
Figure 3. Topographic map of the difference between blind and sighted adults in the amplitude of the N2 component. Dark shading indicates higher activity. The maximum of the group difference is located over centro-parietal recording sites indicating a reorganization of multimodal brain areas in the blind. (From: Röder et al., 1999).

        Functional Reallocation. The term functional reallocation (other authors have used the terms "cross-modal intrusion" (Rauschecker & Korte, 1993), or "vicarious functioning") is used to describe changes that result in an activation of brain structures that are normally primarily associated with the deprived modality by the intact sensory systems, e.g., when the "visual" cortex of the blind is activated by auditory or somatosensory stimuli.

        A major prerequisite for such a "take-over" of new functions by brain structures normally processing inputs of the deprived modality is that they are not atrophied. Morphological studies in visually deprived animals have revealed thinner (Berman, 1991; Cragg, 1975) and smaller (Dehay, Horsburgh, Berland, Killackey, & Kennedy, 1989; Rakic, Suner, & Williams, 1991) occipital cortices in visually deprived than in sighted animals. The most pronounced changes were found for layers IV and V suggesting an impaired thalamo-cortical system. This interpretation is in agreement with observations that the lateral geniculate body shrinks up to 50 percent after visual deprivation (Berman, 1991; Rakic, Suner, & Williams, 1991). Moreover, a thicker layer I was found in visually deprived cats (Berman, 1991) and an additional area (called Area X) located between Area 17 and 18 was detected in monkeys enucleated during the first half of pregnancy (Rakic, Suner, & Williams, 1991). Area X had morphological characteristics of both Area 17 and Area 18. By contrast, if the enucleating was performed after the first half of gestation, an Area X did not emerge. Morphological studies in blind humans are rare. Post-

mortem studies (Globus, 1975) and magnetic resonance imaging studies (Breitenseher et al., 1998) are consistent with the animal literature, showing a degeneration of the lateral geniculate body. However, researchers have not been able yet to detect changes in the macrostructure of blind humans' cortices (Breitenseher et al., 1998; Büchel, Price, Frackowiak, & Friston, 1998; Kujala et al., 1995b).

In order to find out how the function of brain tissue is determined, e.g., whether a genetic code or experience is essential, so-called rewiring experiments have been conducted in ferrets, a very premature born animal (for a review see Pallas, 2001; Sur & Leamey, 2001). In normal ferrets, retinal ganglion cells predominately project to the lateral geniculate nucleus (LGN) and the superior colliculus (SC). Both areas in turn send projections to the primary visual cortex. The medial geniculate nucleus (MGN) receives input from the inferior colliculus (IC) and sends projections to the primary auditory cortex. If the MGN is deafferented from its normal input and LGN is destroyed, retinal afferents grow to the MGN. Therefore, visual instead of auditory information is transferred to the auditory cortex. Indeed, it has been shown that neurons of A1 respond to the new visual input and, moreover, a two-dimensional retinotopically organized map with cells displaying orientation-, direction- and velocity-tuning emerge in A1. The question arises if the visually evoked activity in A1 of rewired animals is interpreted as visual (i.e., if the perceptual quality is determined by the afferent activity) or as auditory (i.e., if the perceptual quality is built into the intrinsic properties of the cortex). Von Melchner, Pallas, and Sur (2000) provided fevidence for the first alternative: rewired animals in their studies reacted to the input mediated by the rerouted afferents as to visual rather than auditory stimuli. While extensive surgery interventions have to be performed in the rewiring experiments, it could be speculated that this kind of cross-modal reorganization is unlikely under natural conditions. In a series of experiments in the blind mole rat Spalax ehrenbergi it was, however, shown that cross-modal plasticity may be an important mechanism in evolution. Mole rats are born with rudimentary eyes that hardly provide any visual input for the animals. At birth they have normal retinal projections to the LGN and SC. However, these degenerate within the first postnatal weeks resulting in a deafferented LGN. It was shown that the LGN of the blind mole rat receives input from the IC and that this information is transferred to the visual cortex (Bronchti, Doron, & Wollberg, 1991). Results of other studies suggest that somatosensory representations may extend into the occipital cortex in blind mole rats as well (Necker, Rehkämper, & Nevo, 1992).

In sum, the rewiring studies and the data from the blind mole rat ehrenbergi suggest that during some developmental stage, cortical areas are capable of taking over processing functions of a different modality. Nevertheless, it should be noted that the auditory cortex of rewired ferrets does not completely turn into a visual one, e.g., marked differences in the receptive field properties exist and the cortical-cortical connectivity does not change qualitatively although quantitatively (Pallas & Sur, 1993).

Functional studies in humans have used electrophysiological and brain imaging techniques in order to investigate the possible functions of "visual" brain structures in the blind. There is now evidence that these brain areas are active even in congenitally blind humans. During non-visual tasks of different complexities, including auditory and tactile stimulus discrimination (Röder, Rösler, Hennighausen, & Näcker, 1996), Braille reading (Büchel, Price, Frackowiak, &

Standardized Topography of slow potential shift
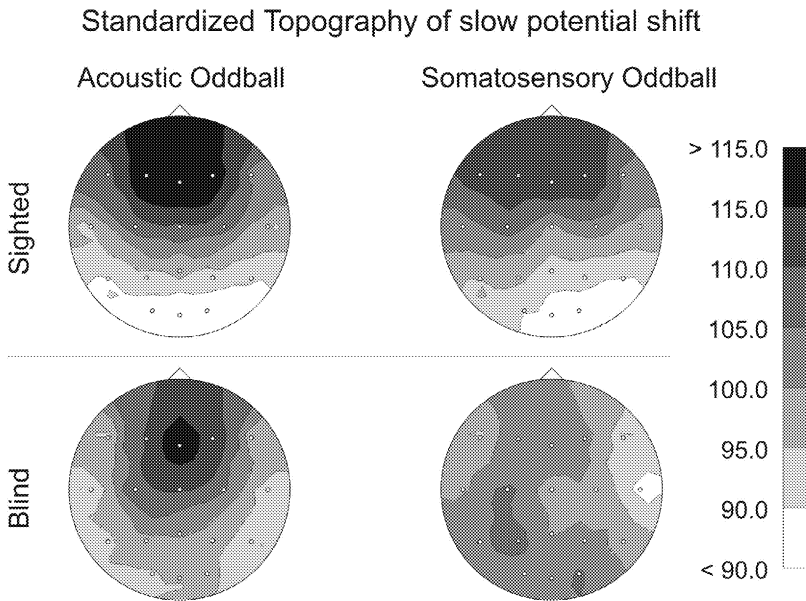
Figure 4. Topographical representation of the electric activity of sighted (first row) and blind (second row) participants during an auditory (first column) and somatosensory (second column) discrimination task. Dark shading indicates higher activity. Brain activity was shifted posteriorily in the blind both for auditory and somatosensory tasks. (From: Röder et al., 1996)

Friston, 1998; Sadato et al., 1996), auditory localization (Arno et al., 2001; Weeks et al., 2000), language perception (Röder, Rösler, & Neville, 2000) and mental imagery (De Volder et al., 2001; Röder, Rösler, & Hennighausen, 1997; Rösler, Röder, Heil, & Hennighausen, 1993; Uhl et al., 1994) blind participants demonstrated higher activity in occipital brain areas than sighted controls. For example, Röder et al. (1996) measured slow cortical potentials while blind and sighted participants had to discriminate either tactile or auditory stimuli. Negative slow brain potentials are associated with an increase in the excitability of brain structures lying underneath the recording sites. As shown in Figure 4, these negative brain waves extended more posteriorily in the blind than in the sighted, irrespective of stimulus modality. However, the activation of occipital brain structures does not seem to be linked exclusively to perceptual stimulation. Röder et al. (1997) used a mental rotation task in which participants first had to haptically encode a nonsense form. Consecutively, a tone was presented that instructed the participants to mentally rotate the haptic form either not at all, by 60 degrees, or by 120 degrees. A comparison stimulus was presented in the announced angle at the end of the transformation phase and participants had to decide whether or not it was the mirror image of the original stimulus. Slow event-related potentials recorded during both the encoding and mental transformation phase revealed evidence

for enhanced occipital brain activity in blind compared to sighted participants (Figure 5). Importantly, occipital slow waves varied as a function of mental transformation load only in the blind. Therefore, in a time interval without any perceptual stimulation, posterior brain areas were found to be more active in the blind than in the sighted.

        Despite the fact that posterior brain activity in the blind varied as a function of experimental load, the fact that tasks differing in complexity and modality activate the visual cortex in the blind makes it difficult to draw conclusions about the functional role of these brain areas when vision is lost. The only direct evidence for an involvement of occipital brain structures in non-visual tasks comes from a study in which transcranial magnetic stimulation (TMS) was used in order to interrupt brain functions. When TMS was applied over the occipital cortex, blind Braille readers experienced problems in perceiving the Braille letters (Cohen et al., 1997).
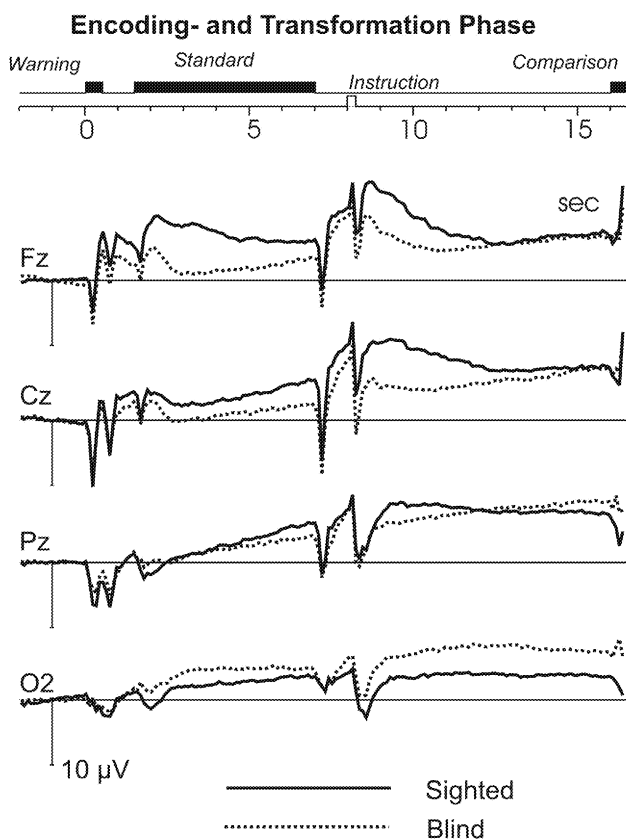
Figure 5. Slow brain potentials elicited by enco-ding and transfor-ming of haptic images. Higher activity for the blind during both processing phases was found at occi-pital recording le-ads (02) located above visual cortex structures. (From: Röder et al., 1997).

Finally, an elevated excitability of the sensory specific areas associated with the deprived modality when stimuli of the intact modalities are processed seems to be a general consequence of sensory deprivation. This effect has been reported for deaf people as well both for auditory (Finney, Fine, & Dobkins, 2001) and tactile tasks (Levänen, Joursmäki, & Hari, 1998).

Mechanisms: Merzenich, Recanzone, Jenkins, Allard, and Nudo (1988, p. 62) proposed that a given brain region's plasticity capacity is determined by the richness of its afferents. Since multimodal brain structures receive afferents from different sensory systems it is easy to image how the Hebbian mechanism leads to cross-modal changes in multimodal subcortical and cortical brain structures, when afferents of one sensory system are eliminated. That is, the deafferentation of a sensory system causes a disturbance of neural representations in polymodal brain areas similar to a partial deafferentation in unimodal brain structures. The intact, non-deprived afferents may be able to take over synaptic space formally associated with the deprived modality (see e.g., Rauschecker, 1995) because they are represented in close vicinity.

In order for functional reallocation to occur, information from the intact sensory system must reach the brain structures primarily associated with the deprived modality. The rewiring studies suggest that cross-modal plasticity originates in reorganizations at the thalamic level, i.e., the sensory-specific relay nuclei receive afferents of a different modality and transfer this input to the sensory cortex of the deprived modality. It is not yet known whether a similar re-organization occurs in humans as well. Primates, including humans, are born with a much more mature nervous system than ferrets. On the one hand, the lack of alpha activity (Birbaumer, 1971; Novikova, 1974) in the spontaneous EEG of the blind has been taken as evidence for deficits in the thalamocortical and cortifugal circuits, particularly of inhibitory connections. Berardi, Pizzorusso, and Maffei (2000) proposed that exposure to sensory stimuli, i.e., adequate experience, elicits the development of inhibitory circuits which in turn terminate critical periods. It could be speculated that, when experience is lacking, as in blind or deaf individuals, deficits in inhibitory circuits emerge, resulting in an overall enhanced excitability of cortical networks associated with the deprived modality. Evidence for this assumption, indeed, exists (Rozas et al., 2001; Singer & Tretter, 1976). Moreover, an involvement of the reticular nucleus of the thalamus (TRN) for lesion-induced plasticity has been discussed above. As mentioned, the TRN has distinct zones for different sensory and the motor systems. It could be speculated that a lack of corticofugal inhibition results in an enhanced excitability of thalamo-cortical connections to the deprived cortex.

Recent evidence from multisensory research has shown that the presence of tactile stimuli is able to change the activation level of the predominantly visual cortex. For example, Macaluso, Frith, and Driver (2000) presented visual stimuli either in the left or right visual field resulting in predominately contralateral activity in occipital brain areas. When tactile stimuli were presented simultaneously with the light flashes they amplified the visual cortex response but only when the tactile stimulus was spatially congruent. This and other brain imaging findings (for review see Macaluso & Driver, 2001) suggest that the activity in one sensory system is able to modify the activation level of other brain structures associated with a different modality. Moreover, electrophysiological investigations have provided evidence that the response to stimuli of an attended modality is higher than to the same stimuli when a different modality is attended (Hötting, Röder, & Rösler, 2002). Furthermore, recent brain imaging data suggest that, if stimuli

of one modality, e.g., sounds, are processed, the activation level of sensory-specific cortices of the remaining modality, e.g., visual cortex, is dropped. These results suggest that the activity of brain structures that have been traditionally considered unimodal are not independent of the activity within other sensory systems. Feedback projections from multimodal brain regions to sensory-specific brain areas have been postulated to be the neural correlates of these findings (Driver & Spence, 2000). Moreover, recently detected direct connections between both auditory and visual and parietal and visual brain areas could contribute to cross-modal effects in healthy individuals (Rockland & Ojima, 2001) and to a higher visual cortex activity in the blind than in the sighted in non-visual tasks.

Finally, it has to be noted that there are an increasing number of reports on neurogenesis in adult individuals (for review see Ormerod & Galea, 2001; van Praag, Kempermann, & Gage, 2000), even in humans (Eriksson et al., 1998). There is evidence that new neurons in the hippocampus are important for learning (Shore, Sprey, & Spence, 2001). Neurogenesis of neocortical neurons has been proven as well, however, only in multimodal association cortices rather than in sensory cortices (Gould, Reeves, Graziano, & Gross, 1999). Furthermore, the axons of newly born neurons are short rather than long, suggesting local rather than distal effects. Although the involvement of neurogenesis for cross-modal plasticity remains to be shown, it could be speculated that new neurons contribute particularly to plasticity in multimodal brain regions.

Differences between Developmental and Adult Plasticity

Given the extensive reorganizations observed after partial deafferentation in adult individuals, one may ask if there is any difference between developmental and adult plasticity. Indeed, there is general agreement that both forms of plasticity share some common mechanisms, e.g., the Hebbian synapse (Kandel & O'Dell, 1992; Neville & Bavelier, 2001). Nevertheless, clear differences have been demonstrated as well: For example, there is evidence for an age-related variability in the LTP capability. Cells showing LTP in thalamo-cortical synapses of the mouse barrel cortex decrease in mice older than 7 days of age (Clair & Malenka, 1995, in Buonomano & Merzenich, 1998). Moreover, the existence of so called "critical periods" has been put forward as evidence for differences between developmental and adult plasticity. Development starts with a massive overproduction of connections that are pruned during the first years of life by up to 50% (Huttenlocher & Dabholkar, 1997). This process in turn has been associated with the end of the critical period for a given area (Bourgeois, Goldman-Rakic, & Rakic, 2000). An impressive demonstration of differences between developmental and adult plasticity are recent findings from language acquisition in the deaf (Mayberry, Lock, & Kazmi, 2002) in which American Sign Language (ASL) proficiency was compared between a group of congenitally deaf adults, who had not been exposed to any language in early life, and a group of late deaf adults, who had learned a spoken language on schedule. Both groups had started to learn ASL at about the same age. ASL skills in the congenitally deaf signer, who grew up without a language were dramatically reduced. Moreover, English skills were compared between congenitally deaf people who had not been exposed to any language during early life, congenitally deaf people who had acquired ASL on schedule, and hearing people for whom English was a second language. While

the second and third group did not differ in their English scores, they both showed significantly higher performance than the deaf group that lacked early language experience. These results are a striking demonstration of the differences between developmental and adult plasticity. Brain systems need to be set up in early development; this initial functional development is based on functional (e.g., enhanced excitability) and structural (e.g., synaptic overproduction) differences between the developing and adult brain (Berardi, Pizzorusso, & Maffei, 2000). Adult plasticity is consecutively based upon and limited by the networks established during early development (see also Knudsen, 1998).

Acknowledgments

4

The Principle of Emotional Learning

Gerhard Roth

The fact that memory and emotions are closely connected is part of our daily life. Often we experience that emotionally arousing events result in better recollection of memories. It appears to us that we will not forget certain events in our life whenever they are accompanied by very pleasant or fearful emotions. A well known example is the "flashbulb memory", in which an extremely vivid memory forms for emotionally very engaging events, such as the sudden death of a close relative or a public catastrophe like that of September 11 in New York City.

However, there are some disturbing aspects of such memories, as we will see in greater detail in the following. First, even details of flashbulb memory sometimes turn out to be incorrect; second, strong negative experiences such as sexual abuse or a terrible car accident may have the opposite effect on memory, viz., lead to the suppression or virtually complete negation of these events, which, however, tend to reappear as flashbulb-like recollections called psychotrauma. Finally, long-lasting emotional loads or stress can have a devastating effect on our declarative memory. While these effects have been known for some time in the field of psychology, only very recently have the underlying brain mechanisms been discovered, at least in their rudiments. Some of these new insights will be presented in this article.

Studies on the Interaction between Memory and Emotional States

Numerous psychological experiments have been carried out in order to investigate the effect of positive or negative emotional states on the formation, consolidation and recall of memory contents (for reviews see Ellis & Moore, 1999; Goschke, 1996a, b; Parrot & Spackman, 2000).

In a first experimental approach, subjects are put into a certain affective or emotional mood, or, more accurately, the subjects are instructed to put themselves in such a mood. Then, material which in itself is neutral (e.g., pictorial images, words, etc.) is displayed. At certain time intervals, the extent to which the subjects' ability to remember is increased or reduced by the congruence of their moods during acquisition and recall (mood-congruent recall) is examined. Alternatively, emotional material is displayed (e.g., terrifying or repulsive pictorial images), and it is investigated whether, when the mood during acquisition or recall is the same as the emotional tone of the material, the ability to remember this material differs significantly from the ability to remember emotionally neutral material (mood-dependent learning and mood-dependent recall, respectively).

The results of such studies support the conventional view that the more evidently things are accompanied by emotional states, the better they are remembered. This is just as true for learning meaningless syllables as for recalling word lists, illustrated stories and personal memories. But this view must be restricted to the following qualifications: (1) emotional states must not be too strong, otherwise they prevent the ability to remember; (2) the reinforcing effect of emotions is valid only for medium-term recall (i.e., after a delay of two minutes or longer); in the short term (i.e., for recall within two minutes) attendant emotional phenomena may actually work to inhibit memory; (3) on average, positive contents are remembered better than negative; memories are often blocked in states of fear or depression; (4) emotional states tend to effect the contents of episodic-autobiographical memory more than they do factual knowledge; (5) in complex scenarios, emotions appear to promote the memory of "core contents" of events more strongly than "peripherals". However, this connection is weak and disputed.

Particular attention in the research on the psychology of memory has been paid to what is known as flashbulb memory, in connection with spectacular events, for instance the assassination of President J. F. Kennedy, the shooting of President Reagan, the Challenger explosion, etc. (Bohannon, 1988; Brown & Kulik, 1977; Pillemer, 1984; Schacter, 1996; Schacter & Curran, 2000). Under these circumstances, subjects were able to state what they were eating when their mothers came into the kitchen to break the news of Kennedy's assassination. However, it is evident that even the emotionally loaded contents of flashbulb memory are subject to deterioration or alteration over time, but to a much lesser degree than contents which were accompanied by little or no emotion. Here, too, the core event is the least affected by deterioration and alteration, while trivial details soon fade or are remembered incorrectly. In spite of clearly confabulatory components, the subjective certainty that things actually happened in a certain manner, and in no other, is quite high for subjects in the case of the contents of flashbulb memory ("false memories"; Loftus, 2000; Loftus & Pickerell, 1995; Schacter, 1996).

In addition to these cases in which strong emotions promote the storage of memory contents, the opposite effect is also discussed, i.e., cases in which strong emotions or stress lead to the deletion of memory contents, resulting in dissociative amnesia (cf. Comer, 1995; Markowitsch, Kessler, van der Ven, Weber-Luxenburger, & Heiss, 1998). This process plays an important role in psychoanalysis, where it is referred to as "repression". Here, too, generally the contents of episodic memory are affected, while contents of knowledge memory remain undamaged. Amnesia may be connected to a certain event or to an entire phase of life, and can

even extend into the present. Many clinical reports substantiate that grave traumatic experiences can lead to states of dissociative amnesia (Schacter, 1996; Schacter & Kihlstrom, 1989). The results of experimental studies on this topic are contradictory, however (cf. Goschke, 1996a, b).

The Memory System Inside the Brain

The neural basis of memory has enjoyed great interest in neurobiology and neuropsychology during the last 40 years or so. Today, it is generally accepted that there are at least two basic types of memory: (1) declarative or explicit memory, i.e., a recollection of those kinds of memories that in principle can be consciously retrieved and reported (Markowitsch, 1999, 2000; Schacter, 1996; Squire & Knowlton, 1995) and (2) procedural or implicit memory, which includes skills and habits, priming, classical and operant conditioning and non-associative learning, i.e., habituation and sensitization (Markowitsch, 1999, 2000; Schacter, 1996).

Within declarative memory, a number of authors (Aggleton & Brown, 1999; Markowitsch, 2000; Tulving & Markowitsch, 1998) distinguish two subsystems, viz., episodic memory which refers to semantically, spatially and temporally distinct events related to our own life ("what happened to me in Hamburg on Monday of last week"), and a semantic or knowledge memory, that is independent of persons, localities and time ("Mars is a planet"). The center of episodic memory is formed by autobiographic memory. Other subsystems that are distinguished by authors include source memory and familiarity memory (Schacter, 1996). Working memory is another, highly specialized type of declarative memory (Baddeley, 1986, 2001). It is a type of memory that for a short period of a few seconds integrates all pieces of cortical information that are relevant to cope with the present situation and problems in the immediate future, and particularly with the exact temporal order of events. Working memory is highly limited in its information processing capacity, but has access to long-term memories. It is the primary source of attention and the "stream of consciousness".

During the last 20 years and after long debates, it has become increasingly evident that the hippocampal formation (Ammon's horn, subiculum, dentate gyrus) and the surrounding entorhinal, perirhinal and parahippocampal cortex (together called EPPC) situated in the medial temporal lobe are the major centers for the formation and the consolidation of traces of declarative memory, at least of episodic (including autobiographic) and semantic memory (Figure 1).

The hippocampal formation is connected with all parts of the associative isocortex; these cortical afferents reach the hippocampus via the perirhinal and parahippocampal cortex, which in turn project to the entorhinal cortex, which represents the cortical "gate" of the hippocampus. The hippocampus projects back to all areas of the associative cortex via EPPC. Allocortical and subcortical afferents stem from the basal forebrain (medial septum, nucleus basalis of Meynert, nucleus of the diagonal band of Broca) and most limbic structures, including the basolateral
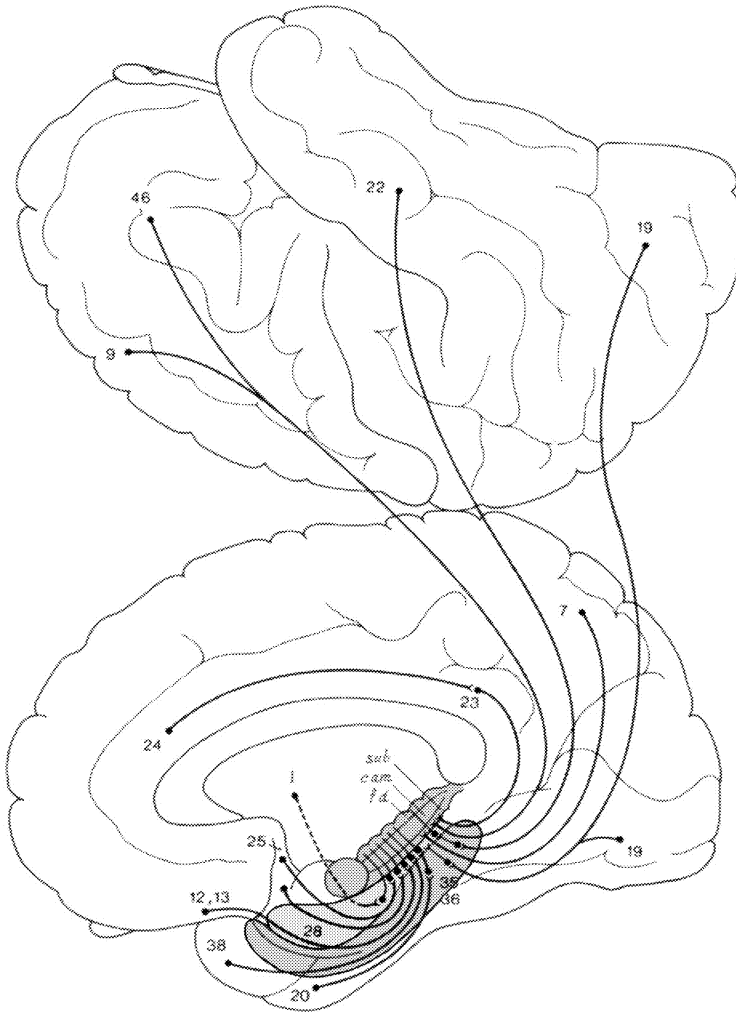
Figure 1 . Connectivity between hippocampus and isocortex. The medial view of the human cortex including the hippocampus and adjacent cortex is shown below, the lateral view of the cortex is shown above upside down. The hippocampus proper consists of subiculum (*sub*), Ammon's horn (cornu ammonis, *cam*) and dentate gyrus (fascia dentata, *fd*). Isocortical areas mostly project either to the parahippocampal and perirhinal cortex (Brodmann areas 35 and 36), which in turn project to the entorhinal cortex (Brodmann area 28), or directly to the entorhinal cortex, which then projects to the hippocampus proper. A few cortical areas, e.g., the prefrontal cortex (Brodmann areas 9, 46) and cingulate cortex (Brodmann areas 24 and 25) and a number of subcortical centers (e.g., amygdala, septum, thalamic and reticular nuclei, not shown in figure) project directly to the hippocampus. The back-projections of the hippocampus are nearly mirror-symmetrical. (From Nieuwenhuys et al., 1989; modified.)
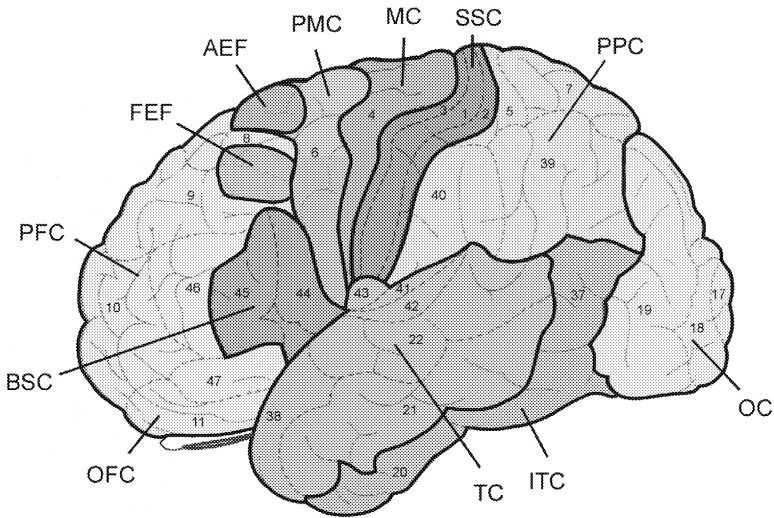
Figure 2. Lateral view of the human cortex. Numbers refer to cytoarchitectonic cortical fields according to Brodmann. Abbreviations: AEF = anterior eye field; BSC = Broca's speech center; FEF = frontal eye field; ITC = inferotemporal cortex; MC = primary motor cortex; OC = occipital cortex; OFC = orbitofrontal cortex; PFC = prefrontal cortex; PMC = dorsolateral premotor cortex; PPC = posterior parietal cortex; SSC = somatosensory cortex; TC = temporal cortex. (From Nieuwenhuys et al., 1989, modified.)

amygdala, the hypothalamus, limbic thalamic nuclei, the raphe nuclei (predominantly the dorsal raphe nucleus), the locus coeruleus and the periaqueductal gray (see below). Efferents run back to the amygdala, the basal forebrain, the nucleus accumbens and the hypothalamus.

There is recent evidence that the organization of episodic-autobiographic memory is due to the hippocampus proper and that the organization of semantic-knowledge memory and of familiarity memory is due to the activity of EPPC (Aggleton & Brown, 1999). Memories that are highly consolidated, such as our own name or knowledge that can be more or less automatically produced, do not need for their recall the mediation of hippocampus or EPPC, but apparently are "read out" directly from isocortical memory networks.

It is generally assumed that memory traces are not stored in the hippocampus or the EPPC, but in the associative isocortex (Figure 2). This is that portion of the cortex which contains no primary sensory or motor cortical areas, but is involved in the higher-order processing of information coming from these areas. It includes the *posterior parietal cortex* (PPC). The left PPC is involved in symbolic-analytic information processing, mathematics, language, and the interpretation of drawings and symbols. Lesions impair reading and writing and respective memory functions. The right PPC deals with real and mental spatial orientation,

the control of hand and eye movement, change of perspective and control of spatial attention. Lesions of the inferior right PPC produce neglect (i.e., ignoring the contralateral half of the body or events in the contralateral visual hemifield) or anosognosia, i.e., lack of insight or denial of disturbances (Kolb & Wishaw, 1993).

The associative *superior* and *middle temporal cortex* houses perception of complex auditory stimuli including (generally left side) Wernicke's semantic speech center, which is crucial for the understanding and the production of meaningful written and spoken language. Perception of music usually involves the right medial temporal cortex. The *inferior* temporal cortex (ITC) and the adjacent inferior occipital cortex are decisive for complex visual information regarding the non-spatial properties of visual objects and scenes along with their meaning and correct interpretation. Lesions in ITC and the adjacent occipital cortex produce object agnosia (left), color agnosia (right), prosopagnosia, i.e., inability to recognize faces (right or bilateral), deficits in categorization, changes in personality and emotionality and deficits in the use of contextual information (Kolb & Wishaw, 1993).

The *prefrontal cortex* (PFC) in the larger sense represents the largest portion of the human cortex and has been viewed by many neuroscientists as the "highest brain center". In contrast to all other parts of the cortex, its anatomical and functional substructures are still a matter of debate (cf. Petrides, 2000; Petrides & Pandya, 1999; Roberts, Robbins, & Weiskrantz, 1998). Usually, two major parts are distinguished in the primate, including human, brain: a *dorsolateral* part (including Brodmann areas 9, 10, 46) and a ventral and medial or *orbitofrontal* part (including Brodmann areas 11, 12, 47). The dorsal portion of the dorsolateral PFC receives cortical input mostly from the posterior parietal cortex, mediating information about the location and posture of the body and its parts, aspects of spatial orientation and action planning. The ventral portion of the dorsolateral PFC receives cortical input mostly from the inferior temporal and adjacent inferior occipital cortex, mediating information about complex visual and auditory perception including objects, scenes and the meaning of words and simple sentences (from Wernicke's speech area).

The dorsolateral PFC appears to be involved in (1) attention and selective control of sensory experience, (2) action planning and decision making, (3) temporal coding of events, (4) judgment and insight, particularly with respect to reality, (5) spontaneity of behavior, (6) strategic thinking, (7) associative thinking, and (8) working memory. Thus, the dorsolateral PFC is predominantly, though not exclusively, oriented toward the external world and its demands including short-term or working memory. Together with the cingulate cortex (see below), it is believed to monitor and adjust one's behavior confidently and to be aware of one's consciousness, thus exerting supervisory functions (Knight & Grabowecky, 2000). Lesions of the dorsolateral PFC result in perseveration and the impairment of making appropriate cognitive or behavioral shifts. The PFC is also the site of the above mentioned working memory, which most experts locate in Brodmann areas 9 and 46.

It is generally assumed that memory traces are stored in the associative cortex in a modality- and content-specific fashion within those areas that process the perception of these modalities and contents. This means that visual memories are stored in areas of the associative

(and maybe even primary and secondary) visual cortex, auditory memories in areas of the associative auditory cortex, linguistic memories in the cortical speech centers, etc.

What are Emotions and Where do they Originate in the Brain?

Emotions in a the broad sense include (1) the sensations of bodily states or needs such as hunger, thirst, tiredness and sexual arousal, (2) primary affective states such as rage and defense/reactive aggression, (3) emotions in a restricted sense such as anger, contempt, happiness, contentment, disgust, fear, shame, etc., (4) moods such as sadness or elation. Usually, a restricted number of basic emotions are distinguished by various authors, varying in number from 6 to about 20 (cf. Ekman, 1999). The neurobiologist Panksepp (1998), for example, distinguishes six basic emotional systems, viz., seeking/expectancy, rage/anger, lust/sexuality, care/nurturance, panic/separation and play/joy, which are distinctly different with respect to their biological role as well as their location inside the brain and their neurophysiological and neuropharmacological properties. Emotions are generally assumed to originate in centers of the limbic system and to become conscious, when these centers activate areas of the associative cortex.

The general functions of the limbic system are (1) control of autonomic-affective responses; (2) control of emotional conditioning; (3) control of conscious emotional, motivational and volitional states; and (4) evaluation of the consequences of action. The most important limbic centers are (1) the ventral tegmental area and the periaqueductal gray in the ventral mesencephalon; (2) hypothalamus, ventral pallidum, mammillary bodies; anterior, medial, intralaminar and midline nuclei in the thalamus of the diencephalon; (3) orbitofrontal, inferior temporal, cingulate, entorhinal and insular cortex, amygdala, septal nuclei, ventral striatum/nucleus accumbens in the telencephalon (cf. Nieuwenhuys, Voogd, & van Huijzen, 1988, Figure 3). These centers will be briefly described according to their functional roles.

The *hypothalamus* is the control center for basic biological functions such as food and water uptake, sexual behavior, sleeping and wakefulness, regulation of temperature and circulatory system, aggression and defense as well as for the sensations of bodily needs and affective states related to these functions. These functions are largely inborn. Due to its central biological role, the hypothalamus is connected with almost all parts of the brain, in particular with other limbic centers such as the septal nuclei, amygdala, hippocampus and orbitofrontal cortex. It controls via the pituitary the hormonal system (including stress reactions) and the autonomic centers of the brain stem and spinal cord, which in turn are points of origin of the sympathetic and parasympathetic nervous systems.

Together with the hypothalamus and the central nucleus of the amygdala (see below), the *periaqueductal gray* (PAG) is an important center for inborn affective states and related behavioral reactions. The PAG is capable of working independently of higher affective-emotional centers such as the basolateral amygdala, hippocampus and cortex, but is mostly influenced by these centers. It controls sexual behavior, aggression, defense and feeding. It also plays an

important role in unconscious pain reactions and affective-emotional vocalizations (Panksepp, 1998).

The *amygdala* is the major center for the generation and control of emotions (Aggleton, 1992; LeDoux, 1996). In most mammals, including man, it is believed to be the center for fear-related behavior. Lesions of the amygdala lead to the loss of the fear and anxiety components of behavior.

The amygdala is a complex of anatomically and functionally different nuclei, usually divided into a corticomedial group of nuclei related to olfactory information (particularly of pheromones), a basolateral group of nuclei primarily involved in emotional conditioning, and the
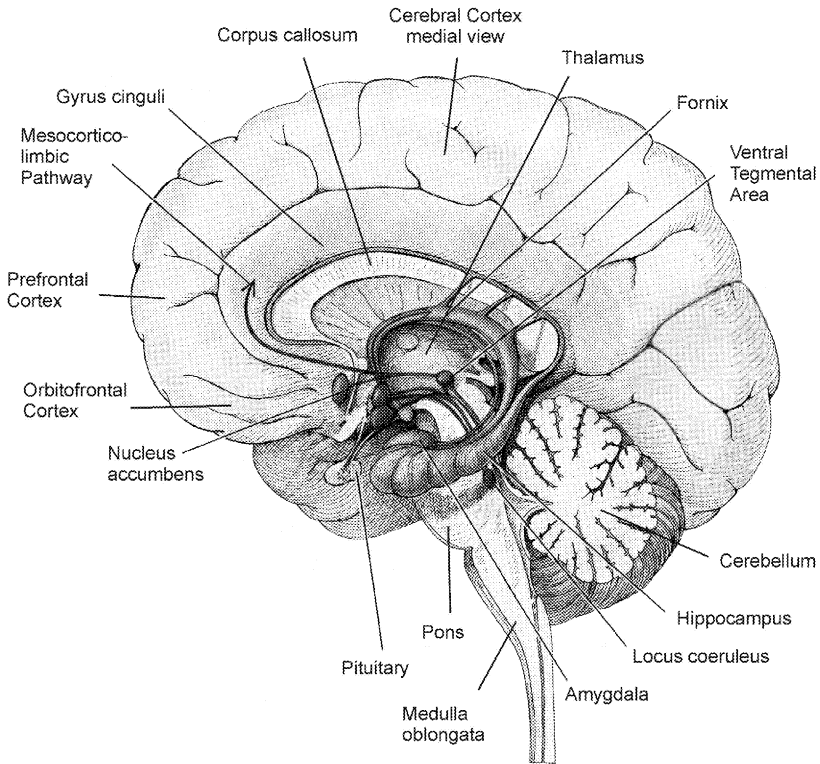

Figure 3. Medial view of the human brain showing major centers of the limbic system and the brain stem reticular formation. The basal ganglia are not shown. For further explanation see text. (From Spektrum/Scientific American, 1994, modified.)

central nucleus, which is the major output structure of the amygdala and, together with the hypothalamus and the PAG, controls "inborn" affective and autonomic functions and states.

The *basolateral amygdala* is reciprocally connected with the associative cortex, particularly with the orbitofrontal cortex, either directly or via the mediodorsal thalamic nucleus, and with the hippocampal formation (Aggleton, 1992, 1993; Holland & Gallagher, 1999). Generally, the connections from the amygdala to the cortex are much stronger than those in the opposite direction. Direct sensory afferents terminate in the basolateral amygdala via thalamic relay nuclei. The *central nucleus* influences – directly or via the hypothalamus and the PAG – the entire hormonal and autonomic system, e.g., through activation of the sympathetic and parasympathetic system (vegetative responses) and through activation of the dopaminergic, noradrenergic and cholinergic systems.

The involvement of the amygdala or parts of it in positive affect is still a matter of debate (Davidson & Irwin, 1999; Holland & Gallagher, 1999). There are close connections of the basolateral amygdala to the ventral striatal dopamine system and the orbitofrontal cortex, which may play a role in food-motivated associative learning; the central amygdaloid nucleus may contribute, via the basal forebrain and the dorsolateral striatum, to the control of attention (Holland & Gallagher, 1999).

The *mesolimbic system* consists of the nucleus accumbens, lateral hypothalamus and the ventral tegmental area and – like the substantia nigra – is characterized by the neuromodulator dopamine. This system has strong connections with the orbitofrontal cortex and is – apparently in cooperation with parts of the amygdala – involved in the formation of positive memories and pleasure, and perhaps in the control of attention in the context of new events (Holland & Gallagher, 1999; Robbins & Everitt, 1995). By the production of endogenous opiates (endorphins, enkephalins) it appears to represent the cerebral reward system. In rats and humans, intracranial self-stimulation within the mesolimbic system, particularly stimulation of the medial forebrain bundle, leads to strong sensations of pleasure, but only when the organism is in a state of bodily or psychic needs (Panksepp, 1998). Its impairment may be involved in cognitive misinterpretation and misevaluation in schizophrenics.

The mesolimbic system is also the site of effect for drugs including alcohol and psychotropic drugs. The latter increase – directly or indirectly via inhibition of inhibitory interneurons – the dopamine level within the ventral tegmental area and nucleus accumbens. According to recent studies, dopamine seems to be necessary only in the initial formation of drug addiction, but not for the maintenance of addiction. In the light of these new findings, dopamine appears to function as a signal for the association between reward and certain events, and such as a predictor for reward rather than a reward substance itself. This function seems to be fulfilled by the endogenous opiates (Panksepp, 1998; Spanagel & Weiss, 1999).

The *insular cortex*, belonging to the (three- to five-layered) allocortex, is covered by parts of the parietal, temporal and frontal isocortex. It processes visceral, viscero-emotional and somatosensory-emotional information, particularly in the context of pain. It is also involved in the guidance of attention. It has close connections with the amygdala, hypothalamus and cingulate cortex.

The *cingulate cortex* is that part of the cortex which surrounds the subcortical parts of the telencephalon and the thalamus. It is tightly connected with the prefrontal, orbitofrontal and parahippocampal cortex, the basal forebrain-septal region, the amygdala, the limbic thalamic nuclei and the reticular formation. The anterior part is involved in the sensation of pain (in combination with the somatosensory cortex, the medial thalamic nuclei and the PAG), and in the memory of painful events. In this sense, it may be the conscious counterpart of the amygdala. It is always active for tasks requiring attention.

The *orbitofrontal cortex* (OFC) includes Brodmann areas 11, 12 and 47 as ventral and medial portions of the frontal cortex. The OFC receives cortical input mostly from the inferior temporal, anterior cingulate, entorhinal and parahippocampal cortices and from subcortical limbic centers, above all from the amygdala. It is involved in social and emotional aspects of behavior, ethical considerations, divergent thinking, risk assessment, awareness of consequences of behavior, emotional life and emotional control of behavior. Accordingly, damage to the OFC results in loss of interest in important life events, loss of self, in "immoral" behavior and disregard of negative consequences of one's own behavior (Bechara, Damasio, Tranel, & Damasio, 1997; Damasio, 1994; Davidson & Irwin, 1999). Thus, the orbitofrontal cortex is predominantly oriented toward the internal emotional and social aspects of life.

Closely connected with the limbic system are the *neuromodulatory systems*. Their neurons of origin produce the "neuromodulators" noradrenaline (norepiphrenine), serotonin, dopamine and acetylcholin. In contrast to the "fast" neurotransmitters glutamate, gamma-butyric acid (GABA) and glycine, which mediate synaptic transmission in the range of a few milliseconds, the neuromodulators work more slowly, in the range of seconds, and modulate via intracellular second messenger pathways the efficacy of the fast transmitters. In combination with a multitude of neuropeptides, these neuromodulatory systems largely control our cognitive and emotional functions and states.

The first neuromodulatory system is the *noradrenergic* system, characterized by the catecholaminergic transmitter noradrenaline. Noradrenaline is produced in cells of the locus coeruleus located in the lateral portion of the pontine reticular formation. These cells send fibers to practically all centers of the limbic system and the associative cortex. The noradrenergic system mediates general activation of emotional and cognitive centers, general attention and induces the early stress response. The second modulatory system is the *serotonergic* system, characterized by the indolaminergic transmitter serotonin. Serotonin is produced in cells of the raphe nuclei which belong to the median pontine reticular formation. It has roughly the same axonal projection pattern as the noradrenergic system, but acts antagonistically by dampening, calming down and inducing a sensation of relaxation and pleasure. The third system is the *dopaminergic* system. Dopamine is produced in cells of the ventral tegmental area and of the substantia nigra pars compacta, both located in the tegmentum (i.e. ventral portion) of the midbrain. The substantia nigra pars compacta projects via dopaminergic fibers to the dorsal striatum and belongs, together with the dorsal striatum, to the basal ganglia representing the most important subcortical centers for the control of voluntary actions. The ventral tegmental area belongs to the mesolimbic system (see above) and sends dopaminergic fibers - (among others) - to the nucleus accumbens, amygdala, hippocampus and frontal cortex.

Besides the control of autonomic responses, the main function of the limbic system is to continuously evaluate the consequences of actions of the body under the control of the brain according to the criteria "pleasant/successful and accordingly to be repeated" or "unpleasant/painful/unsuccessful and accordingly to be avoided". The results of this evaluation are stored in the emotional experiential memory and used for future guidance of action. This process of limbic evaluation of actions already starts in the brain of the foetus and reaches its greatest importance during the first years after birth before juvenile and adult forms of consciousness arise.

The Neuronal Basis of Interaction between Memory and Emotion

The basic assumption regarding the interaction between memory and emotion, first proposed by Joseph LeDoux (1996), is that there is a division of labor between the declarative-episodic memory system (isocortex, hippocampus) and the above mentioned limbic centers (predominantly amygdala, mesolimbic system). While the hippocampus is thought to supply the *details* of the memories of an event and its context in an essentially un-emotional fashion, the amygdala and mesolimbic system supply the *emotions*, but they are incapable of handling and storing large amounts of detailed perceptive and cognitive information.

Support for this assumption of a "division of labor" between hippocampus and amygdala comes from experiments carried out by Damasio and colleagues (Bechara et al., 1995). The investigators studied patients who were lacking either the amygdala (due to the very rare Urbach-Wiethe disease) or the hippocampus on both sides of their brain. Both groups of patients were subjected to shock conditioning by means of a loud fog horn sounding suddenly. The patients with bilateral damage to the *amygdala* could specify exactly which sensory stimulus was coupled with their shock stimulus, but showed no vegetative fear response measured by the change in the electrical conductance of their skin. Consequently they did not develop any sensations of fear or fright and accepted the events "without emotion". In contrast, patients with bilateral damage to the *hippocampus* had no conscious information about the linkage between sensory stimulus and shock stimulus, but showed a distinct autonomic fear reaction, i.e., a sudden increase in skin conductance. Thus, it was clear that although their emotional memory functioned, their declarative memory failed, which was to be expected after a hippocampal lesion (anterograde amnesia). The patients with amygdala and without hippocampus thus experience fear and fright without knowing why.

More recent experiments of the LeDoux and Davis groups, using functional magnetic resonance imaging (fMRI) in human subjects, underline the close interaction between the cortico-hippocampal and the limbic system, particularly in the context of fear (Hamann, 2001; LaBar & Phelps, 1998; Phelps et al., 2001). When subjects were conditioned by using either nociceptive or fear-inducing visual material, there was always strong activation of the right amygdala, and this was the case independent of whether or not subjects are aware of fear-conditioning. The same was true for vividly imagined fearful events or stimuli. The activation of the amygdala was

proportional to the strength of the fear response, and consequently attenuated with the attenuation of that response. The right insular cortex was always co-activated at least at the beginning of the conditioning procedure and when subjects became aware of the conditioned stimulus-unconditioned stimulus contingency. As mentioned above, the insular cortex is generally involved in the anticipation of aversive stimuli including pain. It conveys somatosensory information to the amygdala.
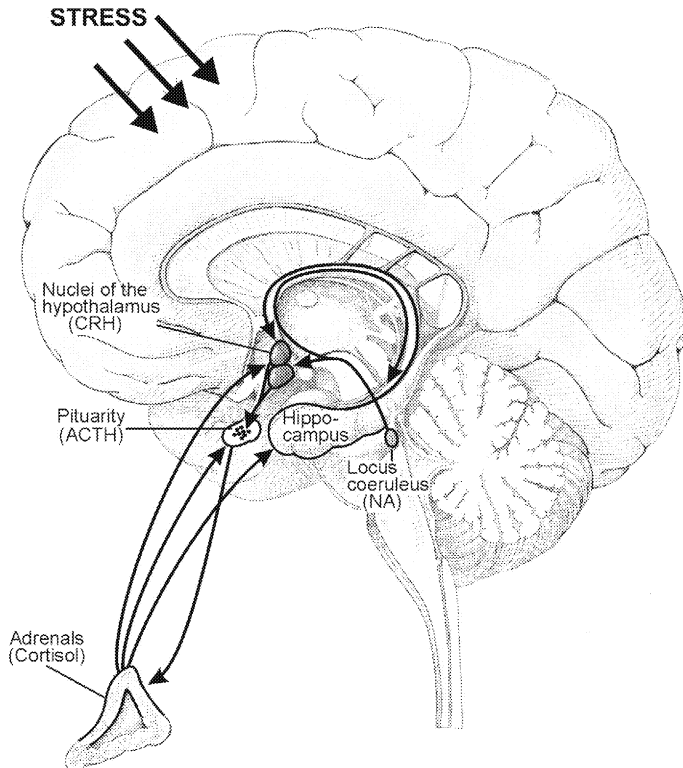
Figure 4. Scheme of interaction of stress-related centers. Psychically stressful events are perceived first subcortically-unconsciously and then cortically-consciously, which activate limbic centers, primarily hypothalamus and amygdala, which in turn activate autonomic centers, above all the locus coeruleus. The locus coeruleus releases the neuromodulator noradrenaline (NA) and with this activates cortex, amygdala, hippocampus and hypothalamus resulting in increasing attention and alertness. A few minutes later, the hypothalamus activates, via corticotropin releasing factor (CRF), the pituitary, which in turn releases the adrenocorticotropic hormone (ACTH). ACTH migrates via the bloodstream to the adrenals, which respond with the release of corticosteroid hormones (glucocorticoids), above all cortisol. Cortisol mobilizes additional bodily reserves in order to cope with the stressful situation. This includes neuroprotective processes and increased neuronal plasticity in the context of learning and behavioral adaptiveness. Prolonged stress, however, leads to damage of neural tissue, especially in the hippocampal area. (From Spektrum/Scientific American, 1994, modified.)

However, when in the fear-conditioning studies subjects were *verbally* instructed that one out of several stimuli would be accompanied by an aversive stimulus (electric shock), then the left amygdala was more strongly activated than the right one upon appearance of that stimulus. At the same time, the left insular cortex was more activated than the right one, as opposed to non-instructed fear conditioning. Interestingly, the "instructed" electric shock was never applied in these latter experiments. Thus, what was observed in the left amygdala and insular cortex was an anticipation rather than the actual experience of aversive, painful stimuli.

The Role of Stress on Memory

Psychic stress brings about two different physiological responses in the nervous system and in the body as a whole (Figure 4). The *first* response is that the situation of stress is recognized by the sensory systems and the cognitive system and leads to the activation of subcortical and cortical centers. In most cases, the activation of subcortical centers, above all the amygdala and the hypothalamus, precedes the activation of cortical centers. The amygdala sends a sort of "express message" to the hypothalamus or other relay stations, activating autonomic centers, chiefly the locus coeruleus. There the neuromodulator noradrenaline is released, acting on the cortex, amygdala, hippocampus and hypothalamus to increase attention and readiness for action.

Parallel to the activity of the locus coeruleus, the sympathetic nervous system is activated by the hypothalamus and autonomic relay centers in the brain stem and spinal cord, prompting the adrenal glands to release adrenaline and noradrenaline into the bloodstream. These substances reach the brain and reinforce the stress symptoms, further increasing readiness for action.

The *second*, slightly later stress reaction also proceeds through the amygdala and above all the hypothalamus, the pituitary and the *cortex* of the adrenal glands (*hypothalamic-pituitary-adrenal axis,* HPAA) and is conveyed by the corticotropin releasing factor (CRF). CRF-positive cells and fibers are located in the central nucleus of the amygdala as well as in the nucleus arcuatus and the small-celled nucleus paraventricularis of the hypothalamus. These cells are activated by the release of noradrenaline by the locus coeruleus or by noradrenaline and adrenaline from the adrenal medulla. Hypothalamic CRF cells release CRF through their processes reaching the eminentia mediana of the stalk of the pituitary. CRF then travels through the system of portal veins to the anterior lobe of the pituitary, where it causes ACTH (adrenocorticotropic hormone) to be produced and released into the bloodstream. ACTH reaches the adrenal cortex and brings about the release of corticosteroid hormones (also known as the glucocorticoids; the best known of these is cortisol). Cortisol affects corresponding receptors in the brain and sets the body in a heightened state of activity and performance. In particular cortisol mobilizes our metabolism by increasing the levels of glucose and fatty acid in the blood.

A moderate level of cortisol in the brain leads to increased production of neurotrophic factors (i.e., factors which stimulate nerve cells), to an increase in the number of glial cells (astrocytes) and thus to better working conditions for neurons and heightened neuronal plasticity.

Immediately thereafter the dendrites of nerve cells elongate and the number of their synapses increases (Hüther, 1996). The symptoms of stress disappear when the problem was mastered (e.g., an unpleasant examination) or the danger is over (e.g., a threat of being bitten by a dog), and, with slight delays, body and psyche return to "normal."

The hippocampus plays an important role in this process. The binding of cortisol to receptors in the hippocampus causes the hippocampus to exert an influence on the hypothalamus with the effect that fewer steroids are released by the adrenal glands. Ultimately the cortical (especially the prefrontal and orbitofrontal) states affect the stress activity of the limbic centers, due to, for instance, the insight that "it's not so bad after all".

According to LeDoux and other neurobiologists, this damping effect by the hippocampus and the isocortex is counteracted by the amygdala, which tends to maintain the state of tension (LeDoux, 1996). Generally the consequence is a sort of "fight" between the more cognitive aspects, conveyed by the hippocampus and the cortex ("insight"), and the more emotional aspects conveyed by the amygdala. We experience this fight subjectively as "being torn" between agitation and keeping calm.

A dangerous situation arises when enduring psychic stress predominates and stress situations appear subjectively to be insurmountable. In such cases the nervous system apparently can suffer permanent damage (Kim & Yoon, 1998). Continuing stress leads to shrinking of the soma volume of pyramidal cells in the hippocampus and their dendrites and – as an apparent consequence of this – to a deterioration of learning and memory performance and thus to such conditions as forgetfulness (Magariños, Verdugno, & McEwen, 1997; Newcomer et al., 1999). Noradrenergic signal transmission is generally inhibited, sex hormones and neurotrophic factors are repressed, with the result that neuronal growth is prevented. The amygdala, however, is *not* damaged by enduring stress. LeDoux claims that stress-related failure of the PFC, OFC and the hippocampus can have the result that the amygdala enjoys "free rein" over the objections of the hippocampus and the PFC. This could be the origin of transformation of fear into anxiety.

However, the brain is equipped with "built-in anti-stress measures". Coupled with the increased release of CRF and noradrenaline, these include an increase in b-endorphins which are associated with a decreased sensation of pain (Julien, 1995). The neuropeptide Y (NPY) also has an anti-stress effect (Heilig, Koob, Ekman, & Britton, 1994). Injecting NPY into the central nucleus of the amygdala has the effect of reducing stress and inhibiting fear. Researchers accordingly differentiate between an initial phase of the stress reaction, characterized by the release of CRF and an increase in stress, and a later phase, characterized by a release of NPY and endogenous opiates and thus a decline in stress.

Cellular Mechanisms of the Interaction between Memory and Emotions

It is now generally believed that the neurobiological basis of learning and the acquisition of memories consists in the modification of the efficacy of synaptic transmission within various

parts of the brain (Kandel, 2001). Usually, short-term memory, STM, and long-term memory, LTM, are distinguished. STM involves modification of synaptic coupling lasting from seconds to minutes, while LTM is longer-lasting ranging from minutes to hours, days and even years (Figure 5). LTM appears to require what is referred to as the consolidation of memory traces such that they allow a relatively robust recall of those traces. Protein synthesis inhibitors such as anisomycin long have been known to impair the consolidation of memory traces, but not the acquisition phase.

A relatively well-understood neuronal mechanism that seems to underlie STM and LTM is long-term potentiation, LTP, first discovered by Bliss and Lomø in 1973 (Bliss & Lomø, 1973). These authors observed that in the mammalian hippocampus repetitive stimulation of fiber bundles afferent to pyramidal cells in Ammon's horn (CA1-3) can lead to a significant, long-lasting enhancement of synaptic transmission. Today, like the two phases of memory formation, two types of LTP are distinguished. A single high-frequency train of stimulation can produce an early phase of long-term potentiation called E-LTP which may last for minutes. It is independent of RNA synthesis, because it cannot be blocked by RNA-synthesis inhibitors. It is believed to involve the modification of already existing proteins at the synapse, e.g., transmitter receptors and channels. Here, the NMDA (n-methyl-d-aspartate) receptor and ion channel are thought to play an essential role. Under "normal" conditions of fast synaptic transmission, this channel is blocked by a magnesium ion, which is removed by additional simultaneous pre- and postsynaptic activation of the synapse. This leads to an increase in the intracellular calcium level, which – via a cascade of intracellular processes – eventually increases the efficacy of AMPA (alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) receptors and channels, which regulate the in- and outflow of the sodium and potassium ions essential for fast synaptic transmission.

In contrast, multiple high-frequency trains of stimulation can lead to a late phase of LTP, called L-LTP, that lasts minutes to hours. It depends on protein and RNA synthesis and is assumed to involve structural modifications of the synapse, e.g., the thinning or thickening of existing dendritic spine synapses or the formation of new ones. This kind of stimulation activates several protein kinases, including kinases called alpha-CaMKII or PKC located inside the postsynapse, which in turn activate other kinases such as cAMP-dependent protein kinase (PKA) or ERK/MAPK. These latter substances are assumed to migrate to the nerve cell nucleus where they induce the transcription of cAMP response element (CRE-)-mediated genes and eventually the production of proteins that lead to the structural changes of the synapse discussed above.

Both E-LTP and L-LTP have been demonstrated under in-vitro conditions in both the hippocampus and amygdala of mammals. In the context of fear conditioning, it is assumed by LeDoux and other colleagues (Fendt & Fanselow, 1999; LeDoux, 2000; Schafe, Nader, Blair, & LeDoux, 2001) that the amygdala is the site of fear memory consolidation and storage based on LTP-like mechanisms. In these experiments, usually carried out in rats, fear conditioning consists in the association of a single tone and a mild foot shock. In the rat as well as in other mammals, the subcortical as well as the cortical pathway terminate in the lateral nucleus. The pairing of auditory stimulation via the subcortical auditory pathway with pain sensation via nociceptive pathways leads to LTP in the lateral nucleus of the amygdala. Here, they meet with

afferents from the hippocampus mediating information about the context, in which fear conditioning takes place.

According to LeDoux and his co-workers, not only damage to the lateral or dorsolateral nucleus, but also application of NMDA-receptor antagonists blocks fear conditioning. This pairing is sent to the central nucleus where it is coupled with inborn fear response. This coupling apparently is not NMDA-mediated. However, there is recent evidence by Fendt and co-workers (Fendt, personal communication) showing that the coupling of the conditioned and unconditioned stimulus is not or not necessarily mediated by NMDA receptors, but rather by what are known as metabotropic glutamate receptors.
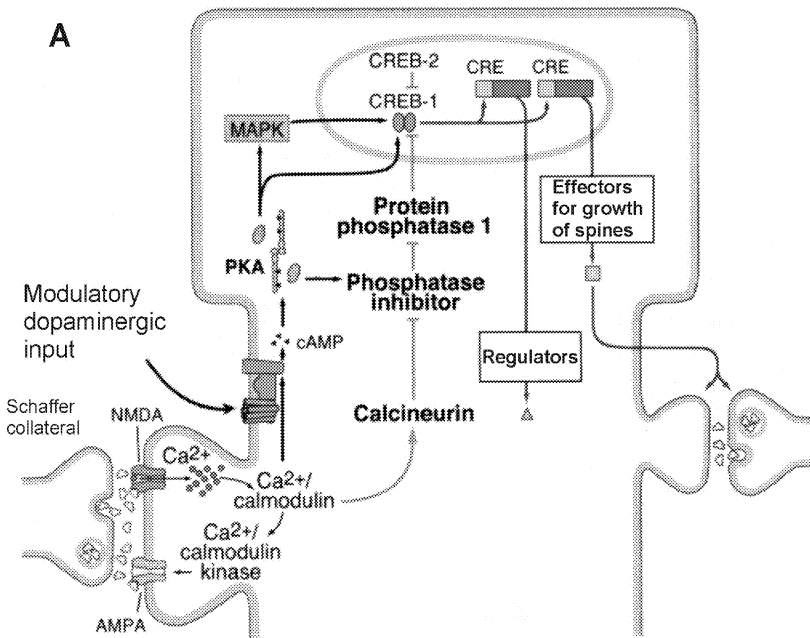
Figure 5. Early and late long-term potentiation (LTP) in the mammalian hippocampus. In **A,** a model for neuronal processes underlying early and late LTP in the CA1 region developed by E. Kandel is given. Early LTP is induced by single stimulation of Schaffer collaterals (left), which activates NMDA receptors at the postsynaptic site of a spine synapse of a CA1 neuron followed by Calcium (Ca^{++}) influx and the activation of Ca^{++}/calmodulin, which leads to enhanced transmitter release. Repeated stimulation leads to additional activation of cyclic AMP (cAMP) and the cAMP-dependent protein kinase A (PKA). PKA in turn recruits the mitogen-activating protein kinase (MAPK), and both enter the cell nucleus and activate the cAMP response element-binding (CREB) protein. This eventually leads to the expression of genes with regulatory functions and with effects on the growth of existing and formation of new spine synapses as the basis of a prolonged increase in synaptic transmission (after Kandel, 2001, modified.)

The processes mentioned above address the fear-conditioning event inside the amygdala, but leave the influence of the amygdala on processes in the cortico-hippocampal system unanswered. However, there are strong direct projections from the basolateral amygdala to the hippocampus impinging directly on hippocampal pyramidal cells as well as on cells of the entorhinal cortex. According to Cahill & McGaugh (1998), the basolateral amygdala essentially regulates via these afferents the consolidation of both episodic and semantic memories. A second way the amygdala controls the hippocampus and EPPC is via the first and second stress responses described above. Emotionally arousing events activate the amygdala, which in turn influence the release of noradrenaline in the locus coeruleus, of adrenaline by the adrenal medulla
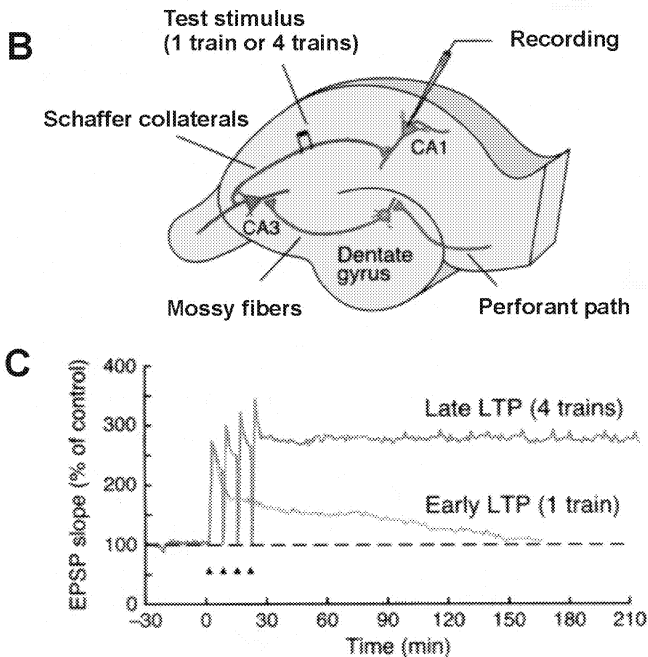
Figure 5 (cont.). The major hippocampal pathways involved are shown in **B**. The *perforant path* runs from the subiculum to the dentate gyrus, where it activates the granule cells. Axons of these latter cells form the *mossy fibers*, which project to pyramidal cells of the CA3 region of Ammon's horn (cornu ammonis, CA). CA3 cells in turn project, via *Schaffer collaterals*, to pyramidal cells in the CA1 region. In **C**, differences in early and late LTP are shown. A single train of stimuli for one second at 100 Hz elicits an early LTP, while four trains at intervals of 10 minutes elicit a late LTP resulting in a prolonged increase in strength of postsynaptic response.

and of cortisol by the adrenal cortex. Accordingly, electrical stimulation of the amygdala during situations associated with emotions reinforces the consolidation of declarative remembrances, while injuries to the amygdala or its efferent pathway, the stria terminalis, impair or even block this consolidation (Cahill & McGaugh, 1998). In the opinion of Cahill and McGaugh, the basolateral amygdala is decisive for the consolidation of memories through emotions. The activity of the basolateral amygdala is high during emotional conditioning and decreases as soon as the conditioned behavior has been established.

Conclusion

The great influence of emotions on learning and the formation of memories is not only an experience of daily life, but a well established fact in psychology and neurobiology. Emotions are formed unconsciously in the limbic system, and they become conscious only when limbic centers such as the amygdala sufficiently activate portions of the associative cortex. Conscious emotions are "short messages" of our unconscious experiential memory, which contains the evaluation of everything we have done since the beginning of our life, including much of our intrauterine existence. This memory strongly influences our declarative memory system (hippocampus/EPPC, cortex) as well as all executive functions of the brain (cf. Roth, 2001).

It is believed that hippocampus and EPPC process and organize information about *details* and the *context* of events in a rather "unemotional" fashion, whereas the amygdala and the mesolimbic system are mainly involved in the *emotional* aspects of events (especially with respect to good or bad consequences), but are poor at recognizing details. Thus, only the combined information from hippocampus/EPPC and from the limbic centers yields a full, detailed and emotionally loaden picture of a situation. This guarantees that all we are planning or doing is done in the light of previous experience.

While present neuroscience is able to present a general view of the interaction between emotions, learning and memory, many details at the cellular and molecular level are still unclear. This lack of knowledge has one simple reason: the more neurobiologists try to investigate these cellular and molecular processes the more they must be studied under more or less artificial conditions. Accordingly, long-term potentiation and its related cellular and molecular processes are best studied under in-vitro conditions far away from the feeling, learning and acting organism. Many new techniques and new experimental approaches need to be developed before neurobiologists can bridge this crucial gap.

Section B

ORGANIZATION OF MEMORIES

5

The Principle of Code-Specific Memory Representations

Frank Rösler and Martin Heil

The hypothesis of distinct memory codes proposes that entities belonging to global categories as verbal and spatial representations, or to more specific categories as faces, objects, living or non-living entities, are stored and reactivated in functionally separate memory partitions. In this chapter we will summarize evidence which supports this principle of code-specificity in memory. First, we will briefly review the empirical roots which can be found in Cognitive Psychology, Experimental Neuropsychology, and Clinical Neuropsychology. We will then outline a general neuroscientific theory which explains why code-specific memory representations do most likely exist, and finally, in the main part of the chapter, we will give an overview over recent brain findings that are highly consistent with the idea of code specific storage and retrieval within topographically distinct neural networks.

Empirical Foundations

In most textbooks on Cognitive Psychology a distinction will be found between verbal and non-verbal storage or between abstract-discrete vs. concrete-analog representations. This "Dual-code theory" has its origins in research on mental rotation and imagery (Kosslyn, 1994; Shepard & Cooper, 1982; Shepard & Metzler, 1971) where it was observed that mental representations of complex visual objects seem to have properties which are analog to their physical properties in the real world. A key finding was that a mental transformation of a visual object, e.g., its

imagined rotation or its imagined change of size, took an amount of time which was proportional to the magnitude of the transformation. This was taken as evidence that complex visual objects are represented in physical-like manner such that all directly observable spatial relations are exactly preserved in memory. In contrast, verbal entities seem to be stored in a much more abstract, symbolic form. For example, the perceived surface structure of a sentence or a longer text, i.e. its exact phrasing, is usually forgotten and only the abstract meaning, the propositional content, will be stored. These and other observations supported the claim that distinct storage principles must exist for verbal and non-verbal or propositional and spatial knowledge (Paivio, 1986).

The claim of functionally distinct codes for verbal and non-verbal memory representations does not necessarily imply a structural distinction in the sense that distinct memory compartments exist for verbal and non-verbal entities. However, results from dual-task studies make it very likely that such distinct codes bear upon separate neural networks. A general finding with dual-task paradigms is that working memory tasks which involve similar representations impede each other much more than tasks which involve less similar representations (Baddeley & Lieberman, 1980; Brooks, 1968; Logie, 1986). These findings led Baddeley to the idea that there may exist two separate working memory compartments, a phonological loop, in which verbal information is kept in form of an auditory-phonological trace, and a visual-spatial sketch-pad, in which visual objects are kept as an analog image.

Heil, Rösler, Rauch, & Hennighausen (1998) studied such a dual-task effect with a long-term memory paradigm. In this experiment participants had to learn associations of different kind. In one condition pictures were associated with spatial positions in a grid-pattern, and in another condition similar pictures were associated with verbal labels. In a first session, participants were trained with anticipation learning procedures to almost perfect memory performance. In a retrieval test, one day later, two pictures were presented as visual cues and the participants had to decide whether these two pictures shared an association with a previously studied spatial position or verbal label. Decision time was the dependent variable. Thus, the same type of cue was used to activate memory representations that were either spatial or verbal associations. The retrieval task was performed either alone or in combination with a secondary task. The latter could be verbal (gender decision of nouns presented visually) or spatial (a mental rotation task). The results were straightforward: In the control condition performance was equivalent with both types of associations while in the two conditions with a secondary task a clear interaction appeared. With a spatial secondary task the retrieval of spatial associations was more impeded than the retrieval of verbal associations and with a verbal secondary task the performance pattern was reversed. There were also some concurrent costs, i.e. response times with a secondary task were in general longer than without one, but the main finding was the kind of a double dissociation between spatial and verbal memory retrieval conditions. This suggests at least a partial independence of the resources which are loaded by the one or the other type of retrieval task.

Another distinction of specific memory codes has been suggested by experimental neuropsychologists for spatial and non-spatial features of visual objects. The empirical basis was a double-dissociation found in monkeys who were trained in a delayed matching-to-sample task and who received lesions of distinct cortical areas (Pohl, 1973). In one task the animals learned

to discriminate between spatial locations, and in another between visual features such as color, shape and texture of objects. The animals with lesions in superior parietal cortical areas were heavily impaired in their spatial discrimination abilities but could still perform object feature discriminations. In contrast, lesions of inferior temporal cortical areas led to an impairment of feature discriminations while spatial discriminations remained unaffected. This pattern of findings, which was corroborated by many further studies, led Mishkin, Ungerleider, & Macko (1983) to propose two distinct routes of higher recognition functions; the well known "what" and "where" pathways. Due to the particular task used in these studies, which comprises both perceptual and working memory functions, the distinction applied to both the on-line processing of these features as well as to their intermediate storage and retrieval. Oversimplified, the theory suggests that on-line processing (encoding), storage, and reactivation of spatial and non-spatial features of objects are functionally and structurally separated in the dorsal "where" and the ventral "what" pathway.

Finally, neuropsychological case studies suggest an even more specialized functional dissociation of memory codes. Category specific recognition memory deficits have been reported among others for faces (the syndrom of prosopagnosia; see e.g.De Renzi, 2000), fruits and vegetables (Hart, Berndt, & Caramazza, 1985) and living vs. non-living entities (Warrington & McCarthy, 1987; Warrington & Shallice, 1984). One explanation of these somewhat peculiar deficits rests on the assumption that members of the distinct categories share distinct basic features (e.g., visual, auditory, tactile, kinesthetic elements, etc.) and that these features are processed in cortical areas that are closely tied to the respective input modalities (Allport, 1985). If access to the basic features are lost due to brain injury, the representations of the tokens of one category which are defined by these features may be lost as well. A similar explanation is given for the double dissociation observed in some patients who have difficulties in accessing either verbs or nouns. It is assumed that verbs are bound to motor features while nouns are closely linked to visual object features. Accordingly, knowledge (memory) of verbs should be more likely impaired with lesions that affect areas close to the motor cortex, while memory for nouns should be impaired with lesions that affect the primary and secondary perceptual areas. At least some data give support to such a compartmentalization of word knowledge (Caramazza & Hillis, 1991; Damasio & Tranel, 1993).

Theoretical Foundations

The aforementioned empirical findings give support to the idea that neither working- nor long-term-memory can be defined as a unitary system in which all types of information are stored in the same code, e.g. as abstract propositions, and which can be localized within narrowly circumscribed brain structures. Rather, memory representations seem to be functionally distinct in that they compete for distinct processing resources, and they seem to be structurally separable, in that anatomically distinct lesions can impair different memory contents.

The hypothesis of code specific storage and representation within anatomically distributed cell assemblies has been further elaborated in recent neuroscientific theories of memory which make an attempt to explain memory from a more elementary, biological perspective. The basic

ideas of this theoretical framework were put forward by, among others, Braitenberg & Schüz, 1991; Damasio, 1989a, b; Fuster, 1995; McClelland, McNaughton, & O'Reilly, 1995; Zola-Morgan & Squire, 1993.

The starting point is the assumption that the neocortex is a gigantic storage-system which houses all memory contents in the form of modified synaptic connectivities. The neocortex is not seen - as it was the case in older models of cognition (e.g., Atkinson & Shiffrin, 1968; Shiffrin & Schneider, 1977) - to be compartmentalized into modules specialized for processing and other modules specialized for storage of information. Rather, it is thought that information is stored in the very same cortical cell assemblies where on-line information processing during perception, imagery, reasoning, motor planning, and other mental activities takes place as well. As a matter of fact, these information processing routines are seen as nothing other than adjustments of input activation patterns to already stored engrams. An engram is seen as a particular connectivity pattern between the synapses of a set of neurons and a memory representation is assumed to be the neural activation pattern that can develop in such a cell assembly due to the established connectivities. Perceptual input, for example, instantiates a particular activation pattern in the involved cell assemblies. If this pattern converges to a stabilized and already familiar pattern - because it resonates with the established connectivities - then the system "recognizes" an object, a person, for example. Thus, perception as well as all other cognitive activities, are seen as adjustments of activity patterns to the given connectivities in cortical cell assemblies. Information processing routines - visual perception, language comprehension, problem solving. etc., - as they are defined in models of cognition are all reduced to the process of memory "resonance". Thus, each cognitive act is in its essence a process of memory access, it is an instantiation of neural activation patterns in the neocortical storage-system.

Information storage is achieved by means of two distinct mechanisms (McClelland, McNaughton, & O'Reilly, 1995). First, each processing activity in the neocortex which corresponds with a particular pattern of neural activity can directly change the involved synaptic connectivities. These changes are minimal, at least during adulthood, and they are usually not great enough to permit a full reconstruction of an activation pattern which was stimulated only once. However, if the very same activation pattern is instantiated repeatedly then the minimal synaptic changes may accumulate and the full engram will be engraved such that the complete activity pattern can be reactivated at a later time by an internal or external cue. Storage, which is achieved by this mechanism, belongs to the category of implicit learning as it takes place, e.g., in priming (Paller & Gross, 1998) or sequential learning situations (Rüsseler & Rösler, 2000). The second mechanism involves the so-called bottleneck structures as the hippocampus, the perirhinal cortex, the mammilar bodies, etc. (Markowitsch, 2000; Squire & Zola-Morgan, 1991). This mechanism allows explicit and fast learning. In a first step, structural changes of synaptic connectivities are established in the hippocampus and related structures. To achieve this, the cortical activation patterns are translated into a compressed version which comprises a much smaller set of neurons than the complete neocortical pattern. It can be understood as a kind of address code by means of which the full set of neocortical cells involved in the representation of an original activation pattern can be accessed. Reactivation of these explicitly and rapidly stored engrams means that the original neocortical activation pattern is reinstantiated by means of the address code. Again, either an internal or an external cue can start the reactivation process. The compressed activation pattern residing in the bottleneck structures can become a stable,

longer-lasting engram due to the plasticity mechanisms which are available there. The connectivity changes which can take place during one instantiation of the pattern are larger in these bottleneck structures (e.g. the hippocampus) than in the neocortical system. Therefore, a long-lasting engram can be established after few repetitions already.

With these two mechanisms it can also be explained why a hippocampal reactivation may no longer be necessary to access memory contents as observed in patients who suffer from complete hippocampectomy (Scoville & Milner, 1957; Squire, 1992). Although these patients are no longer able to explicitly store new information they can still reactivate knowledge that they had learned before the loss of the hippocampal system (MacKay, Stewart, & Burke, 1998). To explain these observations it is assumed that the neocortical activation pattern representing a memory trace can also be reinstantiated "off-line", independently from external cues, e.g., by intentional silent rehearsal or unintentionally by spontaneous recollections triggered by related contextual cues (possibly also during sleep). These reinstantiations of the full neocortical activity pattern lead over a longer time also to changes of the cortical connectivities (due the plasticity mechanism outlined above for implicit learning). Therefore, after a long enough period of consolidation the full engram can be reactivated without the "detour" over the hippocampal system and the compressed code. Declarative, explicitly learned memories will be transformed over time by means of this mechanism into permanent cortical engrams. These changes need time, because the learning constant which changes the cortical synaptic links is very small and, therefore, it needs many repeated reinstantiations. This explains the effects of consolidation and also the gradual reduction of retrograde amnesia relative to time between learning episode and lesion of the hippocampal bottleneck system.

Since the reinstantiations of activation patterns during memory retrieval take place in exactly those areas in which the information was also processed during the first perceptual encounter, it follows that there should be a distinction of codes according to the modality specificity of the cortex. That is, retrieval of representations which are defined by visual features should lead to an activation of the primary, secondary, and tertiary visual cortices in the occipital, parietal and temporal lobes. Likewise, representations which are defined by auditory or somatosensory features should be reinstantiated in the respective auditory or somatosensory cortices, and movement related associations should be reactivated in motor areas, etc. Thus, a specialization of cortical cell assemblies is not given by the distinction of storage or processing functions but rather by the features which define our cognitive entities. These are tied to the input modalities. Considering that cell assemblies for the processing of visual features are highly specialized (van Essen, Anderson, & Felleman, 1992), it is conceivable that members of particular categories that share a set of features may be represented within a distributed but nevertheless characteristic neural network.

A distinction between working memory and long-term memory is given in the framework by the status of the neocortical connectivities and the actual activation patterns rather than by structurally different compartments. Whether an entity has the status of a long-term memory trace depends on whether the neocortical connectivities have changed permanently due to repeated instantiation. A working memory trace is the current activation pattern in a particular cell assembly that has developed, due either to an established long-term memory engram or to a particular input activation pattern. In any case, whether a memory content has the status of a

transient working memory trace or the status of a permanent long-term memory trace, it will be defined by the same activation pattern within the very same cortical cell assemblies.

Finally, an activation pattern which defines a memory representation will most likely involve several distinct neocortical cell assemblies whose elements have distinct functional properties - e.g., color sensitivity, movement sensitivity, etc. Thus an engram will be defined by a distributed activation pattern. All the elements will be activated simultaneously and possibly bound together by special mechanisms as phase locking over short and far reaching and linking connections (Eckhorn et al., 1988; Singer, 1989; Munk in this volume).

To summarize: According to the neuroscientific framework of memory it has to be assumed that distinct codes (e.g. verbal, nonverbal, visual, auditory or other representations) are reactivated within topographically distinct cortical cell assemblies, in particular in those areas which are specialized for verbal, nonverbal, visual etc. information processing. The brain does not have special storehouses for memory contents which are distinct from areas which are specialized for sensory or motor "on-line" processing. Rather, the engram is reactivated in the very same areas as on-line processing takes place, or, seen from the other perspective, on-line processing whether it be visual perception, language comprehension, motor preparation, etc. is in its first and foremost sense a question of memory access. Moreover, long-term memory traces and working memory traces are reinstantiated in the very same cell assemblies, i.e. there is no structural difference between LTM and WM.

There is, however, one caveat. So far the model is incomplete, because it does not make any assumptions about control structures which, for example, guide attention, i.e. which select activation patterns as the currently relevant ones and which suppress disturbing, irrelevant patterns, or which take care that a particular activation pattern is kept alive although the triggering input is no longer available, or which can intentionally change or modify an activation pattern. The work of Goldman-Rakic (1995; Goldman-Rakic, O' Scalaidhe, & Chafee, 2000) strongly suggests, for example, that storage and modification of WM traces is controlled by executive centers which are located in the prefrontal cortex. Other researchers, such as Kosslyn, postulate specialized cell assemblies which are involved, when memory contents have to be modified during imagery (Kosslyn & Thompson, 2000). Such specialized areas for image transformations seem to be located in the parietal cortex. Although most of the neocortex seems to be a memory system which has a code or feature specific topography, there also seem to exist some specialized cell assemblies which control the relative predominance of cortical activation patterns, which - as expressed in the language of cognitive psychology - control information flow.

Findings from Brain Imaging Studies

Both the empirical and the theoretical foundations of a code-specific memory theory provide clear expectations about brain activation patterns which can be made visible by brain imaging techniques such as positron emission tomography (PET), functional magnetic resonance imaging (fMRI), and event-related electro- or magnetencephalography (EEG, MEG). For an introduction

to these techniques see for example (Cacioppo, Tassinary, & Berntson, 2000; Gevins, 1987; Moonen & Bandettini, 2000; Papanicolaou, 2000).

In the following we will review some of the more recent evidence from brain imaging studies in which one or the other code specific distinction was investigated. The material will be organized according to the conceptual distinctions proposed in cognitive and neuropsychology: i.e. verbal vs. spatial working memory (WM), object vs. spatial working memory, verbal vs. spatial vs. motor long-term memory (LTM), and category-specific long-term memory representations.

Spatial and Verbal Working Memory

Smith, Jonides, & Koeppe (1996) studied brain activation patterns with PET while subjects were engaged in verbal and spatial memory tasks. In one experiment they used a spatial and a verbal version of the Sternberg memory paradigm (Sternberg, 1969). In the spatial condition participants had to store the positions of three randomly arranged and briefly presented dots. Three seconds later they had to decide whether a circle indicated a location in the display field corresponding to the position of one of the dot locations. In the verbal version of the task, participants had to store four letters and 3 seconds later they had to decide whether a probe letter belonged to the memorized set or not. Both versions of the task were compared with control conditions in which the same stimuli were used but in which a decision about the probe was based on perceptual comparisons without any memory load. The subtraction images between working-memory and control task revealed that the verbal WM task activated primarily left-hemispheric regions whereas the spatial task activated only right-hemispheric regions. This pattern of findings was confirmed in other studies with similar versions of a verbal and spatial working memory task (Awh et al., 1996; Jonides et al., 1993; Mellers et al., 1995).

Another approach to show a double dissociation between verbal and spatial working memory was pursued by Rolke, Heil, Hennighausen, Häussler, & Rösler (2000). One intention of this study was to compare verbal and spatial WM with a parametric variation of the load imposed on each type of WM "device" postulated by Baddeley. The reasoning behind this study was that a systematic variation of load should activate the corresponding neural networks in gradual steps and these intratask activation differences should show a clear topographic difference. Such a design controls for overall differences in task difficulty, because even if the verbal or the spatial version of a task are not completely equal in their overall demands it is nevertheless possible to study the relative activation differences within one task which are due to a task specific difficulty manipulation. Moreover, the study aimed to stimulate activities which are postulated to take place within the code-specific working memory devices - "rehearsal" within the phonological loop and the visuo-spatial scratch-pad - than rather invoking pure storage.

In the verbal version of the WM task, the participants saw a series of words - three or four - which they had to remember. Presentation time of each stimulus was 600 ms with a 200 ms ISI. Two seconds later an instruction stimulus informed the participant about a working memory operation to be performed before a probe stimulus would be presented. The participants had to either maintain the sequence as it had been presented or exchange some of the items with

one other. In a condition of medium difficulty participants had to exchange two items, e.g., if the presented sequence had been "island, fog, coat, and zebra", the participant was instructed to exchange positions 2 and 3 and thus he or she had to produce in WM the string "island, coat, fog, and zebra". In a more difficult condition items 1 and 2 and items 3 and 4 had to be exchanged, such that the sequence "fog, island, zebra, coat" resulted. Then, 4.5 sec later, a sequence of probe displays was presented which contained one word at a particular position and it had to be decided whether the position of this word corresponded to its position in the stored and possibly modified sequence of words.

The very same set-up was used to create a non-verbal working memory task, one which loads the visual-spatial scratchpad. First, the participant saw a sequence of displays each showing a grid pattern built from 12 squares. In each of the three or four displays one square always popped out due to a distinct luminance. The locations of the darker squares were the critical information that had to be memorized. This was again followed by an instruction stimulus which indicated whether the sequence had to be kept as it was, whether two elements, or whether the elements of the first and the last item pair had to be exchanged. Finally, a series of test displays was presented each showing the grid pattern and in one display a square popped out again due to a darker shading. The participant had to decide whether this stimulus matched with the corresponding stimulus in the memorized and possibly modified sequence of grid patterns.

In a pilot study response times were measured in a version of the task in which the participant had the option of releasing the series of test displays as soon as she felt ready. Both versions of this working memory task did not differ substantially in overall response speed and both showed a monotonic increase of response time with increasing difficulty. The decision times amounted to about 850 ms for the two baseline levels ("keep the sequence as it is") and increased to 2500 and 3300 ms for the most difficult levels of the spatial and the verbal rehearsal and reordering conditions.

Activation of cortical cell assemblies was measured in this study by monitoring slow event-related brain potentials. Extracranially measurable slow waves are most likely generated by synchronized postsynaptic potentials and negative and positive slow waves are correlated with relative increases and decreases of excitatory PSPs, respectively, within circumscribed neural networks (see among others Birbaumer, Elbert, Canavan, & Rockstroh, 1990; Elbert, 1993; Mitzdorf, 1991; Skinner & Yingling, 1977; Yingling & Skinner, 1976). Thus the topography of event-related slow waves of the EEG can indicate which cortical areas are activated by a task and their amplitude can reflect the amount of activation prevailing in the predominantly active areas (Rösler, Heil, & Röder, 1997).

As figure 1 reveals there were substantial slow wave shifts in both WM conditions. In the verbal condition the maximum of the slow wave activity was found over the left to central anterior cortex (maximum at electrode FC3) and in the non-verbal, spatial condition over more central areas (at Cz and Pz). To measure the intratask amplitude modulation the difference of the average slow wave amplitude was computed between the most difficult and the baseline condition. These difference scores were standardized (mean = 100, sd =10) and plotted as topographic maps (inserts below the voltage time traces in Fig. 1). The topographic difference of this load-related net-effect is very striking and highly significant. Its maximum is located in the same area as the overall amplitude maximum, over left anterior to central areas in the verbal

condition and over central to parietal areas in the spatial condition. Thus, it can be concluded that the two working memory tasks which by definition should either load the visuo-spatial scratch pad or the phonological loop invoke topographically distinct cortical activation patterns. The topography is not only distinct for the two tasks as such but also for the intra-task amplitude effects which reflects a task-specific load variation.
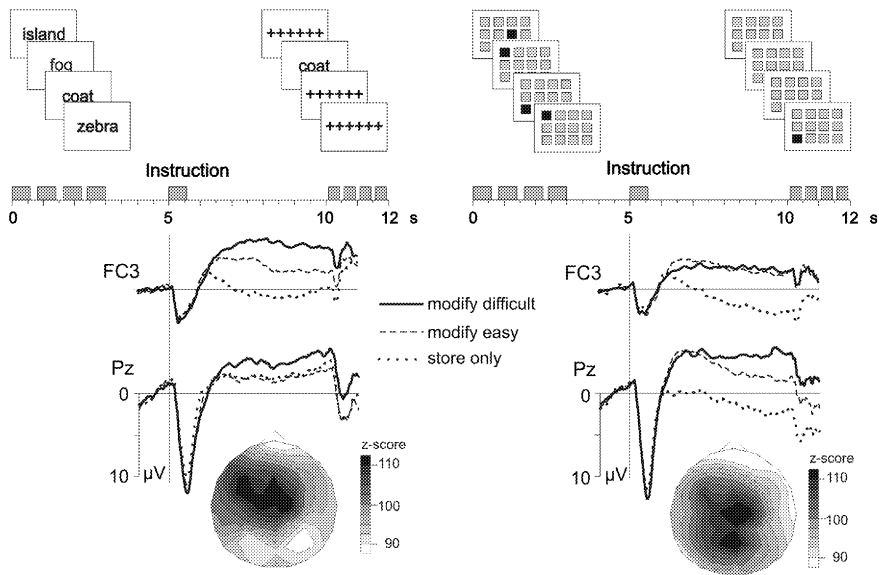

Figure 1. Slow wave ERPs during storage and modification of verbal (left) and spatial (right) working memory contents. The top row shows the experimental paradigm (s. text for details); underneath are the slow waves which are triggered by the instruction cue (negativity in this and the following figures is drawn as an upward deflection). The topographical maps show the standardized amplitude difference between conditions "modify difficult" and "store" (relative more negativity is shown as darker shading and indicates more activation of the modify condition). (Data from Rolke, Heil, Hennighausen, Häussler, & Rösler, 2000).

In the study of Rolke, Heil, Hennighausen, Häussler, & Rösler (2000) pure storage was defined as the baseline condition and the other conditions involved storage plus a modification of the memory set. Within each task both aspects of WM were related to a similar topography but between the verbal and the spatial task these topographies were clearly distinct. Marshuetz, Smith, Jonides, DeGutis, & Chenevert (2000) tried to dissociate the aspects of storage and of modifications of verbal working memory contents. To this end they contrasted three conditions in an fMRI study. One required mainly the storage and rehearsal of verbal information, i.e subjects had to memorize a sequence of letters (the memory set) and later had to make decisions about the identity of probe letters with respect to the elements of the memory set (a typical Sternberg paradigm). In the second condition the same stimuli were used but subjects were

required to memorize the ordering of the elements of the memory set, for example, if the to be stored letter string was "DNPLT" subjects had later to decide whether a particular letter, e.g. T, did actually follow another letter, e.g., N. These memory tasks were compared with a purely perceptual task.

Both memory conditions, if compared with the perceptual control, resulted in a substantial fMRI activation of Broca´s area, the left premotor cortex and posterior parietal areas. The parietal activations were more pronounced within the left hemisphere. These findings substantiate the already mentioned observations about the cortical areas being activated during verbal WM storage and rehearsal (see Henson, Burgess, & Frith, 2000; Jonides et al., 1997, 1998+; Jonides this volume). Additional activations within the dorsolateral prefrontal cortex (DLPFC) and also within posterior parietal areas were revealed by comparing the ordering task with the item task. Thus, the condition with verbal working memory *operations* produced a somewhat different and stronger activation pattern than pure *storage* and rehearsal. The authors assume that these additional activations in the ordering task are related to executive functions, because the subjects have to scan the stored letter string. Both regions, the DLPFC and the superior parietal cortex have been related to executive functions in other studies as well. In particular, DLPFC activations have been found in many tasks which ask for attentional control (see e.g., D'Esposito, Postle, & Rypma, 2000) and parietal activations were found when spatial memory traces had to be modified (see below) or when decisions were required about set magnitudes and arithmetic facts (Chochon, Cohen, Van de Moortele, & Dehaene, 1999; Cohen, Dehaene, Chochon, Lehericy, & Naccache, 2000).

A dissociation between storage-related and transformation-related activity has also been observed for the domain of spatial working memory contents. A standard paradigm to study spatial working memory is given by mental rotation and other imagery tasks. Kosslyn (1987; Kosslyn & Koenig, 1992) presented a very detailed theory on higher vision and imagery in which he distinguishes various subprocesses which contribute to real and imagined visual representations. Among others, Kosslyn postulates WM or buffer modules which store visuo-spatial information and executive modules which read and rewrite information from and to the buffer modules and which modify the stored information. These constructs were mainly derived from analyses of performance deficits of patients who suffered from brain damage. Kosslyn´s theory applies in the first place to higher vision and visual imagery, but his theoretical framework can be generalized to other modalities as well. In so doing, it can be postulated that there exist buffer and transformation modules for haptic representations, too, because haptic imagery is possible independently from vision as revealed by studies with congenitally blind people (Röder & Rösler, 1998; Röder, Rösler, & Hennighausen, 1997; Röder this volume).

We tested subjects in two versions of a mental rotation task in order to see whether storage and transformation-related activation patterns can be dissociated when a spatial working memory task has to be performed. The first version was a visual mental rotation task (Rösler, Heil, Bajric, Pauls, & Hennighausen, 1995) in which line-drawings of six-sided stars, constructed from equilateral triangles, were used as stimuli. Each star showed a characteristic pattern of white and grey triangles. On each trial such a figure had to be stored during an inspection time of 3 seconds. After this the stimulus disappeared and the subject heard one of three tones of different pitch which gave the instruction to either keep the figure in memory as it was, or to rotate it 60

or 120 degrees clockwise. Finally, about 10 sec later the subject saw a test stimulus and he or she had to decide whether this formed a match with the image (the one kept in working memory from the very beginning, or the one transformed). An almost identical condition with tactile stimuli was also used by Röder, Rösler, & Hennighausen (1997), i.e. the subjects scanned and stored a tactile stimulus by touching a 2 cm diameter pixel field with their index finger. After disappearance of the stimulus they received an instruction tone and had to remember the image as it was presented or as it would be if rotated 60 or 120 degrees clockwise. Finally, a probe stimulus was presented 8 s after the instruction stimulus and the subjects had to decide whether this probe matched the image or not. So, in this experiment the subjects had to perform a haptic imagery task.

A pilot study proved the equivalence of the two versions of the task with respect to difficulty or task load, i.e. error rates and response times were comparable in the visual and in the haptic version. The cortical activation was monitored by means of slow ERPs. In the visual task very pronounced negative slow waves emerged over the occipital cortex when the to be stored stimulus was presented and prevailed during the retention interval until probe presentation. This slow wave pattern with a maximum over the visual projection areas was present in all three rotation conditions (0, 60, and 120 degrees). However, in the two rotation conditions an additional negative slow wave appeared over the parietal cortex whose amplitude increased with the rotation angle. It was largest in the 120° condition, medium in the 60° condition and not present in the 0° condition. A similar pattern was present in the tactile condition. In the tactile tasks little negativity was found over the occipital cortex. Rather, the presentation of the tactile stimulus and the storage and sustaining of the tactile image was accompanied by a very pronounced negative slow wave over the left central cortex, i.e. over the somatosensory projection areas contralateral to the hand used for stimulus encoding. It is important to note that this negativity over the somatosensory projection area prevailed during the storage period while there was no additional tactile input. There was again a rotation related negativity which increased with the rotational angle. This effect had its maximum over the parietal to central cortex as in the visual task.

A direct comparison of the standardized topographies revealed that the topography of the activation pattern was clearly distinct for the two versions of the task during encoding and storage. The maximum was found over the occipital projection areas for the visual task and over the left central cortex for the tactile images. By contrast, the difference potential which reveals the net rotation effect (difference between the 120° and the 0° condition) had its maximum over the parietal cortex on both versions of the task (see Fig. 2).

These results suggest that storage and maintaining of analog representations evoke modality specific patterns of activation which have their maxima over the projection area of the stimulus modality. Most likely these areas serve as a buffer which represent the images by means of their constituting features. In addition, transformations of analog representations evoke modality unspecific patterns of activation over the parietal cortex. This activation seems to be generated by a transformation module which handles modality-unspecific spatial information.

Converging evidence for this conclusion comes from a study of Carpenter, Just, Keller, Eddy, & Thulborn (1999) who used the fMRI technique to monitor brain activation patterns of mental rotation. Their subjects were tested with a classic mental rotation task in which two-

dimensional projections of three-dimensional "brick figures" had to be compared. In one display two figures were presented which were rotated against each other either in the fronto-parallel plane or in the plane which is perpendicular to fronto-parallel one. Subjects had to decide whether the two objects could be transformed into each other by a simple rotation operation or not. This condition was compared with a baseline in which the participants had to scan columnwise a pair of two-dimensional grid patterns. Recording time was 24 sec for each condition.
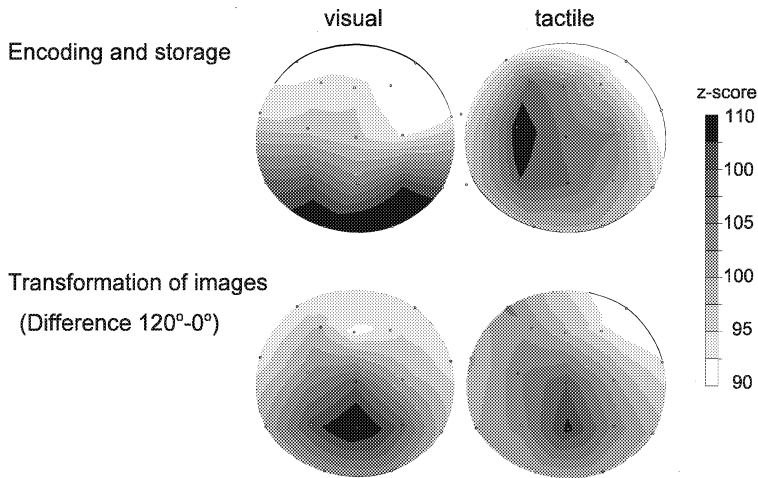

Figure 2. Topography of slow wave ERPs during encoding and storage and transformation of visual and tactile images during a mental rotation task. (Data from Röder, Rösler, & Hennighausen, 1997; Rösler, Heil, Bajric, Pauls, & Hennighausen, 1995).

The grand average showed pronounced activation patterns bilaterally within the primary visual cortices (area 17/18), the secondary visual cortices (area 19), and within the parietal cortex (area 7a/b). The activation within the parietal cortex proved as dependent from the rotational angle - it increased monotonically with larger angular disparities. This was shown by both the number of active voxels as well as the mean activation level relative to the baseline. It is worthwhile to mention that the rotation-related activity was not lateralized to the right hemisphere but prevailed in the left and right parietal cortex with about the same strength. The same was observed in our slow wave study described above. There, too, no lateralization of the activation pattern could be detected if the data of all subjects were averaged. A lateralization was only revealed in a post hoc analysis which contrasted two subgroups of subjects who differed in their mental imagery abilities (Rösler, Heil, Pauls, Bajric, & Hennighausen, 1994). Thus, the rotation-related activity as such seems not to be lateralized.

With the fMRI method Awh et al. (1999) also provide evidence that the early visual areas are primarily in storing (and rehearsing) spatial positions in a briefly presented display. This could be shown by contrasting the rehearsal activities in a retention interval which followed left- and right hemifield stimulations with a set of spatial locations to be remembered. The interesting finding was that the activation during the retention interval was more pronounced within primary visual areas contralateral to the hemifield in which the stimuli to be remembered had been presented. This clearly supports the claim that those areas which are involved in on-line processing of stimulus features are also involved in keeping and reactivating a corresponding memory trace.

Taken together the studies that monitored brain activation patterns during verbal and spatial working memory tasks give support to the idea that these two types of representations are stored within distinct cortical cell assemblies. The studies also suggest that there exist not only areas which sustain these representations in a code which matches the input modality but also additional areas which enable transformations of the stored representations. These latter areas can be localized within the dorso-lateral prefrontal (DLPFC) cortex and within the parietal cortex.

There is a continuing debate whether the DLPFC areas which seem to enable executive functions in WM tasks also have a code specific topography. One idea is that a verbal-spatial differentiation does not only hold for more posterior cortical areas but also within the DLPFC. Owen (2000), however, reviewed a large number of neuroimaging studies with spatial and verbal working memory tasks and did not find compelling evidence for such a code-specific differentiation within frontal areas. Rather, he came to the conclusion that the activation patterns during verbal and spatial WM tasks are generated within the same frontal and prefrontal areas. This would support the idea of so called convergence centers (Damasio, 1989a) in which a more abstract address code is held which points to the code specific, more posterior areas where the code-specific representations are reconstructed.

Spatial and Object Working Memory

Motivated by the work of Mishkin et al. (1983) several studies were conducted to objectify the "what" and "where" pathways by means of brain imaging techniques. For example, Postle & D'Esposito (1999) used identical stimuli to probe shape and location memory in a delayed recognition task. Subjects saw an initial target, i.e. a nonmeaningful polygon at a particular location of the display. They were instructed to store the shape of the polygon. Six and a half seconds later the subjects saw two other polygons at other locations and had to decide whether one of the shapes matched the previously presented and stored shape, and also store the locations of the new polygons. Another 6.5 seconds later a new polygon was presented and the subjects had to decide whether its location corresponded to the location of one of the two previously presented polygons. To control for sequence effects the procedure was also reversed, i.e., subjects had first to store locations and after this the shape of polygons. The study was designed to record event-related fMRI signals and so the timing of the activation functions was also available. The results revealed a clear code-specific dissociation within posterior areas. The superior parietal lobe was activated in the spatial condition and the ventral posterior temporal lobe during the shape or object condition. By contrast, the prefrontal cortex was activated in the very same

manner by both tasks. So, this study substantiates the findings reported above on verbal and spatial working memory tasks. A code-specific dissociation is found only in the posterior part of the brain while the anterior "executive" areas seem to be code-unspecific (see also D'Esposito, Postle, & Rypma, 2000; Mecklinger, Bosch, Grunewald, Bentin, & Von Cramon, 2000; Postle, Berger, Taich, & D'-Esposito, 2000).

Somewhat at variance with these findings are the results of studies of Belger et al. (1998) and Banich et al. (2000). Belger et al. also compared a shape and a location version of a Sternberg-type WM task and observed a code-related dissociation in the prefrontal cortex: The shape task induced a bilateral prefrontal activation while the location task activated the right PFC only. Banich et al. (2000) found a prefrontal dissociation in two versions of a Stroop test. In one the subjects had to process incongruent color information and in the other incongruent spatial information. The spatial task led to a more dorsal activation and the color task to a more ventral activation within the DLPFC which again suggests a code-specific dissociation in the executive areas.

So, the issue of a code specific dissociation within anterior executive areas, in particular, within the DLPFC is not yet settled. Some researchers have found such a dissociation for verbal vs. spatial and spatial vs. color representations while others have not. However, as will be outlined below, even a completely overlapping activation pattern in one area, as it may be revealed by the grand average of fMRI recordings, does not exclude a code specific representation in this area. With a better spatial resolution and a different methodological approach code-specific subdivisions may be revealed within small brain areas. Therefore, the contradictory findings with respect to a code specific dissociation in frontal areas may be due to the limitations of the methods used for analysis.

Long-term Memory for Verbal, Spatial, Color, and Motor Associations

In all of the aforementioned studies brain activation patterns were studied in the one or the other version of a working memory task. Thus, cortical activation patterns were recorded while representations were stored for a few seconds only. The hypothesis, however, that there exist code-specific storage systems for abstract-verbal and concrete-spatial representations, applies not only to transiently stored but also to permanently stored memory contents. Likewise, the neuroscientific theory outlined above suggests that memory representations are reactivated within the same code-specific areas, irrespective of whether the memory traces are stored for a few seconds, a couple of hours, or a lifetime. The mechanism of how these representations are reactivated may be different for one or the other retention interval: For very brief intervals of typical working memory tasks an activation pattern may prevail in the cortical areas being sustained by PFC control activity. For intermediate intervals a short-script may be stored in the hippocampus which reactivates the representation within the cortical areas. Finally, for permanently available engrams, the representation may be reactivated within the cortical cell assemblies directly, without the hippocampal short-script. Irrespective of the particular mechanism, the cortical locations where these activation patterns prevail or where they are reconstructed should always be the same.

We studied the hypothesis of code specific activation patterns during long-term memory retrieval in a number of experiments in which the retention interval amounted to at least half an hour but ranging mostly from 24 hours or longer. So, a memory representation had to be reactivated at a time when the original activation pattern was definitely not available any more as a prevailing working memory trace.
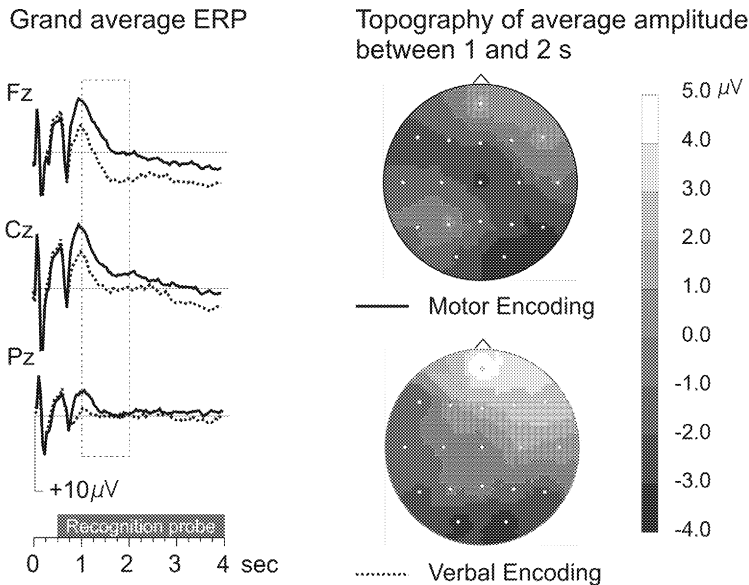

Figure 3. Slow wave ERPs during retrieval of action phrases from intermediate-term memory. The items had been stored either passively by reading the verbal phrases or actively, by enacting the described actions. The topographic maps show the activity during 1 and 2 s after presentation of the retrieval cue. (Data from Heil et al., 1999).

In one study we contrasted the retrieval of representations which were either stored in a passive listening situation (as verbal phrases) or which were linked in a more active learning situation to self-executed motor programs (Engelkamp, 1998; Heil et al., 1999). Subjects first listened to action phrases of the type "lift the pen", "comb the hair", etc. One group of subjects received the instruction just to listen and to memorize for a later recognition test. Another group received the additional instruction to perform the action with an imagined object, they would really pretend to comb their hair, etc. There were 200 phrases, 100 were selected for learning and the other 100 served as distractors for a recognition test. In the learning phase the items were presented auditorily with a presentation rate of 1 every six seconds. After a retention interval of half an hour during which part of an intelligence test was applied in order to suppress rehearsal a recognition test took place. For this the action phrases were presented on a computer screen and the subjects had to decide whether the phrase was "old" (formerly learned) or "new".

Simultaneously, event-related brain potentials time-locked to the onset of the action phrase were recorded. The retrieval related ERPs are shown on the left of figure 3.

Clear differences between the two memorization conditions can be seen. There is an overall amplitude difference between the two groups - the motor group showed a stronger activation than the passive, verbal group - but in addition, the topographic maps disclose that motor enactment during storage lead to more negative potentials (i.e. more activation) over anterior cortical areas during retrieval while a passive, verbal encoding strategy led to a larger negativity over left posterior areas during retrieval (s. right side of Fig. 3). Notice: The stimuli which triggered these topographic differences were the very same in both retrieval conditions, the visually presented action phrases. The functional difference which is reflected in the activation patterns during retrieval relates to how the representations were encoded during learning (as self performed motor acts or as verbal associations). This supports once again the claim of code specific representations which are reactivated within those cortical areas in which they had been present in the learning situation. See also Nilsson et al., 2000; Nyberg et al., 2001, who used the same paradigm and who found PET activation within the motor cortex).

In the study just described an over-all dissociation was found between two types of associations, but the possibility cannot be excluded completely that this difference was also due to some other aspects which set the two tasks apart (e.g., vividness or accessibility of a memory trace, difficulty of the retrieval situation, etc.). In another series of studies we tried to control for such possible task differences by using a paradigm which allowed exchanging the type of association without changing any other aspect of the task, and, moreover, which allowed varying the difficulty or extensiveness of the retrieval process in gradual steps (Heil, Rösler, & Hennighausen, 1994).

We, among others, compared the retrieval of spatial, color, and verbal associations. In the spatial condition subjects had to learn associations between line drawings of objects and spatial positions marked in a grid of squares. There were 18 positions in the grid and 54 objects. During learning objects were combined with either 1, 2 or 3 of the positions, such that their associative fan was 1, 2, or 3. The material had to be learned by means of an anticipation procedure and after a couple of hours the associations were fully established. In the retrieval test, which took place one day later, the participants saw two objects and had to answer whether these were linked to one another via one of the grid positions, i.e. whether they shared at least one spatial "mediator". In another experiment another group of participants learned associations between the same line drawings and color patches instead of spatial positions, and in a third experiment the participants learned associations between line drawings and words. In each case the participants were trained until they knew the associations by heart, and in each experiment the retrieval test was the very same, i.e. the same line drawings were used to trigger associations to distinct representations serving as mediators.

To summarize the features of this paradigm: The subjects had to reactivate the mediators - spatial, color, or word associations. Whether the decision was yes or no, they had to truly reactivate memory representations because they could not give a correct answer by any other means. Another nice feature was, that the mediators could be easily replaced without changing any other aspect of the paradigm. Subjects could be trained to learn associations between line drawings and spatial positions in one situation and in another, associations between line drawings

and color plates or words, but the retrieval cues remained the very same. Finally, the paradigm allowed studying retrieval situations of graduated difficulty, because the retrieval cues trigger a different number of to be checked associations depending on the fan. This paradigm was used in several versions, with independent samples of subjects or in a repeated measurement plan (Heil, Rösler, & Hennighausen, 1996, 1997; Rösler, Heil, & Hennighausen, 1995). In all versions the results were basically the same and can be summarized as follows.

A. Standardized topography during reactivation of distinct mediators
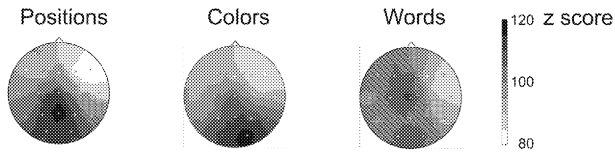
B. Grand average ERPs during reactivation of distinct mediators
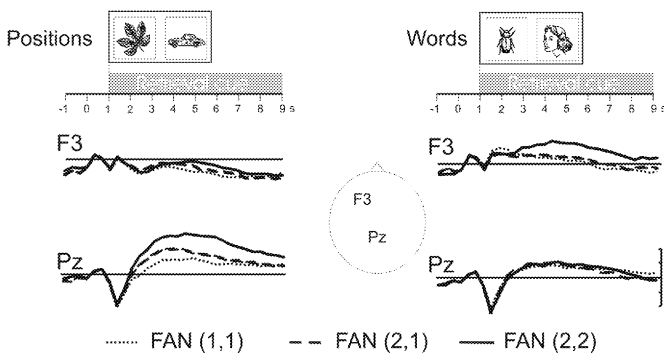

Figure 4. Slow ERPs during retrieval of different associations in long-term memory. **A.** Shows the topography of the average slow wave pattern between 3 and 4 s after a retrieval cue which triggered either spatial, color, or verbal associations (darker shading indicates relative larger negative amplitude, i.e. more activation of the underlying cortical areas) (Data from Rösler, Heil, Bajric, Pauls, & Hennighausen, 1995). **B.** Shows the time course of the retrieval situation and the slow waves for different levels of fan, i.e. a different number of associations which had to be scanned during retrieval. A more difficult task (larger fan) evokes a larger amplitude increase with a code-specific topography (Data from Heil, Rösler, & Hennighausen, 1997).

        The behavioral data always showed a clear fan-effect, i.e. an increase of response time with an increasing number of associations which had to be checked. The response times ranged between 4 seconds for the easy fan-1 and 8 seconds for the difficult fan-3 conditions, irrespective of the type of association tested. The retrieval cue, the two line-drawings, always triggered very pronounced slow waves over various cortical areas. These extended over several seconds with the duration depending on the number of associations which had to be scanned. Most important

is the finding that the retrieval situation was accompanied by slow wave patterns which had a clearly code-specific topography. The topographic maximum was located over left-frontal areas with verbal mediators, over occipital to right temporal areas with color mediators, and over central parietal areas with spatial mediators (s. Fig. 4A). This pattern held for both positive and negative test trials, i.e. whether the subject could find a common link between the two triggering stimuli or not.

The second and even more striking finding of this series of experiments is shown in Fig. 4B. Depending on the amount of search activity, which is defined by the fan level, the amplitude of the slow waves varied. This amplitude modulation had a code-specific topography as well. The overall maximum for a particular type of association appeared in exactly the same place as the relative maximum of the difficulty-related intratask modulation of the amplitude. With spatial mediators the effect maximum was found at electrode Pz and with verbal mediators at electrode F3.

Converging evidence for code specific activation patterns during retrieval of long-term memory contents also comes from others who have used different techniques. For example, Martin, Haxby, Lalonde, Wiggs, & Ungerleider (1995) found clear topographic differences with PET scans when subjects had either to generate typical color words or action words for visually presented objects. For example, participants had to think "grey" or "dial up", if a telephone was presented as an achromatic line-drawing. Generation of an action word led to an additional activation in the motor areas of the left hemisphere (Brodman areas 6, 44) while generation of a color association activated right posterior temporal areas (BA 37, known to be relevant for color processing, e.g., Meadows, 1974). The finding that a reactivation of knowledge about colors involves color sensitive primary and secondary visual areas agrees with the slow-wave results presented earlier and with further PET findings of Chao & Martin (1999).

Category-specific Representations

The code-specific dissociations described so far concerned global categorical distinctions, as representations of verbal meaning, spatial relations, object shapes, or colors. These categorical distinctions are related to the input modalities via which corresponding stimuli are normally picked up from the environment. That is, the topography of the observed brain activation patterns were found to be at least partially congruent with the topography of the primary and secondary projection areas of the sensory modalities. However, as outlined in the introduction, the selective impairments for faces, animate or non-animate entities, verbs and nouns, or other categories that are observed in brain damaged patients suggest an even more specialized representation within narrowly circumscribed cortical areas. A number of imaging and electrophysiological recording studies also reported discrete cortical areas in the ventral temporal cortex (the what-pathway) to be selectively activated by faces (Allison et al., 1994; Druzgal & D'-Esposito, 2001; Jha & McCarthy, 2000; Kanwisher, McDermott, & Chun, 1997; McCarthy, Puce, Gore, & Allison, 1997; Puce, Allison, Gore, & McCarthy, 1995), buildings (Epstein & Kanwisher, 1998), animals or tools (Martin, Wiggs, Ungerleider, & Haxby, 1996), hands (Allison, Puce, Spencer, & McCarthy, 1999), and letters (Puce, Allison, Asgari, Gore, & McCarthy, 1996). Although such findings are intriguing it seems nevertheless unlikely that highly specialized processing modules

exist for each and every narrowly defined category. For faces, the situation might be special. Due to the special biological importance of face representation, a dedicated module for faces could have evolved in the primate cortex during phylogeny. For categories such as buildings, tools, letters, or vegetables such an evolutionary explanation seems unlikely. And even the "face"-area hypothesis has been challenged repeatedly by the argument that the respective cell assemblies in the fusiform cortex might not be specialized for faces as such but rather for the processing of highly complex textural features and their relationships (e.g., Gauthier, Behrmann, & Tarr, 1999). Thus the face area findings could be a methodological artefact, because in most studies face stimuli were not compared with equally complex visual stimuli.

An alternative explanation to account for the category specific activation patterns within the "what"-pathway of the temporal cortex suggests a feature-based rather than an object-based representation. This hypothesis assumes that specialized cell assemblies represent elementary and higher order features of stored entities rather than the entities themselves. In some sense, the highly specialized functional topography of the visual projection areas (van Essen, Anderson, & Felleman, 1992) is continued within the temporal cortex in that other and possibly multi-sensory features are processed and represented there. An object, a perceptual or mnemonic entity, is then represented by the activated set of its constituting features. This implies that a larger number of narrowly circumscribed but widely distributed cell assemblies should be activated synchronously, when an entity is stored or reactivated. Such a model of distributed activity could well explain the systematic topographic differences between distinct categories as they are described in some brain imaging studies or for brain damaged patients: If all members of a category share a specific set of features, an activation study should reveal a center of gravity for this category within the temporal cortex, and likewise, a damage of the neurons where a center of gravity normally develops should bring about a category specific memory deficit.

Importantly, if these feature-specialized cell assemblies form a widely distributed patch-work within the temporal cortex, in which members of distinct categories activate always distinct but widely distributed and overlapping sets of neurons it might sometimes be difficult to detect such different patterns with standard brain imaging techniques. Standard imaging techniques average the brain activation pattern over trails (and subjects) and this could result in very similar average activation patterns despite the fact that within each trial and subject distinctly distributed patterns do exist.

Ishai and colleagues (Ishai, Ungerleider, Martin, & Haxby, 2000; Ishai, Ungerleider, Martin, Schouten, & Haxby, 1999) systematically studied the question of category specific activation patterns within posterior areas of the brain. This group used a delayed-matching-to-sample task in which a sample stimulus had to be stored for a brief interval and later a decision had to be made about which of two simultaneously presented probes was identical with the sample. The stimuli were either photographs or line drawings of faces, houses or chairs, or, in a control condition, meaningless figures made from scrambled elements of the real objects. Brain activity was monitored with fMRI. The studies revealed distinct but substantially overlapping activation patterns for the three categories within the temporal and the occipital cortex. In the temporal cortex houses, faces, and chairs evoked a distinct center of activation in the medial fusiform gyrus, the lateral fusiform gyrus, and the inferior temporal gyrus, respectively. A comparable dissociation was found in the more posterior, occipital parts of the brain with

activation centers located in the posterior fusiform gyrus for houses, in the inferior occipital gyrus for faces, and in the mid occipital gyrus for chairs. These distinct activation patterns were present also during passive viewing of the stimuli, i.e. without a recognition memory task, but in this situation the amplitude was much smaller. The results suggest that information about objects is represented with a topological organization that reflects distinctions between categories. Moreover, the results also suggest that such a segregation of objects is not restricted to the ventral temporal cortex in which already higher order visual features are processed (the what pathway). Rather, the dissociation starts as early as in the occipital extrastriate cortex where more primitive features are processed. Based on these findings, the authors proposed an object form topology hypothesis, "according to which the functional architecture of the neural systems for face and object perception is based on a distributed representation of attributes of object form, such that attributes that are shared by members of a category cluster together. The responses to different object categories in this system are distributed and overlapping but are nevertheless distinct by virtue of differential patterns of response strength" (Ishai, Ungerleider, Martin, & Haxby, 2000, p. 47). It is striking that this topological arrangement is consistent across subjects.

Further support for the hypothesis that memorized entities are represented by their constituting features in a distributed but also strongly overlapping network was provided by a recent study of Haxby et al. (2001). A 1-back working memory task was realized with stimuli belonging to eight distinct categories: faces, cats, houses, household tools, scissors, shoes, chairs, and random textures: The first two categories comprise natural living entities, the next five comprise types of man-made artifacts, and the last category comprises meaningless entities. The activation patterns within the ventral temporal cortex that were evoked by these stimuli showed substantial overlap, if analyzed with standard regression tools. Nevertheless, the already known centers for houses, faces, and chairs were found again. In an additional analysis the authors correlated the mean response strength of each voxel obtained in distinct activation epochs (runs) such that within and between category correlations could be estimated. The data of each subject were split into two sets, one set representing odd runs, the other set representing even runs with the same stimulus material. The consistency of the distributed activation pattern within one category could be determined by correlating odd and even runs while the distinctness of the activation pattern of different categories could be determined by correlating even and odd runs of two distinct categories. The results show that all of the within category correlations were positive and of considerable size (e.g., .81 for faces, .87 for houses, .45 for chairs, .55. for shoes), while most of the between category correlations were negative or close to zero (e.g., faces ~ houses: -.40 and -.47, chairs~shoes: -.12 and -.10). These findings demonstrate that distinct regions within the temporal cortex are not exclusively dedicated to processing a single category, e.g., faces, or chairs or houses, but rather that these areas process features that constitute the members of several distinct object categories. The critical aspect which distinguishes between different memory entities is not a distinct focus of activation restricted to a narrowly circums- cribed cell population but rather a distinct pattern of activations which is widely distributed. These activation patterns are very similar for members of one category and dissimilar for members of distinct categories and this can result in clearly distinct activation foci for some categories. On the other hand, these activation patterns cover widely overlapping cortical areas such that the average activation pattern as it shows up in a grand average may be indistinguisha- ble for some categories.

Conclusion

Several lines of evidence suggest the existence of multiple processing codes within working and long-term memory. Among others, supporting evidence comes from behavioral dual task-studies, from experimental lesion studies with a double dissociation of the what and where pathway in the monkey brain, and from clinical case studies involving dissociations of selective memory deficits related to distinctly localized brain damage. Brain activation measures including slow negative waves, PET, and fMRI recordings have substantiated the idea of code-specific memory codes by revealing distinct topographies for different types of memory representations, for global categories (e.g., verbal, spatial, and object codes) and, specific object categories (e.g., faces, houses, and tools). These specific topographies were observed in a wide range of procedurally distinct tasks, among others for storage, rehearsal, and transformations of representations from working-memory traces. In addition, the topgraphies were also present in retrieval of representations from intermediate-term or long-term memory. The topographically specific activation patterns proved dependent on the difficulty of the task, i.e. the maximum of a code specific-topography increased with increasing difficulty. Moreover, recent evidence suggests that these distinct activation patterns are not manifestations of an object-based but rather a feature-based code. Memory entities are to be seen as represented by an activation of a set of primitive and higher-order features for which widely distributed, specialized cell assemblies exist. Since members of a particular category share a great number of features and thus activate a similar network, the resulting activation patterns produce narrowly circumscribed centers of gravity. These activation areas are topographically distinct although the total activation patterns are widely distributed and show a substantial overlap.

In addition to the code specific activation patterns, which clearly support the idea of a topographically distinct representation and reactivation of memory traces, code unspecific processing modules were also observed. These correspond to the well known executive areas within the frontal and prefrontal cortex. In addition, they were found within the parietal cortex in the form of areas specialized for spatial transformations. These processing areas seem to represent superordinate functions in that the activations residing there control the more specific activation patterns by sustaining, amplifying or inhibiting them.

The brain activation results are compatible with neuroscientific theories of storage and retrieval which assume that memory traces are encoded as connectivity changes within modality specific projection areas and that memory representations are to be seen as reinstantiations of activity patterns within these cortical areas.

So all in all there exists substantial evidence that corroborates the principle of code-specific memory representations.

6

The Principle of Multiple Memory Systems

Axel Buchner and Martin Brandt

One of the guiding principles of memory research is that different types of memory systems need to be assumed in order to explain differences in learning and performance. Some of these distinctions are relatively uncontroversial (e.g., the distinction between working memory and long-term memory), but some are not (e.g., the distinction between episodic and semantic memory). This chapter examines the validity of these distinctions and analyzes theoretical alternatives. Distinctions between memory systems are discussed at three levels: descriptive, functional and neural.

The currently most popular model of working memory is modular in that it assumes specialized working memory systems for the processing of specific types of information. However, working memory may also be viewed as an activated subset of long-term memory. In addition, a formal model is introduced which assumes only one primary memory store.

In the domain of long-term memory, the distinction between declarative and non-declarative memory is discussed as a relatively uncontroversial, albeit coarse distinction, which is supplemented by a number of hypothetical subsystems. The distinction between implicit and explicit memory has often been treated similarly. However, it is better viewed as originally intended, as a purely descriptive distinction which implies, in the case of implicit memory assessment, that learning was incidental and memory was tested without explicit reference to a preceding study episode. The distinction between episodic and semantic memory has serious problems at functional and neural levels. We close by discussing global memory models as theoretical alternatives to the multiple systems approach. This class of formal models implies only one long-term memory store but still can explain a large number of empirical phenomena.

Distinct Memory Systems

The dominant approach to the study of memory aims at decomposing the general faculty of memory into distinct memory systems. Different memory systems are assumed to support certain specialized functions and to differ in their processing characteristics. The distinction between working memory and long-term memory is a good example. It is commonly accepted that a major function of working memory is to maintain information for immediate use. Its capacity to hold information is assumed to be limited to a few items, with rapid information loss occurring in the absence of rehearsal processes. In contrast, long-term memory supports the retrieval of information even after very long study-test intervals, and its capacity is very large.

Both working memory and long-term memory have been subdivided further and, as will become clear in this chapter, many of these subdivisions are controversial. What is more, the trend towards identifying more and more specialized memory systems is opposed by a trend towards greater parsimony of the theoretical explanations of memory performance. For instance, a class of formal models of long-term memory, often referred to as *global memory models*, can be characterized as trying to explain as large a variety of memory phenomena as possible with as few mechanisms as necessary. Applications of global memory models demonstrate that a number of phenomena that have been thought to require the assumption of distinct memory systems may also be explained by a unitary memory system. The situation is similar in the area of working memory.

Levels of Distinction

Multiple memory systems may be distinguished at various levels. The distinction may occur at a *descriptive* level, at a *functional* level, or at a *neural* level.

Distinctions between memory systems at a descriptive level are based on differences in the *information* stored or the *tasks* used to probe the to-be-distinguished memory systems. Graf & Schacter's (1985) distinction between implicit and explicit memory is a typical instance of a task-based descriptive distinction. Explicit memory was assumed to be required for tasks, such as recognition or recall, that involve the conscious recollection of the prior study episode. Implicit memory was thought to be revealed by tasks that measure the effects of prior experiences in terms of performance changes that occurred in the absence of conscious recollection. For example, previously experienced objects or events are preferred over new objects or events even if they cannot be recognized (Bornstein, 1989).

At the descriptive level, memory systems may also be distinguished according to the information that they presumably store. For instance, information about faces has been assumed to be stored in a specialized memory system (Ellis & Young, 1989). A special face memory has some plausibility because it may have been an evolutionary advantage for social animals to identify the other animals efficiently.

This a-priori plausibility is more important than one would think at first glance. This is so, because at a descriptive level there is, in principle, absolutely no limit as to the kinds of memory systems that can be postulated. For instance, we all know people who claim to have a

particularly bad memory for faces, for names, for phone numbers, or for passwords. Should this lead us to assume a memory system dedicated to the storage of names, phone numbers, or passwords? Clearly, there must be a set of filters that protect us against having to accept the arbitrarily large number of memory systems that can be invented at a descriptive level. The evolutionary plausibility of a proposed memory system is probably the most important of these filters.

With this in mind, we would certainly disregard the phone number memory, but we would consider a specialized memory for faces. The kind of evidence we would be looking for is whether, indeed, memory for faces functions differently from the memory for other visual objects. In other words, we would analyze the characteristics of the hypothetical face memory at a *functional level*. For instance, Ellis & Young, (1989) note that newborns have a preference for "correct" faces as opposed to faces in which the features have been rearranged. Also, newborns seem to be able to diagnose emotional states from facial expressions and to imitate facial expressions very early on.

Whereas such characteristics are compatible with the assumption that memory for faces is functionally distinct from memory for other visual objects, they may be just as compatible with other conceptualizations. For instance, newborns may not only have a preference for intact over rearranged faces, but rather for intact ("closed-form") over rearranged objects in general. There does indeed seem to be evidence supporting this hypothesis (Levine, 1989).

Many researchers have come to prefer experimental or quasi-experimental functional dissociations as evidence of functionally distinct memory systems. A study by Halpern & O'Connor (2000) illustrates this approach. They compared, among other things, memory for novel melodies of younger and older persons using two types of memory measures, recognition memory and preference judgments. The former requires the conscious recollection of a preceding study episode and thus qualifies as a measure of explicit memory in terms of Graf & Schacter's (1985) above-mentioned distinction. The latter only requires the respondents to judge whether or not (or how much) they like a particular object or event. In preference judgment tasks, memory is expressed in terms of an above-baseline probability of preferring an object or event that had occurred during the preceding study phase. No conscious recollection of the prior study episode is necessary. Thus, preference judgments can be considered as implicit memory measures. Halpern and O'Conner found a dissociation between recognition memory and the preference measure: Recognition memory for novel melodies was worse in elderly compared to younger persons, but both groups did not differ with respect to their preference for previously heard melodies over new melodies. The typical interpretation of such a pattern of results is that aging affects recognition memory selectively, whereas the memory system supporting preference judgments remains intact. Indeed, this is a very frequent conclusion, but it is problematic as will become clear further on.

Memory systems may also be distinguished at a *neural level* at which memory performance is typically related to the anatomical structure of the brain based on results from brain imaging studies or from studies involving people with circumscribed brain damage. For instance, unimpaired face memory may depend on the intactness of brain structures not involved in the processing of other types of materials. Specific brain lesions seem to covary with deficits

in recognizing familiar persons, a finding that is compatible with this assumption (Kapur, 1999). The finding that particular cells in the sheep temporal cortex respond preferentially to familiar as opposed to unfamiliar sheep faces (Kendrick & Baldwin, 1987) may be interpreted in the same way.

Strictly speaking, the neural and functional levels need not be linked in the form of a one-to-one mapping, which complicates the integration of functional and neural levels of analysis. To use an analogy, the tax form of person *A* may be processed in one office and that of person *Z* in another, but the processing of the two forms may (in this case: should) still follow the same regulations. With respect to the face memory example, the fact that memory deficits for familiar faces seem to co-occur with right-temporal lesions whereas memory deficits for familiar names seem to co-occur with left-temporal lesions of the neocortex (Eslinger, Easton, Grattan, & Van Hoesen, 1996) does not mean that memories for faces and names cannot share functional characteristics (developmental course, forgetting functions, etc.).

Working Memory

Melton (1963) has presented an elaborate set of arguments in favor of the view that rather than being qualitatively different, working memory and long-term memory form end points on a continuum. However, most contemporary researchers agree with early theorists such as James (1890) or the very influential multiple store model by Atkinson & Shiffrin (1968) in accepting the distinction between working memory and long-term memory as two qualitatively different memory systems.

The concept of working memory refers to a hypothetical memory faculty specialized in the maintaining of limited amounts of information for immediate use. Notions such as primary memory, short-term store, or short-term memory have also been used to refer to this theoretical entity, albeit those concepts were usually embedded in different research traditions where they tended to come with somewhat different connotations. We think it justified to neglect these differences for reasons of simplicity and also because often the heterogeneity with which these concepts were used appears just as large within as between research traditions.

Modular Working Memory

The currently most popular model of working memory is modular (cf. Baddeley, 1986). Originally it comprised a central executive and two slave systems, one for the processing of phonological information and one for visual-spatial information. More recently, the model has been extended by Baddeley (2000) to comprise an additional episodic buffer in which information is assumed to be stored in a multimodal code, assembled by the central executive. This module is said to enable the conscious experiencing of coherent episodes.

At a functional level, evidence supporting the idea of qualitatively different working memory components largely comes from studies conducted within the interference paradigm.

Within this paradigm, large interference between two simultaneously performed tasks is taken to indicate that the tasks tax the same processing units. For instance, a primary verbal task (e.g., memorizing consonant strings) suffers much more when the secondary task is also verbal (e.g., counting from 1 to 9) than when it is visual-spatial in nature (e.g., hitting a sequence of nine different keys in a particular order); the reverse is also true for visual-spatial primary tasks (e.g., Meiser & Klauer, 1999; Quinn & McConnel, 1996). This pattern of results is commonly interpreted as support for the modular model's two functionally distinct phonological and visuo-spatial subsystems.

The module assumed to process phonological information can be decomposed further into a passive phonological store, which is related to speech perception, and an articulatory control process, which is related to speech production (cf. Baddeley, 1986). Auditory information such as spoken language is assumed to enter the phonological store automatically. Visually presented verbal information may be recoded phonologically and thus also reach the phonological store. In this way, irrelevant auditory information may disrupt the serial recall of visually presented verbal items. Consistent with the modular model, only phonological, but not semantic properties of the irrelevant auditory information affect the degree of disruption (Buchner, Irmen, & Erdfelder, 1996; Salamé & Baddeley, 1982). The articulatory control process (metaphorically referred to as "subvocal rehearsal") is used to continuously refresh the contents of the phonological loop. When "subvocal rehearsal" is impossible, for instance due to the requirement to pronounce the same word over and over again (referred to as articulatory suppression, cf. Salamé & Baddeley, 1982), then the information in the phonological store decays within 1-2 seconds and becomes unusable. The visual-spatial module may also be decomposed further into a component related to the processing of visual object features such as color or form, and a spatial component (Logie, 1995).

There is also evidence at a neural level that supports the distinction of a phonological and a visual-spatial working memory component. For instance, Smith, E. E. & Jonides (1997) reported increased left-hemisphere brain activity, particularly in Broca's area, the prefrontal cortex, and the posterior parietal cortex during a phonological task that required the judgment of whether a letter in a sequence was the same as a letter that had occurred three letters earlier. Because the letters were presented in either upper or lower case it was assumed that the comparison must have been based on phonological information. In contrast, increased right-hemisphere activity, mostly in the prefrontal and premotor cortex, the parietal cortex, and the occipital cortex was observed with an analogous visual-spatial task that required judgments about whether successive events occupied the same or different spatial positions.

Given the obvious correspondence between the phonological component on the one side and the faculty of speech perception/production on the other, and between the visual-spatial component on the one side and the parvo-cellular and magno-cellular pathways of the visual system on the other, we may wonder whether additional working memory components corresponding to other sensory systems need to be distinguished. This does indeed seem to be the case. For instance, memory for head and arm movements is more impaired by concurrent sequential tapping of body parts than by tapping of black squares printed on white background. In contrast, memory for spatial positions in a 4 by 4 matrix is more impaired by simultaneous sequential tapping of black squares printed on white background than by tapping of body parts

(Woodin & Heil, 1996). Thus, it seems that a kinesthetic module may have to be assumed as well.

In addition to the phonological and visual-spatial modules, Baddeley (2000) added a multimodal "episodic buffer" in which information from different sensory modalities is supposed to be integrated to form a coherent episode. Such episodes are said to correspond to the contents of consciousness. Also, this subsystem is assumed to subserve the integration and manipulation of information. It remains to be seen how this extension of the modular model stands the empirical test.

Finally, a so-called central executive "controls" the processing modules within Baddeley's working memory model. The central executive essentially is an attentional system that is invoked for the processing of tasks that are not automatized and for tasks that require the splitting of processing resources among, and the switching between, multiple subtasks.

Working Memory as Activated Memory

The working memory model suggested by Cowan (1995) follows Baddeley's modular model in postulating a central executive, but the two models differ in their functional focus. Within Cowan's model, the primary function of working memory is to keep information in an extraordinarily accessible state so that it can be used for higher cognitive processes such as problem solving, decision making, or speech production.

According to Cowan's model, mentally represented information can be in one of three states. First, information can be represented in long-term memory, but in an inactive state. Second, memory items can be in an activated state in which they are readily accessible. This occurs, for instance, when the items have been recently involved in cognitive operations. Third, a subset of the activated items can be within the focus of attention where relations between items may be formed that may subsequently be stored in long-term memory.

Activated memory and the focus of attention are assumed to differ qualitatively. The focus of attention is limited less by time than by capacity (with a capacity limit of about four items, cf. Cowan, 2001), whereas activated memory is limited less by capacity than by time: Activation is assumed to decay within 10-20 seconds unless the items are reactivated.

Obviously, the two models of working memory discussed so far differ in their perspective and, as a consequence, in their primary subdivision of the hypothetical working memory systems. Whereas Baddeley's (1986) model implies a set of qualitatively distinct subsystems that may be mapped, to some degree, onto a set of corresponding sensory systems, the model proposed by Cowan (1995) distinguishes between the set of temporarily activated long-term memory items and a subset of (at most four of) these items that represent the focus of attention. However, Cowan's model does not deny that information processing is modality specific so that the processing of items that are similar and thus likely to share processing units interfere more with each other than items that are dissimilar. In this way, the activated-memory model of working memory can also integrate findings from the interference paradigm such as those mentioned in the introduction to this working memory section.

A Formal Model of Working Memory: The Feature Model

Another feature that is common to Baddeley's modular model and Cowan's activated-memory model of working memory is that they are both verbally formulated theories and thus somewhat imprecise in the mechanisms they specify and the predictions they allow. This is one aspect in which the feature model (Nairne, 1988, 1990) differs. The assumptions of this formal model are specified in a set of mathematical equations. A second difference is that loss of information in the feature model is not due to decay but rather is caused by interference between successive items. Thirdly, the feature model does not assume a modular working memory structure. Instead, all represented items are stored in one homogenous "primary memory" structure, but each item may have both modality-dependent and modality-independent features.

More specifically, stored items are represented as vectors of features. For simplicity, each feature may assume a value of -1 or $+1$ only. For instance, a stored item may be represented by the feature vector $[1, 1, -1, 1]$. Some of these features are modality-specific and some are not. If two successive items have the same feature value at a certain feature position then a later item may, with a certain probability (set to 1 for the purpose of the present illustration), "overwrite" and thus nullify that particular feature value in the preceding item. For instance, if item n is represented by $[1, 1, -1, 1]$ and is followed by item $n+1$, which is represented by $[1, -1, 1, 1]$, then the representation of item n may be degraded to $[0, 1, -1, 0]$. Thus, later items tend to degrade earlier items to the degree to which their features overlap. Items may also be generated internally (e.g., by rehearsal) but these items lack the modality-specific features. Of course, internally generated items may also degrade items that precede them in the continuous stream of events, albeit to a lesser degree due to the lack of modality-specific features. In this way, even the features of the final item of an externally presented list of items may be degraded.

When recently presented items need to be recalled, their degraded feature vectors are matched against a finite set of intact long-term memory traces (that is, nondegraded feature vectors), the so-called search set. Usually the search set item with the largest proportion of matching features will be selected. An additional assumption is that items that have already been selected for recall on a current trial have a drastically reduced probability of being recalled again.

Despite its simplicity, the feature model can account for a variety of different working-memory phenomena, some of which have been typically interpreted as supporting the assumption of a modular working memory. A simple example is the negative effect of articulatory suppression on immediate serial recall. The typical articulatory suppression task requires people to quickly pronounce the same word over and over again while memorizing another list of words. Within Baddeley's (1986) working memory model, the resulting deterioration of immediate serial recall performance has been attributed to an unavailability of the articulatory control process for the refreshing of representations in the articulatory store (as described above). Without refreshing, the representations are assumed to decay within 1-2 seconds. The feature model suggests a different explanation of the articulatory suppression effect. It is possible to assume that the features of the continuously repeated word become encoded as part of the feature vectors of the to-be-memorized words. As a consequence, the to-be-memorized words become more similar to each other and, in turn, more difficult to match with representations in long-term

memory. This reduces the probability of recalling items under articulatory suppression conditions.

Summary of Working Memory Models

Three different models of working memory were discussed. The modular working memory model developed mainly by Baddeley (cf. 1986, 1996, 2000) represents the dominant view according to which working memory is best understood as a collection of memory systems that support the maintenance of information in particular formats or modalities. Cowan (1995) argued that working memory is better understood as an activated subset of long-term memory representations. According to him, the primary function of working memory is to keep information in a highly accessible state. Despite this basic difference, the modular model and the activation model also have much in common. For instance, an attentional system referred to as "central executive" is a component in both models. Also, information is lost due to decay, which occurs autonomously if the memory trace is not refreshed. In contrast, the feature model (Nairne, 1988, 1990) is a formal model in which interference, rather than decay is assumed to be the mechanism by which information is lost. The feature model also differs in that it can explain a large number of working memory findings without having to rely on the assumption that working memory consists of a collection of qualitatively distinct modules. This latter aspect shows that although the multiple systems view of working memory is popular and compatible with a large body of research, a unitary working memory concept cannot be rejected at this point.

Long-Term Memory

At the broadest level, long-term memory subdivisions usually take the form of dichotomies. Three such dichotomies will be analyzed in this section. The first is the distinction between declarative and nondeclarative memory. A closely related distinction is that between explicit and implicit memory which has already been mentioned in Section 2 of this chapter. We will argue that the explicit-implicit dichotomy should be confined to the descriptive level of analysis where it is better understood in terms of a particular combination of study and test situations. Finally, a popular differentiation within the domain of declarative memory is that between episodic and semantic forms of memory. Despite its popularity, there is little evidence supporting the episodic-semantic dichotomy at levels other than the descriptive level.

Declarative versus Non-declarative Memory

Probably the least controversial distinction of long-term memory systems is that between declarative and nondeclarative memory. It has its roots in the distinction between declarative and nondeclarative knowledge, the former of which is often referred to as "knowing what" whereas the latter is referred to as "knowing how." The distinction between these two forms of knowledge has been the subject of philosophical speculation for a long time (cf. Reber, 1993).

At a descriptive level, declarative memory comprises knowledge about facts and events that can be reported very easily. This form of knowledge is typically assumed to be particularly important at the beginning of a learning process (Zola-Morgan & Squire, 1990). For instance, when people learn to use a new device such as a digital camera, they first need to learn which inputs, given a certain current state of the system, lead to which outputs. The use of this knowledge is relatively slow, but it can be verbalized easily, and it can be applied flexibly to reach many different goals. With extended practice the knowledge used to guide actions becomes more and more "procedural," several input-output sequences may be "composed" to form one coherent procedure that can be executed quickly and without intervening control, and it may be finely tuned to a particular situation and become inflexible. For the present purpose, an important point is that procedural knowledge is typically hard to verbalize, which is best epitomized by those experts who find it easier to demonstrate how a problem is solved than to describe the solution path verbally.

A formal model that takes into account this distinction between declarative and non-declarative memory is ACT-R (Anderson, 1993). This model is a good example for a formal theory of human memory which aims at explaining various phenomena from the different areas of cognitive psychology within a unified framework. In ACT-R declarative knowledge is represented in a network of connected *chunks*. The accessibility of each chunk is mainly determined by its state of activation. Activation is assumed to spread out automatically between connected chunks. The representation of procedural knowledge is separate from that of declarative knowledge. The basic unit representing procedural knowledge is called a *production rule*. A production rule consists of a condition specifying the goal of the task, and an action which is performed if the condition matches. Usually many production rules are combined in order to solve a specific task. It should be noted that although in this model declarative and procedural memories are explicitly differentiated, both forms of memory usually work hand in hand: The retrieval of declarative knowledge is guided by productions rules and, conversely, productions rules need declarative knowledge structures to operate on.

ACT-R predicts situations in which declarative and procedural knowledge should be dissociable at a functional level. For instance, Anderson & Fincham (1994) taught people to construct novel input-output rules from examples. During the initial (declarative) stage in which knowledge is assumed to be easily accessible and flexible, subjects were as good at determining the output from the input as they were at determining the input from the output. After extended practice, that is, after procedural knowledge should have been established, an asymmetry developed such that subjects were better at predicting outputs from inputs than at predicting inputs from outputs. This asymmetry is one of the qualitative changes that indicate a shift from declarative to procedural knowledge.

Evidence supporting the declarative-procedural distinction at a functional level also comes from sleep research. Sleep is commonly assumed to support the consolidation of knowledge that has been acquired during waking periods (cf. Stickgold, 1998). Sleep is often described as a sequence of (typically five) sleep stages. Simply speaking, sleep is characterized by cycles through these sleep stages, with each cycle lasting roughly 90 minutes and ending with a REM phase. For the present purposes, it is convenient to distinguish between sleep stages characterized by slow waves in the EEG pattern (SWS phases) and sleep stages characterized by rapid eye

movements (REM phases). SWS and REM phases are not distributed evenly within normal nocturnal sleep. SWS sleep occurs mostly during the first half, whereas REM phases become longer during the second half of the nocturnal sleep period. Plihal & Born (1997) have used this shift and have shown that recall of word pairs benefitted more than mirror-tracing skills from the SWS-rich first half of the nocturnal sleep period. In contrast, mirror-tracing skills benefitted more than word recall from the REM-rich second nocturnal sleep period. The recall of word pairs can be conceived as a task that should rely primarily on declarative forms of memory, whereas the mirror-tracing skills can be assumed to rely primarily on procedural memory. Thus, Plihal und Born's finding may be interpreted in terms of a dissociation between consolidation in declarative memory (which benefits more from SWS-rich than from REM-rich sleep) and consolidation in procedural memory (which benefits more from REM-rich than from SWS-rich sleep).

Analyses at a neural level seem to indicate that the hippocampal formation may be involved in consolidation processes. For instance, Zola-Morgan & Squire (1990) reported that hippocampal lesions in the monkey brain resulted in a loss of knowledge learned during a particular pre-lesion interval (four weeks in that case), whereas knowledge acquired before that interval did not seem to be lost. It appears as if this pre-lesion interval could be interpreted as the temporal window in which the hippocampal formation was needed for consolidation processes.

A large body of evidence that supports the distinction between declarative and procedural memory at a neural level comes from studies with patients who suffer from amnesia due to brain damage. It is not quite clear whether amnesia should be treated as a (more or less) uniform syndrome because not only damage to the medial temporal lobe (mostly the hippocampal formation), but also diencephalic damage, may cause amnesia (Downes & Mayes, 1997). However, many researchers continue to neglect the etiological differences, either because they agree with the assumption of one functionally coherent hippocampal-diencephalic system (Aggleton & Brown, 1999) or because the specific patterns of memory performance simply do not differ much between etiologically different amnesic disorders (Cohen & Eichenbaum, 1993). In general, amnesic patients have severe difficulties when it comes to recalling recently learned facts or autobiographical events but seem fairly normal with respect to the retention of cognitive skills (e.g., solving the Tower of Hanoi problem) and motor skills (e.g., mirror tracing) across comparable intervals (e.g., Cohen & Eichenbaum, 1993; Cohen & Squire, 1980).

As yet, we have only mentioned cognitive and motor skills and, hence, procedural knowledge as aspects of nondeclarative memory. However, amnesic patients seem to show normal performance on a variety of other tasks as well. For instance, they can acquire simple associative knowledge in a sequence learning task (Nissen & Bullemer, 1987). In this task, visual events appear at certain spatial positions and have to be responded to by a key press associated with the relevant position. Reactions are faster when the sequence of positions is systematic than when it is random. Such performance improvements have been observed for both amnesic patients and controls. Amnesic patients also show normal conditioning (Parkin, 1982) and normal levels of identity priming with words (Cermak, Talbot, Chandler, & Wolbarst, 1985), pictures (Cave & Squire, 1992), line drawings of novel objects (Schacter, Cooper, Tharan, & Rubens, 1991), or novel dot patterns (Gabrieli, Milberg, Keane, & Corkin, 1990). Findings such as these have lead researchers to include separate faculties that support simple associative learning,

conditioning, and the learning about word and object shapes as "subsystems" in the broad category of nondeclarative memory (e.g., Schacter & Tulving, 1994).

The dissociations between declarative and procedural forms of memory at a neural level support the hypothesis that declarative forms of memory depend crucially on intact medial temporal lobe structures (hippocampus, entorhinal, perirhinal, and parahippocampal cortices), intact midline diencephalon structures, and intact pathways between these areas. The hippocampal structures receive afferent pathways from many neocortical areas, and they send corresponding efferent pathways into these areas. Thus, the anatomy of hippocampal structures fits the idea that declarative forms of memory require the binding of information about many different aspects of events that are processed and stored in different areas of the brain (Fuster, 1995; Zola-Morgan & Squire, 1993).

Explicit versus Implicit Memory Measurement

The idea that past experiences may affect our current behavior in the absence of being reportable is a virtually undeniable contention that has long been accepted by memory researchers. For instance, Ebbinghaus (1966) was convinced that by far the largest number of our experiences fall into that category. From Ebbinghaus' point of view it was a big problem for memory research that this large set of memories was unavailable for measurement with traditional memory tests such as free recall and recognition. One way for him to deal with this problem was to develop the so-called savings method. A typical task in this paradigm would consist of long lists of pronounceable three-letter strings that had to be learned until they could be recalled without error. Under highly standardized and controlled conditions, Ebbinghaus recorded the number of trials he needed to learn a particular set of lists on a particular day. When he relearned the lists on subsequent days he needed fewer and fewer trials. The difference between the number of trials needed on day n and on day $n+1$ served as a measure of how much was retained. Obviously, this measure reflects memory whether or not it is verbally reportable.

In contrast to Ebbinghaus' (1966) attempt to overcome the problem of measuring only selected aspects of memory, the multiple systems approach aims at the opposite. The primary goal is to decompose the general faculty of memory into distinct memory systems. For that purpose, memory measures are needed that can be assumed to selectively reflect the operation of one particular memory system. By far the most common practice is simply to derive a memory measure from a task that has some face validity of selectively tapping one particular memory system. For instance, recall tasks are usually thought to tap declarative memory because it seems intuitively clear that they require the recollection of information about a particular item and the context in which it was experienced. Furthermore, it is easy to imagine that the subjective experience accompanying recall is that of conscious recollection. In contrast, when previously read and novel words need to be identified under difficult viewing conditions, memory is expressed in terms of better performance (faster and less error-prone processing) rather than in a conscious recollection of the study context (Cermak, Talbot, Chandler, & Wolbarst, 1985; Jacoby & Witherspoon, 1982). This is why nondeclarative memory may be assumed to support performance in identification tasks.

In fact, it is typical of the tests which supposedly tap nondeclarative forms of memory that they measure the effects of prior experiences implicitly, that is, subjects are not asked to recollect consciously the context that was present during the prior study episode. Following Graf & Schacter's (1985) descriptive distinction, the memory assessed by measures from this class has often been referred to as "implicit memory" in contrast to "explicit memory" which is usually assessed by measures derived from recall or recognition tasks. It should be noted, however, that the notions of explicit and implicit memory only qualify the measurement process and do not normally refer to memory *systems* except in cases in which those notions have been used synonymously with declarative and nondeclarative memory.

Another feature that is typical of the assessment of nondeclarative forms of memory is an incidental study phase, that is, a learning situation in which participants are not informed about the fact that their memory for the materials they study will be assessed at a later point in time. For instance, participants in Graf & Schacter's (1985) Experiment 1 simply compared the numbers of vowels of two words, or they constructed sentences that related the two words during what was functionally the study phase except that participants were not informed of the subsequent memory test. In an attempt to further disguise the study-test relationship, an additional filler task was implemented. The final part of the experiment consisted of a word-stem completion task that served as a test of implicit memory. In this task, word stems have to be completed with the first word that comes to mind. Implicit memory is reflected in above-baseline completions with words from the (disguised) study phase.

The method of simply deriving a memory measure from a task that has some face validity of tapping one particular memory system has a number of problems, two of which we mention here. The first problem is that the assumption that one memory measure (e.g., the priming score derived from a word-stem completion task) reflects the operation of one memory system is too simplified. For instance, participants may become aware of the study-test relationship despite the best efforts to disguise it. From then on, the word-stem completion task will take on characteristics of an explicit memory test and deliver "contaminated" memory measures. In an attempt to tackle this problem, Jacoby (1991) presented a "process dissociation procedure" that was intended to decompose observable memory performance into two underlying components that could be interpreted, according to Jacoby, as relatively "pure" measures of controlled recollections and automatic, familiarity-based processes. The process dissociation procedure itself turned out to be a source of much debate, which need not concern us here. What we would like to mention nevertheless is that the measurement model presented by Jacoby can be interpreted as a so-called multinomial model. As such, it falls into a very broad class of stochastic models of cognitive processes that all aim at decomposing observable memory performance into underlying processing components. These models have been successfully applied to a wide variety of memory paradigms (Batchelder & Riefer, 1999).

The second problem is that the implicit and the explicit memory measures may have very different psychometric properties. In fact, it turns out that many implicit memory measures are less reliable measurement instruments than the explicit memory measures with which they have been compared in the past (Buchner & Wippich, 2000; Meier & Perrig, 2000). This raises problems for many of the simple dissociations between implicit and explicit memory measures that have been reported in the literature. These dissociations often take the shape of a difference

between two groups (e.g., amnesic patients and controls) on an explicit memory measure such as recognition but no difference on an implicit memory measure such as word-stem completion (e.g., Warrington & Weiskrantz, 1970). The modal interpretation of such a data pattern is that the explicit memory measure taps a memory system that varies as a function of the independent variable in question (e.g., is impaired by amnesia) whereas the implicit memory measure taps a memory system that is not affected. Unfortunately, such dissociations are quite likely when the explicit memory measure is more reliable than the implicit memory measure, even when these two measures reflect the operation of exactly the same memory system.

Episodic versus Semantic Memory

Tulving (e.g., Tulving, 1972, 1985b, 1999) has introduced and propagated the distinction between episodic and semantic memory, both of which may be interpreted as declarative forms of memory in that information retrieved from both episodic and semantic memory is overtly reportable by definition. At a descriptive level, episodic memory comprises the remembering of personally experienced events defined by temporal and spatial coordinates. For instance, remembering a specific personal holiday trip to the capital of France would be based on episodic memory. Tulving added to this original distinction that the process of remembering from episodic memory can be characterized, from a phenomenological perspective, as implying autonoetic consciousness. Semantic memory, in contrast, was conceived of as some sort of mental thesaurus, that is, a structure that supports remembering facts without coordinates in space and time. For instance, remembering that the capital of France is Paris in the absence of knowledge about where and when that was learned would be based on semantic memory. From a phenomenological perspective, remembering from semantic memory is said to be accompanied by noetic consciousness.

According to Tulving (e.g., 1972, 1985b, 1999), the two types of memories can also be dissociated at a functional level. A basic assumption is that retrieving from episodic memory corresponds to the subjective experience of "remembering" an event, whereas retrieving from semantic memory is associated with the subjective experience of simply "knowing" a fact. When people are asked to qualify acts of retrieval according to this remember-know distinction, simple dissociations may indeed be observed. For instance, Gardiner & Parkin (1990) reported that divided attention at study reduced the probability of consciously "remembering" words relative to a control condition, whereas the attentional manipulation did not affect word recognition accompanied by subjective experiences of "knowing." Similar dissociations have been reported for manipulations of encoding conditions (Gardiner, 1988), word frequency (Gardiner & Java, 1990), and retention interval (Gardiner & Java, 1991), among others.

The episodic-semantic distinction may seem plausible at a descriptive level, but serious problems surface at other levels. For instance, Strack & Förster (1995) criticized the remember-know distinction because, among other things, they found that "know" judgments were affected by response biases. Hence, simple guessing processes contaminated the measure that was assumed to reflect retrieval from semantic memory. They also showed that judgments along the remember-know dimension were confounded with confidence ratings suggesting that remember judgments were given when subjects' confidence that a recognition judgment was correct

exceeded a certain level. Donaldson (1996) extended this point in showing that the difference between "remember" and "know" judgments may simply correspond to a difference between two response criteria that are applied to items that vary along one single familiarity dimension rather than being retrieved from different declarative memory stores. More precisely, Donaldson assumed that subjects answer on the basis of a feeling of familiarity only, and that they give a "remember" judgment if the familiarity value of a test item exceeds a conservative response criterion (in other words, a "remembered" item would have to be quite familiar). A "know" response was assumed to occur for items with familiarity values that fall midway between the conservative and a second, more liberal criterion. A final assumption was that test items with familiarity values below the liberal criterion are rejected as new. Given this simple model, Donaldson was able to show that the manipulation of an independent variable such as attention during study (cf. Gardiner & Parkin, 1990) may produce several different patterns of results. For instance, the manipulation may affect only one of the response categories (e.g., "remember" judgments but not "know" judgments), it may affect both response categories in the same way (e.g., increase both "remember" and "know" judgments), or it may even increase the probability of one type of judgments while decreasing the probability of the other. These analyses clearly show that findings within the remember-know paradigm do by no means uniquely favor the assumption of separate episodic and semantic memory systems.

Another argument that has been put forward in favor of the episodic-semantic distinction is that performance on tasks thought to measure episodic memory (e.g., recognition) often do not predict performance on tasks thought to measure semantic memory (e.g., Tulving, 1999). If memory performance on these two tasks is stochastically independent, so the argument goes, then the underlying memory systems must also be independent. However, this argument has serious problems. For instance, Hintzman (e.g., Hintzman, 1980, 1990; Hintzman & Hartry, 1990) demonstrated that even trivial factors such as the particular items used can affect the contingency relation between two tasks, so that, contrary to common practice, contingency measures cannot be interpreted as uniquely reflecting the relations between tasks, let alone the memory systems that supposedly underlie task performance. Furthermore, Ostergaard (1992; Ostergaard & Jernigan, 1993) has shown that the small range within which many memory measures typically vary makes the finding of stochastic independence almost inevitable. Taken together, this means that virtually nothing can be learned from stochastic independence between memory measures about the supposedly underlying memory systems.

Tulving (Schacter & Tulving, 1994; Tulving, 1999) argued that the two forms of memory may also be dissociated at a neural level. For instance, according to Tulving (1999) amnesic patients often have their most pronounced problems when trying to remember autobiographical events, whereas they seem to function relatively normally in those areas of cognitive performance that rely on semantic memory, such as reading, writing, and problem solving. Furthermore, it seems that retrieval from semantic memory may be associated with higher levels of activity in the left than in the right prefrontal cortex, whereas retrieval from episodic memory may be associated with higher levels of activity in the right than in the left prefrontal cortex (Wheeler, Stuss, & Tulving, 1997).

However, the fact that amnesic patients appear most impaired when trying to remember autobiographical events does not necessarily mean that their episodic memory (e.g., their

recognition of objects seen a short while ago) is impaired whereas their semantic memory (e.g., their knowledge of object names) is not. One important reason for this is that the semantic knowledge such as knowledge of object names is usually acquired early in life, and long before the onset of the amnesic syndrome. It is well known that the likelihood with which knowledge is lost as a function of brain damage or aging increases with the age in which the knowledge was acquired (Hirsh & Ellis, 1994). An additional factor is that semantic knowledge may be represented more redundantly than episodic knowledge, in that facts may form components of many different episodes (e.g., we may have heard or read that Paris is the capital of France on many different occasions). The probability of losing information after pathological or age-related changes in the brain should decrease to the degree to which the information is represented redundantly. This may help to explain why amnesic patients who have severe frontal lobe lesions in addition to the typical medial temporal lobe and diencephalic damage may show particularly severe loss of episodic remembering; amnesic patients with lesions limited to the medial temporal lobe and to diencephalic areas show serious impairments in remembering both new events and new facts (Squire & Zola, 1998).

Finally, the finding that fact retrieval and event retrieval tasks are associated with differences in the brain areas that seem most active (Wheeler, Stuss, & Tulving, 1997) is hardly surprising. These tasks differ along so many dimensions that anything but diverging patterns of brain activity would be most surprising. For instance, the retrieval of episodes is usually more difficult than the retrieval of simple facts (Wiggs, Weisberg, & Martin, 1999).

To summarize, the episodic-semantic distinction may seem plausible at a descriptive level, but it is more than doubtful whether the distinction has any validity at other levels. The next section will provide even more evidence suggesting that this distinction is not a necessary component of a theory of memory.

Global Memory Models

McKoon, Ratcliff, & Dell (1986) argued that the controversy concerning the episodic-semantic distinction could only be resolved by explicating the underlying theoretical mechanisms more precisely. Formal models of long-term memory are natural candidates when it comes to specifying with greater precision the assumptions about memory structures and processes and, as a consequence, the predictions derived from these assumptions. During the last two decades several such formal memory models have been introduced. The common claim of these models is to explain a maximum number of empirical phenomena with a minimal set of theoretical assumptions. It follows directly from the principle of theoretical parsimony that separate memory systems must be postulated only when a unitary system definitely cannot account for the empirical data.

So-called *global memory models* assume only one long-term memory (also referred to as secondary memory). They usually also assume that the retrieval of an item is influenced by every item represented in long-term memory. Influential global memory models are SAM (*search of associative memory*; Gillund & Shiffrin, 1984; Raaijmakers & Shiffrin, 1981), TODAM 2 (*theory of distributed associative memory*; Murdock, 1982, 1997), CHARM (*composite holographic*

associative recall model; Metcalfe, 1982), the Matrix model (Humphreys, Bain, & Pike, 1989; Pike, 1984), MINERVA 2 (Hintzman, 1986, 1988), and REM (*retrieving effectively from memory*; Shiffrin & Steyvers, 1997). We will focus on MINERVA 2. This is a relatively simple but powerful model that is similar to the feature model of working memory which was discussed in Section 3.3. We will analyze MINERVA 2 with regard to the issue of multiple memory systems in general, and with regard to the episodic-semantic distinction in particular.

In MINERVA 2 an item T is represented as vector of M features, whereby each feature T_j ($j = 1,...,M$) may take on values of 1, 0, or -1. Values of 1 or -1 may be interpreted as the presence or absence, respectively, of a certain feature. A value of 0 typically indicates that a feature is either not defined or not encoded. Each feature can represent aspects of the target or of the context in which the target was experienced. However, not every encoded feature must be physically present, because subjects may also generate features internally. Note that in this way episodic information (e.g., the spatial and temporal context in which the target was experienced) is always represented in one feature vector together with semantic information about the target item.

MINERVA 2 is primarily a model of long-term or secondary memory. A primary memory is also assumed, but the only function of this primary memory system is to maintain an encoded item as a retrieval cue. In the secondary memory system every item is represented as a separate feature vector, so that this memory structure can be modeled as an $N*M$ matrix M representing N different items with M features each. In MINERVA 2 learning is conceived as the probabilistic copying of feature information from primary to secondary memory with the following conditional probabilities: $P(M_{i,j} = 1 \mid T_j = 1) = P(M_{i,j} = -1 \mid T_j = -1) = L$, $P(M_{i,j} = 0 \mid T_j$ $^1 1) = 1 - L$, $P(M_{i,j} = 1 \mid T_j$ $^1 1) = P(M_{i,j} = -1 \mid T_j$ $^1 -1) = 0$ and $P(M_{i,j} = 0 \mid T_j = 0) = 1$.

Aside from this simple learning process, two retrieval components are defined. One component—the *echo content* process $R_j(T)$—retrieves specific information from the memory store, whereas the other component—the *echo intensity* process $A(T)$—elicits a "feeling of familiarity." Formally, the echo intensity process is defined as

$$A(\mathbf{T}) = \sum_{i=1}^{N} \left(\frac{1}{N_i} \sum_{j=1}^{M} T_j \cdot M_{i,j} \right)^3 \qquad (1)$$

where N_i is the number of items for which either T_j or $M_{i,j}$ are not 0. Thus, every item in secondary memory is assumed to be activated as a function of its similarity to the test item which is held in primary memory. These 'local activations' of separate memory representations are finally summed up into $A(T)$, which can be interpreted as the global activation of the memory system that results in response to the test item.

Whereas the echo intensity process produces only one single familiarity value, the outcome of the *echo content* process is a full feature vector $\mathbf{R}$. Each feature in this vector R_j is assumed to be the sum over the corresponding features of all items in secondary memory, weighted by their corresponding local activation:

$$R_j(\mathbf{T}) = \sum_{i=1}^{N} \left(\frac{1}{N_i} \sum_{j=1}^{M} T_j \cdot M_{i,j} \right)^3 \cdot M_{i,j} \tag{2}$$

The echo content process is best illustrated using the cued-recall task. Suppose that two items $\mathbf{T}$ and $\mathbf{U}$ were learned together as a word pair (e.g., an English word and its French translation). Item $\mathbf{T}$ is given as the retrieval cue. Thus, the retrieval cue consists only of a subset of the features of the original learning episode. The echo content process allows the reconstruction of the missing features of the feature vector representing the original learning episode. The missing features that are reconstructed will probably resemble $\mathbf{U}$, since the local representation of $\mathbf{T}$ in $\mathbf{M}$ will be highly activated. Note that $\mathbf{U}$ also could have been assumed to represent the context in which item $\mathbf{T}$ was experienced, so that a reconstruction of the missing features would have been equivalent to a reconstruction of the study episode.

The first main characteristic of the model is that the results of both retrieval components are functions of all items represented in memory. The second main characteristic is that the result of both retrieval components depends strongly upon the retrieval cue in primary memory.

Despite its simplicity, MINERVA 2 has been applied successfully to many memory tasks and phenomena, including schema abstraction (Hintzman, 1986), frequency judgments (Hintzman, 1988), global similarity effects (Arndt & Hirshman, 1998), lexical access (Goldinger, 1998), and even social cognition phenomena (Dougherty, Gettys, & Ogden, 1999; Smith, E. R., 1991). In the present context, we need to focus on what we may learn from MINERVA 2, an instance of a formal memory model, about the episodic-semantic distinction. For that purpose, we sketch how MINERVA 2 can handle data from the remember-know task discussed in Section 4.3

According to Tulving (e.g., 1985a), retrieval from episodic and semantic memory systems is accompanied by different states of consciousness, which enable subjects in recognition memory tasks to classify their memories as 'remember' (episodic memory) and 'know' (semantic memory). MINERVA 2 does not distinguish between an episodic and a semantic memory system, but it can nevertheless handle data from the remember-know paradigm. There are two ways in which this can be achieved. A first way is simply to apply Donaldson's (1996) approach, which rests on the assumption of two response criteria acting on a single familiarity continuum. MINERVA 2's echo intensity process delivers a familiarity value directly (represented by $A(\mathbf{T})$, see Equation 1), so that the position of this value relative to the two response criteria on the familiarity continuum can be judged. The second way to model remember-know data using MINERVA 2 is to use the results of both the echo intensity and the echo content retrieval components. Judgments on the basis of the echo intensity component would lead to a "know" response, and judgments on the basis of the echo content component would lead to a "remember" response. For the latter, one should note that the item presented in the recognition test differs from the item that was learned together with contextual features of the learning situation. Given the test item and the new contextual features of the test situation as retrieval cues, it is possible to remember other details from the learning episode via the echo content process, which - given

compliance with the instructions - will lead to a "remember" response. Thus, "remember" and "know" responses would not reflect different memory systems but the success of different retrieval components.

MINERVA 2 also questions the episodic-semantic distinction indirectly, by allowing the integration of data from the false memory paradigm (Deese, 1959; Roediger & McDermott, 1995). In this paradigm word lists, each of which is associated with a non-presented critical test item, are to be learned (e.g., pin, thread, stitch etc. are learned, but needle is not presented). In subsequent free recall and recognition tests the critical test items are typically falsely produced or recognized at a rate that is comparable to presented list words. Interestingly, subjects often choose the "remember" responses when they are asked to qualify their states of remembering when "retrieving" the critical test items which is astonishing because the critical test items have never been part of the learning episode. This pattern of results challenges the validity of the episodic-semantic distinction, because there is no straightforward way to explain the high amount of "remember" responses to the critical test items that were never presented during the study phase. In MINERVA 2, in contrast, both false memories and the high rate of "remember" responses to the critical test items are fundamental model predictions. This is so because both retrieval processes depend on all items stored in memory. Since there are many related items in memory, it is quite likely that a critical test item achieves a high familiarity value as a result of the echo intensity component during recognition. For the same reason, some details of the learning episode may be reproduced via the echo content component of retrieval.

These examples should suffice to illustrate that from the perspective of a formal memory model such as MINERVA 2 there is no need to postulate different memory structures to explain data from the remember-know task.

A final aspect which we would like to mention concerns the finding that amnesic patients have serious problems in recall and recognition tasks, but often do not seem to differ from normals in implicit memory tasks (we will ignore for the moment the reliability problem mentioned above). From the point of view of a global memory model, the main difference between these two types of memory tasks is whether contextual information is relevant (e.g., during free recall) or not (e.g., during perceptual identification). This interpretation offers another possible explanation of the dissociation of explicit and implicit memory tasks between amnesic patients and controls. At least part of the problems of amnesic patients might be the inability to bring in adequately the necessary contextual information (for a detailed discussion see Humphreys, Bain, & Pike, 1989).

To summarize, formal memory models can explain a large variety of empirical data - including phenomena thought to require the assumption of separate episodic and semantic memory systems - while assuming only one coherent long-term memory system. This holds true for the global memory models discussed in this section, but also for ACT-R which was discussed in Section 4.1. For instance, ACT-R has recently been applied to a variety of episodic memory tasks without assuming a specialized memory structure for episodic information (Anderson, Bothell, Lebiere, & Matessa, 1998).

Conclusion: Limits of the Principle of Multiple Memory Systems

Models based on the assumption of multiple memory systems are popular in both working memory and long-term memory research. Such models have a certain degree of a-priori plausibility in that they allude to the brain anatomy which we customarily conceive as a collection of "structures" or "systems." The approach is generally useful, for instance, when analyzing particular memory deficits such as those typically used to define the amnesic syndrome. However, several factors complicate the multiple systems approach. One such factor is that there need not be a one-to-one mapping between what appear to be systems at functional and neural levels. Another is that quite often findings first thought to require the assumption of multiple memory systems have later turned out to be explicable by more parsimonious models. In addition, many important memory phenomena such as forgetting, context effects, or depth-of-processing effects do not lend themselves to being explained within a multiple systems approach. These considerations suggest that a promising direction for future research should be the integration of models inspired by the multiple memory systems principle with more precise formulations of the processes assumed to operate within the hypothetical systems. Formal models of memory such as the feature model of working memory or the global memory models of long-term memory clearly fulfill this requirement. What is more, they are theoretically more precise and therefore allow for stronger empirical tests of the postulated structures and processes.

7

Modules of Working Memory

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Working memory is best conceived as a set of modules responsible for the storage of information for a brief period of time and for the manipulation of this information in the service of ongoing tasks. To date, there has been considerable evidence from behavioral studies of normal and brain-injured individuals implicating separable storage and rehearsal processes as well as separable processes for verbal and spatial information. However, little evidence has accumulated about the architecture of executive processes. The addition of neuroimaging evidence concerning the executive processes as well as processes of storage and rehearsal enhances the picture of working memory provided by behavioral data.

Working memory is often defined as the memory system responsible for the storage of limited amounts of information for brief periods of time. With so narrow a definition, one may wonder what role working memory plays in our overall cognitive lives - lives that are concerned with solving problems, with inductive and deductive reasoning, with language production and comprehension in the service of communication, and with intelligent behavior in general, whether in humans or other animals. By now there is growing evidence that working memory is indeed critical to higher cognitive life: We know this from studies of the strong relationship between performance on working memory tasks and performance on a large range of other cognitive tasks (e.g., Salthouse, 1991). We also know that when the brain structures that mediate working memory are compromised by illness or injury, not only does working memory itself suffer, but deficits also pervade the cognitive skills that it supports (see, e.g., Shallice & Vallar, 1990). In short, understanding the mechanisms of working memory will have benefits not only

for understanding the architecture of this isolated memory system, but also for understanding changes in a large repertoire of cognitive skills.

At present, we know a good deal about the architecture of working memory. Our knowledge derives principally from three sorts of empirical programs: behavioral studies of normal adults, behavioral studies of brain-injured patients, and neuroimaging studies of normal adults. Together, these sources of information are leading to the development of a comprehensive view of both the psychology of working memory and the underlying neural architecture that supports the psychology. What has become increasingly clear from the accumulated research is that working memory is best conceptualized not as a monolithic construct, but rather as a set of modules. One conceptualization is that the modules can be grouped along two dimensions. One dimension has to do with function, whether a module is involved in storage of information, in rehearsal of that information, or in manipulation of that information for some cognitive purpose. The other dimension concerns the nature of the information that is stored in working memory, whether verbal, spatial, or some other code.

To appreciate the modularity of the organization of working memory, let us begin with the theoretical framework first introduced by Alan Baddeley and his colleagues (Baddeley, 1986, 1992). While not uncontroversial, the current version of this framework proposes that the storage of information in working memory is accomplished by a set of storage buffers, each responsible for a different sort of information – that is, the buffers are defined by the type of information they store. Each buffer has a rehearsal function associated with it to refresh the information stored there so that it can survive the normally short durations of unrehearsed memory traces. The contents of each of the buffers are then available to a set of executive processes that can manipulate the memorial representations in the service of some ongoing task, such as mental arithmetic, comprehending spatial directions, or reasoning.

To see how such a system might work, consider the processes required to solve a mental arithmetic problem such as:

$$74 \times 12 = ?$$

First, of course, the problem itself must be stored in working memory until a solution is reached. In one way of solving the problem, the solver must attend to the "tens" digit of the "74" (i.e., "7") and retrieve a rule or table from memory in order to multiply this by "12" to yield "840." This intermediate solution must then be stored temporarily while attention is turned from it to the units digit of the "74." Again, a multiplication rule or table must be retrieved from long-term memory so that the "4" can be multiplied by "12" to yield "48," another intermediate solution that must be stored. Then the first intermediate solution, "840", presumably being rehearsed in the background, must be retrieved and addition rules or tables also retrieved so that "840" can be added to "48" to yield the final answer of "888". Of course, all this storage, retrieval and computation must be completed in the face of irrelevant information in the environment that might interfere with performance. Even this simple arm-chair analysis of the processes involved in mental arithmetic reveals that the working memory mechanisms that are recruited to the task are both storage processes, and executive processes that coordinate operations performed on the stored information.

Of course, intuition suggests that while the processes involved in this sort of problem-solving involve arithmetic information, they are also heavily language-based. However, working memory extends to other information domains besides language. Consider another example to appreciate this. Suppose someone gives you directions from your home to the local grocery. She might tell you to make a left at your driveway, go to the second traffic light, make a right until you reach the gasoline station, make a left there to the elementary school on the right, proceed one block past the elementary school to the stop sign, make a left there and go 5 blocks to the grocery. Many people find that an effective strategy for storing such directions is to store a mental route that is described by the directions. That is, the listener would construct a spatial representation from the verbal information and use that to guide himself. To do so, one would have to encode the information in terms of spatial features (such as visualizing the directions left and right or creating images of the landmarks that are named), organize these spatial features in appropriate order, store the whole spatial representation of the route, and retrieve parts of it appropriately. Once again, this analysis suggests that working memory and executive functions play roles in problem-solving by mediating the storage of information and the manipulation of that information. Of course, this task may also require the use of long-term memory to retrieve familiar landmarks, information about directions, and so forth. Indeed, it may be that most of the route is stored in long-term memory, with only a portion of it activated as it is needed. In spite of these considerations, the task still clearly places heavy demands on working memory.

These examples nicely illustrate the intuitions that working memory is characterized by distinguishing different kinds of processes (storage, rehearsal, and executive functions) and by different kinds of information (verbal and spatial in the examples given, but others as well, such as visual information that is not spatial). However, a proper theory of working memory must be built on more than intuitions, and there is by now a wealth of evidence supporting the architecture that is suggested by these examples. Rather than being comprehensive in reviewing this literature, we shall concentrate on experimentation from our own laboratory using both behavioral and neuroimaging techniques to offer evidence that is relevant. First, we shall review studies indicating that storage mechanisms for different kinds of information in working memory are separable from one another. Second, we shall show that storage can be separated from rehearsal for verbal information, and possibly for spatial information as well. Finally, we shall offer evidence that executive processes are best characterized not as a single controller, but rather as largely separable mechanisms which share some common neural underpinnings.

Verbal versus Spatial Storage

To show that working memory for different kinds of information recruits different brain mechanisms, one would like an experimental setting in which the same memory task can be performed on different types of information, with little involvement of executive processes; that is, the processes that should be the focus of the task are those involved in storage and rehearsal. One task which fits this requirement is the item-recognition task. In the item-recognition task, subjects are given a set of items to store for several seconds, after which a probe item is given,

and subjects must indicate whether this item was a member of the memorized set. Notice that this task places little requirement on executive processes because there is no manipulation required of the stored information; instead, the task emphasizes the storage of the items, the rehearsal of those items, and retrieval processes necessary to decide if the probe had been presented as part of the memorized set.
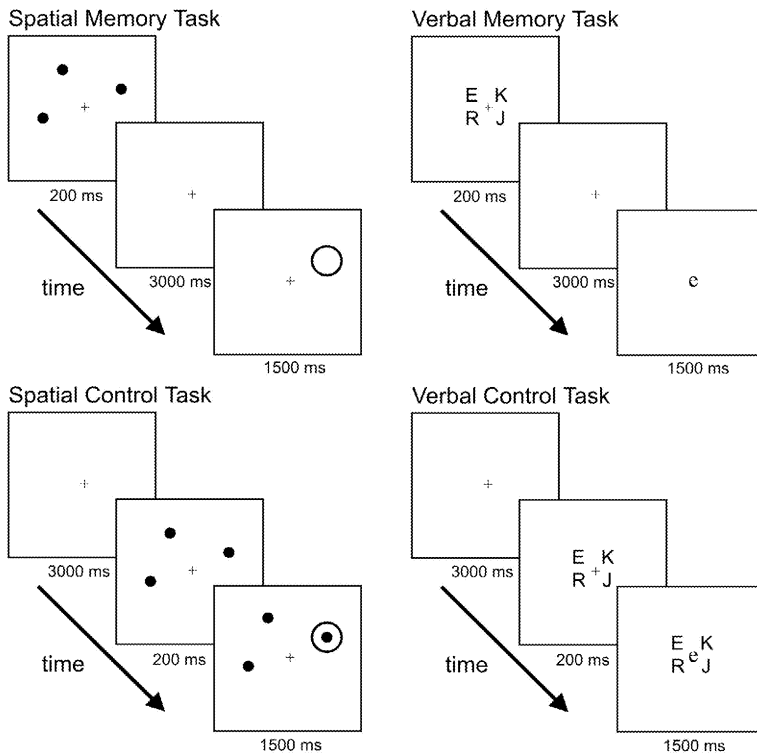

Figure 1. A schematic of spatial and verbal working memory tasks and their respective control tasks. The figure show the events that occurred on typical trials. Note that the control tasks were designed to mimic as closely as possible the events in the memory tasks, with the storage requirement removed.

The item-recognition task is nicely suited to studying working memory for different types of information because one can easily prescribe what items must be stored. In a pair of experiments, we have done just this, as illustrated in Figure 1 (Smith, Jonides, & Koeppe, 1996). In the Memory condition of a Spatial working memory task, subjects saw three dots at unpredictable locations on a screen that they had to store in memory for three seconds. Following this retention interval, a single location was probed, and subjects had to indicate whether this location was one of the three they had stored in memory. The comparable Verbal

Memory task is indicated in the right panel of the figure. Here, subjects were presented four letters that they also had to store for three seconds, following which a single letter was presented, and they had to indicate whether this was one of the stored letters. Different groups of subjects participated in these two tasks while being scanned using positron emission tomography (PET). Appropriate control conditions for each memory task are also shown in Figure 1. The control tasks were designed so that subjects were presented with similar perceptual displays and had to make similar matching judgments, but the memory requirement in each control condition was minimal. Consequently, contrasting the activations of the Spatial and Verbal Memory conditions with each of their control conditions should yield activations due to the storage and rehearsal of spatial and verbal information respectively, and not due to encoding operations or response processes.
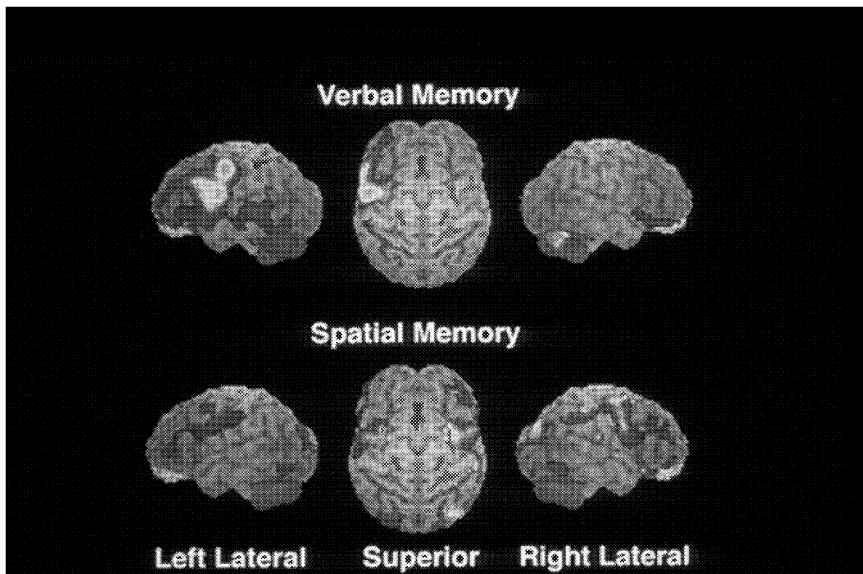
Figure 2. Brain activations for the verbal and spatial working memory tasks (shown in lighter greys for the higher levels of activation and in darker greys for the lower levels of activation) schematized in Figure 1. The top row of images shows brain activations of the memory-control subtraction superimposed on three views of a representative brain. The bottom row shows comparable activations for the spatial-control subtraction.

Behaviorally, subjects were quite accurate in these tasks. Of interest is that their response times for the Memory conditions exceeded the response times for the Control conditions. This is consistent with the assumption that the Memory conditions required processes in addition to those engaged in the Control conditions, presumably processes of storage and rehearsal.

The brain activations reveal a pattern that indicates a dissociation between verbal and spatial working memory. These activations are shown in Figure 2, with the verbal condition shown on the top row and the spatial condition on the bottom. Perhaps the most obvious feature of the activations shown in the figure is that they differ by hemisphere, with greater right-hemisphere activation in the spatial condition and greater left-hemisphere activation in the verbal condition. This difference is of great interest in describing the architecture of working memory because, by virtue of the design of the experiment, it represents largely the storage and rehearsal components of the task, not those due to encoding or retrieval. Thus, the difference in hemispheric asymmetry in these activations indicates that there is a difference in the mechanisms responsible for maintenance in working memory based on the type of information being maintained.

Beyond this gross difference, there are also more detailed features of the activations that merit comment. In the verbal task, the major sites of activation are in inferior frontal gyrus near Broca's area, in premotor cortex in the supramarginal gyrus of posterior parietal cortex, and in superior parietal lobule, all concentrated in the left hemisphere. As we shall see below, the activation in Broca's area can be distinguished from the activation in parietal cortex in such a way as to associate the former with rehearsal and the latter with storage. For the spatial task, the most noticeable activations appear in prefrontal cortex in the region of superior frontal sulcus and inferior frontal gyrus, as well as in extrastriate cortex in the occipital lobe. The functions of these regions have not yet been clearly described, compared to those for the verbal task, but there is some evidence, reviewed below, that the extrastriate activation reflects the operation of a spatial rehearsal process, possibly involving the use of covert spatial orienting. The dissociation revealed by these data has been replicated by others, indicating the robustness of the finding that the neural circuitries for storage in spatial and verbal working memory are different from one another (see, e.g., Courtney, Ungerleider, Keil, & Haxby, 1996; Paulesu, Frith, & Frackowiak, 1993). Beyond this, there is also some evidence that information about object form recruits yet another set of storage mechanisms (Courtney, Ungerleider, Keil, & Haxby, 1996). It should also be noted that the different circuitries that appear to be involved in working memory are not simply defined by input modality; the distinction seen in this task between visually presented spatial information versus visually presented non-spatial information makes this point. In addition, there is evidence from another PET study that verbal information entered into working memory by ear or by eye makes little difference to the storage mechanism that is used (Schumacher et al., 1996). Thus, what appears to be the defining characteristic of the different storage mechanisms is the information that is stored, not the way that information first enters the system.

Rehearsal

The information stored in working memory is fragile; without being refreshed, it will decline in strength in a matter of seconds and be unavailable for retrieval. To keep the information active, one must engage in some sort of rehearsal process that recycles and refreshes the traces, thereby

mitigating the effects of decay and interference. This view of working memory highlights the distinction between processes responsible for storage of information and processes responsible for rehearsal, and there is behavioral evidence to support this distinction both from normal and brain-injured subjects (e.g., Basso, Spinnler, Vallar, & Zanobio, 1982; Longoni, Richardson, & Aiello, 1993). The behavioral evidence is not itself completely satisfying, however, largely because it is difficult to investigate the effects of rehearsal separately from the effects of storage, and because patients with damage to one system often show carryover effects in other systems. We have documented the separability of storage and rehearsal using positron emission tomography (PET) measurements of a task that has been used widely to study working memory, the n-back task (Awh et al., 1996).

In this task, subjects are presented a sequence of single-letters at a fairly leisurely pace (once every 3 sec in the experiment to be described). In the 2-back version of the task, when each letter is presented, a subject must decide whether it matches in identity the letter presented two items back in the sequence. So, for example, if the letters P, N, P, R, J, R, L, D, D were presented, subjects should respond positively to the third and sixth letters in the sequence ("P" and "R"). Note that subjects should not respond to the last letter ("D"). This is because while the third letter matches the first, and the sixth matches the fourth, the last letter matches the one just before it, not the one two items before it. This is a demanding task that requires focused attention, but with a bit of practice, subjects become quite accurate, scoring above 90% in accuracy. The task clearly requires storage of each letter in memory at least until two more letters are presented, and to maintain this storage, rehearsal is also required otherwise the interfering effects of successive letters would cause the memory traces to degrade substantially. In addition, of course, unlike the item-recognition task, the 2-back task requires considerable executive processes that are responsible for updating the contents of working memory and for inhibiting positive responses to letters that do not match the letter two items back in the series.

In this experiment, our intention was to focus on the processes required for storage and for rehearsal, not the executive processes about which we shall comment below. In order to isolate storage and rehearsal, we also had subjects participate in two control conditions. In a "Search" control, a single target-letter was presented to subjects at the beginning of a series of single-letter presentations (as in the 2-back condition), and this letter served as the target for the entire series. When subjects saw it, they were to respond positively; otherwise, they were to respond negatively. Compared to the 2-back task, the Search control has a smaller storage and rehearsal requirement, so contrasting activations in the Search condition to those in the 2-back condition should reveal regions responsible for storage and rehearsal. In the "Rehearsal" control condition, subjects were again presented a series of single letters at the same pace as in the 2-back task. When each letter was presented, they were instructed to rehearse it silently until the next one appeared, at which time they were to rehearse that one, and so on. This condition has an even smaller storage requirement than the Search condition, but places substantial demand on rehearsal. Thus, subtracting the Rehearsal control from the 2-back task should substantially subtract out rehearsal processes, but leave intact activations due to storage.

Figure 3 displays the activations from the PET measurements that resulted from subtracting the Search and Rehearsal controls respectively from the 2-back task. The data are displayed for 4 comparable horizontal brain slices from each subtraction, revealing the relative

activations. Consider first the activations shown in the left panel for the subtraction of the Search control from the 2-back task. This panel reveals prominent bilateral activations in parietal, premotor, and supplementary motor cortex, inferior frontal gyrus on the left, as well as cerebellum. Contrast this with the subtraction of the Rehearsal control from the 2-back task, shown in the right panel. The major difference between this subtraction and that with the Search control is that the activation in inferior frontal gyrus is dramatically reduced. By the logic of the subtraction method, this difference leads to the conclusion that the left inferior frontal gyrus is a major contributor to verbal rehearsal processes. This makes sense when one considers that this same region is heavily involved in overt articulation as well, suggesting that the same region that is critical to speech production is co-opted for internal rehearsal. Note also that the activation in parietal cortex in the subtraction of the Rehearsal control from the 2-back condition is somewhat larger than in the subtraction of the Search control from the 2-back condition. This is as it should be if these parietal activations reflect storage processes because the storage requirements of the Search control are larger that those of the Rehearsal control.
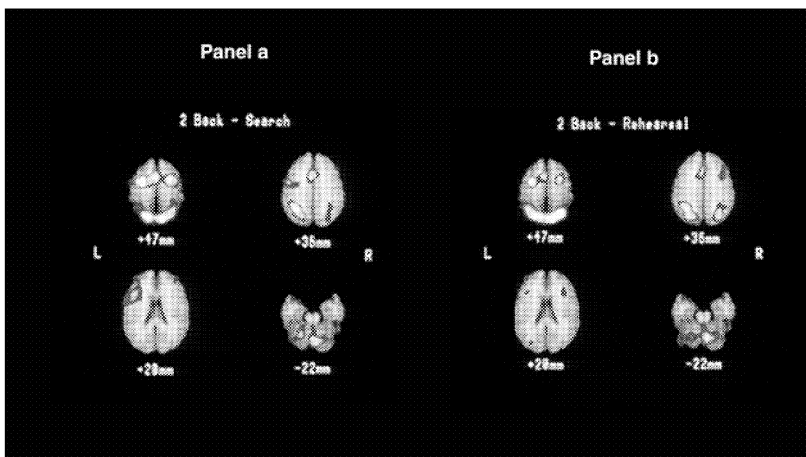
Figure 3. Brain activations superimposed on horizontal slices at the z-values indicated on the figure. Panel a shows the subtraction of the Search condition from the 2-back condition; panel b shows the subtraction of the Rehearsal condition from the 2-back condition. Activations are shown as lighter grays superimposed on darker greys that reveal the anatomy of a representative brain.

The concept of rehearsal for verbal material has much intuitive appeal to it because many subjects engaged in working memory tasks do have the introspection that they devote effort to "talking to themselves" to keep traces fresh. If the storage/rehearsal architecture is a general one, though, it ought to apply to other types of material stored in working memory as well. Consider again storage of spatial material, as required in the item-recognition task described above. If this material is not rehearsed during a retention interval, the traces of the locations that were encoded

will quickly fade from memory. Thus, one might propose that there is rehearsal for spatial information similar to that for verbal information; more generally, one might propose that working memory for any sort of information requires a rehearsal process. What is interesting about this proposal is that the nature of rehearsal must differ for different types of information. For example, it is not effective to use a verbal rehearsal strategy for the dot-locations of the spatial item-recognition task because the probe may appear in a location that is categorically similar to one of the target locations (e.g., upper left or lower right third of the screen), thereby activating the same verbal code, but it may nevertheless not match a target location. What is required for each type of information is a rehearsal strategy that is tailored to the type of information in question.

What might this strategy be for spatial information? One interesting possibility is raised by the striking similarity in brain regions involved in spatial working memory and the allocation of attention to places in space, as reviewed by Awh & Jonides (1998, 2001). This analysis suggests that in both humans and other animals, there is substantial commonality in the brain mechanisms involved in the two tasks. This commonality raises the hypothesis that rehearsal of spatial information may involve an allocation of spatial attention to the specific locations that are being stored. We have tested an implication of this: If spatial rehearsal engages an internal attention-allocation mechanism for a rehearsed location, then there should be evidence of improved processing at that location if a visual discrimination task is inserted during the reten- tion interval of a spatial memory task (Awh & Jonides, 1998). The task is illustrated in the top panel of Figure 4. A letter was presented briefly in a location followed by a retention interval of 5 sec. Following this interval, another letter appeared at a location on the screen, and subjects made a judgment about whether this letter matched the earlier presented target. Half the subjects judged whether the letters matched in their spatial location, regardless of the identity of the letters, and half judged whether the letters matched in identity regardless of spatial location.

What is critical in the experiment is what transpired during the retention interval. During this interval, subjects made speeded discrimination judgments about the left or right orientation of a nonsense symbol that was presented on the screen, as shown in Figure 4a. This figure sometimes appeared in the location that subjects were storing in memory and sometimes in another location. The critical prediction was that when subjects were storing spatial information, if the figure appeared at the memorized location, it would be discriminated faster than if it appeared at a non-memorized location. However, if the memory task involved letter identity and not position, there would be no difference in discrimination speed regardless of where the figure appeared during the retention interval. As Figure 4b shows, just this pattern of response times emerged. What these data reveal is that some processes engaged by the memory task have a carryover effect on a visual discrimination task (during the retention interval) that should be influenced by the allocation of visual attention to a spatial location. Thus, these data suggest that spatial rehearsal engages the same attention mechanism used for visual discrimination. What the data do not indicate, however, is whether this spatial attention mechanism is functional for the memory task itself.

To address this issue, we conducted another experiment that used the same main memory task, working memory for a single spatial location, as shown in Figure 5 (Panel a) (Awh & Jonides, 2001). Again, a visual discrimination task intervened during the retention interval (dual-

task), but in this case the discrimination task involved judgments about hues (whether a color patch was red or blue) rather than letter or location. In the condition schematized at the top of the panel, the color discrimination had to be made to a small patch presented eccentrically on the screen, and so attention had to be directed to it in order to make that judgment. In the task shown just below this, the color patch was large and occluded all of the potential memory locations. Thus, in this condition subjects could discriminate the color of the large patch without shifting attention away from the memorized location. There was a significantly larger decline in memory accuracy for the target spatial location when subjects had to discriminate the color of the small patch during the retention interval (i.e., when the color discrimination required a shift of attention
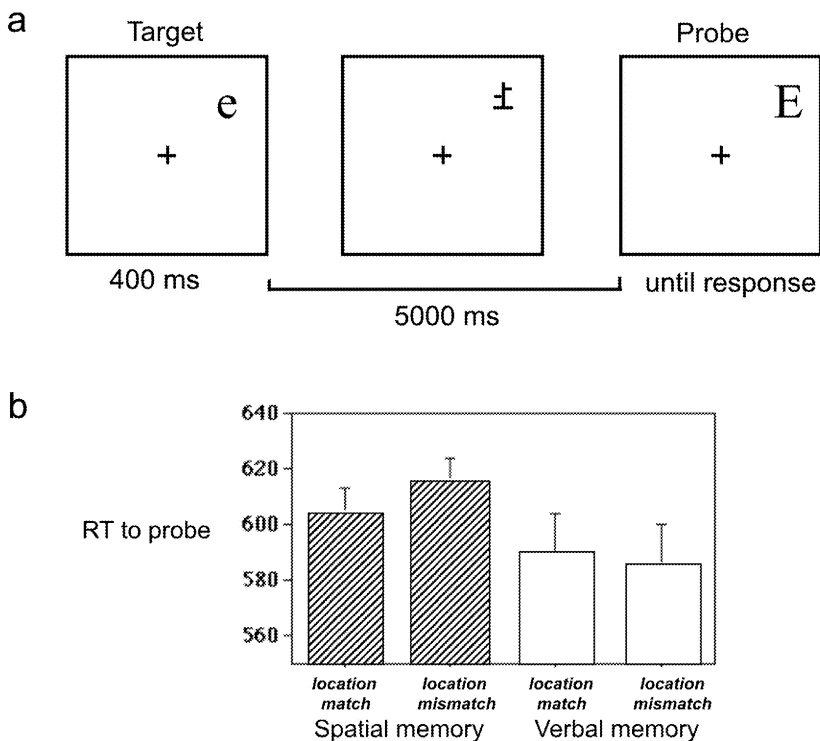
Figure 4. Panel a: A schematic of a task used to examine the hypothesis that spatial rehearsal recruits a process that influences the allocation of attention to visual objects. Panel b: Response times for probe items presented during the retention interval of the task shown in Panel a. The four bars represent whether the location matched or mismatched the location of the memorandum for the spatial and letter memory tasks respectively.
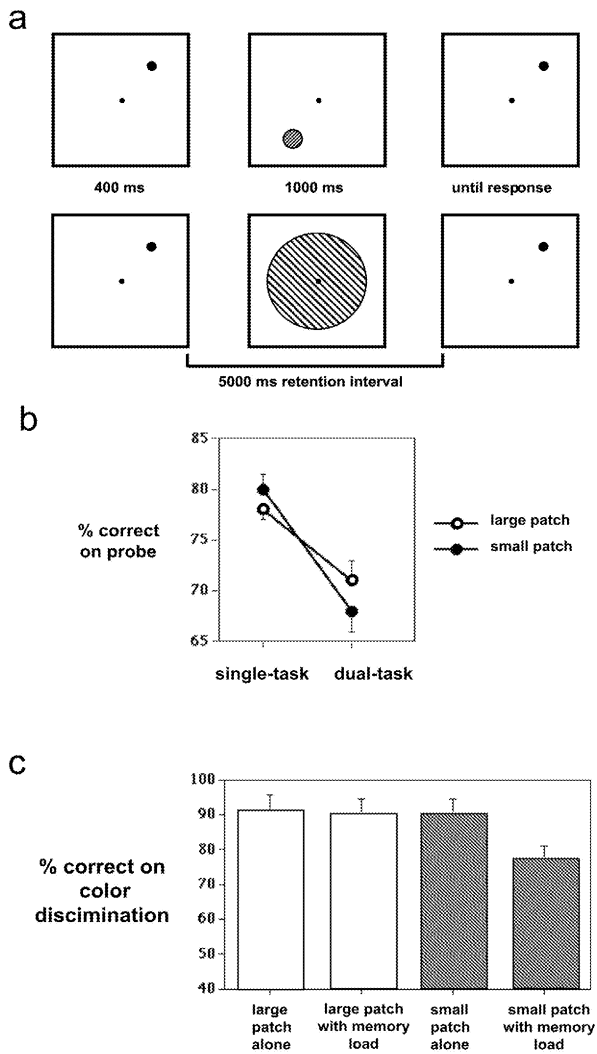
Figure 5. Panel a: A schematic of a task used to test whether allocation of attention to a visual location during a retention interval would affect memory for a spatial location that had to be stored. The retention interval was filled by either a large or small patch of color (represented by the striated region in the figure). Panel b: Accuracy of memory for the spatial location as a function of whether subjects had to perform a color discrimination during the retention interval (right pair of points) or merely viewed the colors but only had to perform the spatial memory task (left pair of points). Panel c: Accuracy on the color discrimination task when it was presented alone or with the spatial memory task.

away from the memorized location) than when subjects discriminated the color of the large patch (as shown by the right two points in Figure 5b). To be sure that this effect was a function of the intervening shift of attention to the target color, a control condition was included in the experiment in which the colors were presented during the retention interval, but no judgment had to be made about them; subjects just had make judgments about the target spatial location in this control condition. The data from this control (single-task) condition are shown in the left two points of Figure 5b; these data reveal that without the dual-task requirement, memory performance was approximately equivalent when the large and small color patches were presented during the retention interval. Note also that the experiment yielded a replication of the effect of attentional allocation on the intervening color discrimination task during the dual-task, as shown in Panel 5c. When the color patch was large and presented in the center of the screen, having this judgment made in the context of a memory task did not make performance worse compared to when it was made alone. However, when the spatial memory task was required, then performance suffered for the color judgment on the small color patch, presumably because attention was not allocated to the location of the patch.

The data from these two experiments taken together suggest that spatial working memory and spatial attention share a mechanism in common, a mechanism that for spatial working memory operates during the retention interval of a memory task. Recall from the item recognition experiments that one of the regions activated by spatial storage in working memory was extrastriate cortex. It is now well-documented that activity in visual cortex can be modulated by spatial selective attention, with larger visually-evoked responses in the brain regions that process the attended locations. Following the possible analogy between spatial attention and spatial working memory, perhaps rehearsal in spatial working memory is related to modulation of activity in extrastriate cortex, not necessarily in the service of better perception of spatial information, but in the service of better retention of that information. To address this issue, we conducted an experiment in which functional magnetic resonance imaging (fMRI) was used to measure whether extrastriate cortex was modulated in its activity when subjects were engaged in a spatial working memory task, compared to a verbal working memory task (Awh et al., 1999). In particular, we sought to test whether rehearsal of a spatial location produced increased activation of extrastriate cortex contralateral to that location, just as attention to a visual stimulus produces activation in occipital cortex contralateral to the position of that stimulus.

The paradigm is illustrated in Panel a of Figure 6. Three target memoranda were presented sequentially and followed by a retention interval of 7 sec during which time a checkerboard was flashed to both visual fields. The memoranda were false-font characters in either the left or right visual fields. After the retention interval, a single false-font character was presented, and subjects had to judge whether it appeared in a location marked by one of the target characters. We measured the activations in extrastriate cortex due to the flashing checkerboard to see whether these activations were larger in the field contralateral to the memorized locations. To control for the fact that the stimuli themselves were presented unilaterally, in a control task the memoranda were letters rather than false-font characters. Subjects then had to judge whether a probe letter presented after the retention interval matched in identity one of the target letters,regardless of position. For individual subjects, the regions of occipital cortex that were activated by the checkerboard were mapped using data from a separate
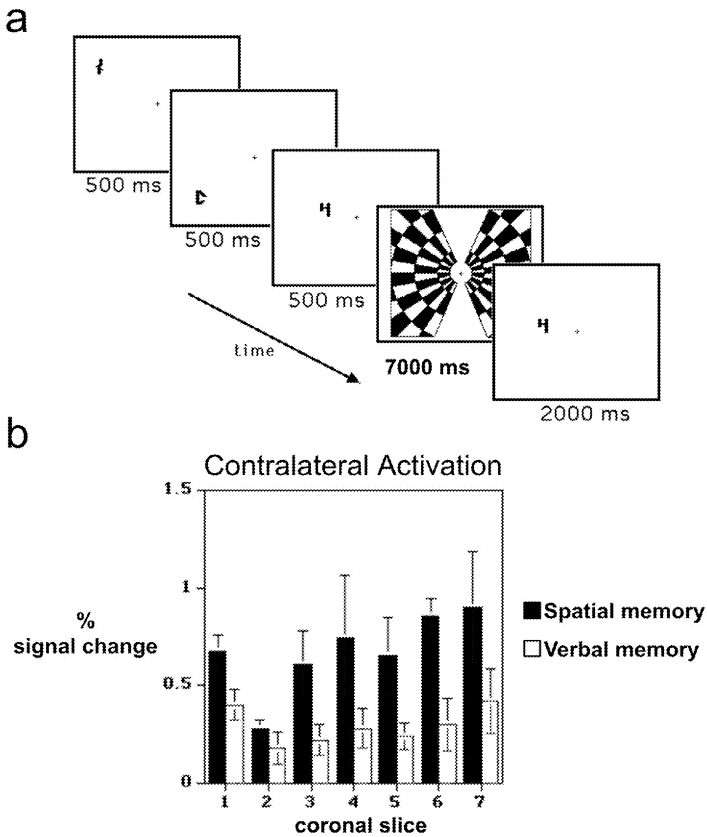
Figure 6. Panel a: A schematic of a task used to study the brain basis of spatial working memory in posterior cortex. Subjects were sequentially presented with three characters to memorize, after which there ensued a 7 sec retention interval and a probe item. The memory task was either for the spatial location of the items, or, in another condition not shown, for the identities of letters presented at those locations. Panel b: Percent signal change in 7 posterior coronal slices for the spatial and verbal memory tasks.

control task so that we could examine individually whether these areas were modulated by the spatial rehearsal task compared to the verbal rehearsal task. Panel 6b shows that the spatial rehearsal task yielded greater activation in these contralateral voxels than the verbal task for all the slices measured in posterior cortex. Thus, it appears that spatial rehearsal in working memory leads to a modulation of activity in extrastriate cortex in just the same way that spatial selective

attention does. This supports the view that there is significant functional overlap between these two processes.

To sum up our discussion of storage and rehearsal in working memory, we have found evidence illustrated by research in our laboratory, but confirmed by work in other laboratories, of two central features. One is that working memory storage appears to be mediated by different mechanisms as a function of the type of information stored. The second is that rehearsal provides support for continued storage of information beyond the brief period during which it would be viable without intervention. Furthermore, the particular mechanisms of rehearsal are tied to the type of stored material. For verbal material, mechanisms ordinarily responsible for the production of speech play a central role in internal recycling of information. For spatial material, mechanisms responsible ordinarily for visual selection are co-opted to the task of maintaining internal spatial codes. These two examples illustrate nicely how the nervous system manages to harness single mechanisms for multiple tasks based on the computational competence of the mechanisms. We speculate more generally that there may be many memory processes that ride piggyback on posterior mechanisms that evolved for the purpose of processing sensory information from the outside world (see, e.g., Miller, Erickson, & Desimone, 1996, for a similar point about working memory for information about objects).

Executive Mechanisms

We turn now to the final set of modules important for working memory, the executive functions responsible for manipulating information. There has been a good deal of theoretical debate about the nature of executive processes that has focused on one issue: Are executive processes of a piece, or are there multiple such processes each largely different from the others but acting in concert to accomplish various task goals?

One might think that the singular view, on the face of it, must be a straw man: Any task that makes heavy use of executive processes, such as mental multiplication or the n-back task discussed above, appears to recruit many different processes.

Recall the processes of mental arithmetic and the n-back task to illustrate this point. The mental arithmetic task requires at least two seemingly quite different kinds of attention-switching processes in the service of manipulating information in working memory. One of them is responsible for switching between different internal representations of parts of a problem (e.g., the "units" digit versus the "tens" digit) in order to perform some operation on it. By contrast, at some point in the problem, one must also switch between one mental computation (multiplication) and another (addition). While both of these require shifts of attention, the processes that underlie each of the shifts seem, on the face of it, to be different from one another.

Now consider the n-back task, which seems to feature a set of seemingly very different executive processes, those involved in inhibitory functions. One such kind of inhibition in the 2nd-back task is the ability to inhibit a positive response to an item that appeared just previously in a sequence (i.e., 1-back) because that item, although familiar, is not a 2-back match. Note also

that this task requires another kind of inhibition – the inhibition of the item that is two items back in the sequence so that a new letter can be entered into memory to replace the current letter. For example, in the sequence, "L, P, L, R", when the second L appears and is matched to the item two letters back, the first L must then be discarded from memory in order for the new letter, R, to enter and be marked as the current letter to be matched against its two-back candidate, P. Thus, the n-back task relies more on processes responsible for inhibiting irrelevant representations rather than those responsible for switching between internal representations or internal computations. In the face of such seemingly different sorts of switching and inhibitory processes, how could one argue that executive processing is "of a piece?"

In fact, such an argument is not a straw man if one conceptualizes all executive processes as variants of attentional allocation mechanisms. In the case of switching between representations or operations in mental arithmetic, perhaps the central mechanism that is required is one that activates the alternative representation or operation, and suppresses the currently active one. In the case of inhibition in the n-back task, an analysis in terms of attentional allocation may also be appealing. For example, perhaps what is involved in avoiding an incorrect positive response to a match with an item that is just one letter back in the series is allocation of attention to a representation tied to the episodic tag of when an item appeared in a series, and inhibition of the potency of a familiarity representation. Similarly, to rid memory of an item in a series to make way for a new item, perhaps what is involved is an activation of the representation of the newest representation, and suppression of the representation of the oldest item of the set. This view casts executive processes entirely in terms of attentional allocation, and as such, it has a respectful place among theories of executive processing. Indeed, papers by Baddeley and his colleagues (Baddeley, 1986, 1992; Norman & Shallice, 1986), and others are all examples that make a good theoretical case for a singular view of what has been called the "central executive," a term that suggests a singular vision of this sort of processing.

By contrast, consider an alternative view of executive processes, in which individual processes are different computationally from one another, and therefore could be mediated by quite different brain mechanisms. Using our examples of mental arithmetic and the n-back task, we might suppose that there are several quite different processes involved. In the case of mental arithmetic in which attention must be switched from the representation of one digit to the representation of another, this switching might be accomplished by a mechanism that changes the activation values of the two memory representations, bringing one to the forefront and relegating the other to the background. This sort of change in activation levels may be the sort of mechanism needed when two representations have equivalent status and changes need to be made rapidly between them to accomplish some task, such as multiplication of numbers. To change from one mental computation to another (say, multiplication to addition), what may be required is a switch in what rules or tables are retrieved from long-term memory. Thus, even though these two kinds of processes may be cast similarly by using the term "switching," what is actually involved may be computationally quite different.

The n-back task may involve yet different executive processes from those used in mental arithmetic. Perhaps removing the oldest item from working memory and adding a new item does involve some sort of attentional allocation scheme that changes the relative activations among items in memory. By contrast, preventing a positive response to an item that was just presented

and that matches the current item (a 1-back false alarm) might involve an inhibitory process that blocks the prepotency of highly familiar items. This way of looking at the difference between switching and inhibition suggests that the two should be dissociable behaviorally. Further, if they are dissociable, then there should be evidence of different brain mechanisms responsible for their mediation.
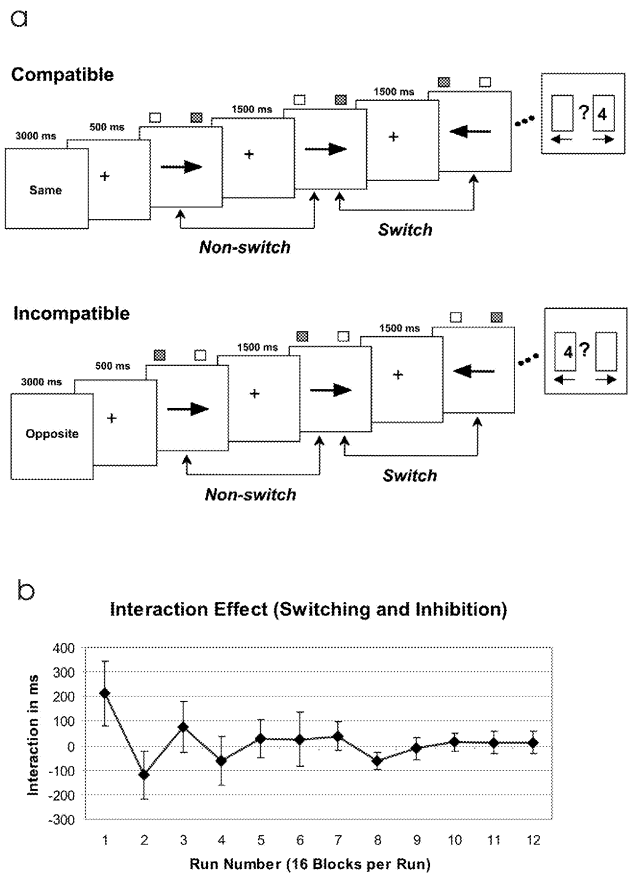
Figure 7. Panel a. A task used to examine the effects of switching between representations of counters stored in working memory as well as inhibitory effects induced by an incompatible response requirement compared to a compatible requirement. Panel b: A graph showing that in early stages of practice, there was a modest interaction in response times between the switching and compatibility variables, but with a small amount of practice, the interaction reduced in size sufficiently that there appears to be an additive relationship between switch-cost and the effect of compatibility.

We have recently conducted a combination of behavioral and neuroimaging experiments to determine whether switching of attention between representations in working memory and inhibiting attention to a prepotent response are separable processes (Sylvester et al., submitted).

Our research began with the behavioral task illustrated in Figure 7. Subjects were presented with a sequence of arrowheads that pointed left or right, each presented until the subject made a response. One of their tasks was to keep track of the number of left-facing arrows and the number of right-facing arrows in a sequence of 8 to 11 arrows. After each sequence of arrows, subjects were probed about their counts to assess accuracy. Note, as shown in the figure, that the sequence of arrows yielded two types of trials of interest: those on which a succession of two arrows pointed in the same direction so that subjects did not have to switch counters versus those on which a succession of two arrows pointed in different directions, necessitating a switch in counters in order to update the counts. This task is modeled after one introduced by Garavan (1998) who showed that the response time to each stimulus that had to be counted depended on whether it indicated the same counter as the previous stimulus (non-switch trials) or whether it indicated a different counter from the previous stimulus (switch trials). Switches took longer. The other task that faced subjects was to respond with a manual keypress to the presentation of each arrow. In one condition, subjects' responses were compatible with the direction in which the arrow pointed, (i.e., a left keypress to the presentation of a left-facing arrow and a right keypress to the presentation of a right-facing arrow). In the other condition, the assignment of responses to arrows was reversed so that the responses were incompatible with the directions of the arrows. A large corpus of previous research using manipulations of stimulus-response compatibility has shown that there is a reaction time cost when the required response is incompatible with the prepotent response to stimulus. Compatible and incompatible blocks were alternated across each 8-11 arrow sequence. The main issue underlying this experiment was whether the cost in switching between counters and the cost in responding incompatibly are dependent on one another as they might be if there is a single mechanism underlying them; alternatively, these two performance costs might be statistically independent of one another if there are two separate executive mechanisms involved in mediating the two operations.

The behavioral results from the experiment are quite clear. Very early in performance, as can be seen in the left side of Figure 7b, one can see the interaction of switching and compatibility reaction time costs.This interaction was initially over-additive in nature (accuracy in both tasks is near ceiling, so response time is the dependent measure of choice to examine performance on this task). Note, though, that the small over-additivity was ephemeral, converging to zero after several 16 block runs of trials, after which, as shown on the right side of Figure 7b, the two factors affected performance independently. These results lead to the following hypothesis: That there are two separable mechanisms, one mediating switches of attention to internal representations and another mediating rules that map stimuli onto incompatible responses (see Sternberg, 1969, for the rationale that underlies this hypothesis from response times). While these two mechanisms are separate, early in practice their independent operation is overcome by a common resource limit that is placed on performance by the unfamiliarity of the task, so it appears as if they interact; but this effect soon dissipates.

The behavioral results are not unambiguous, however. It may be that there is a single mechanism that mediates counter-switching and stimulus-response rule assignment, and that this mechanism (which speeds up with practice) operates on the two tasks in turn. If this were so, it could result in a pattern of seeming independence between the two performance costs, as was obtained. To gather further evidence of the independence of the two mechanisms, a functional MRI experiment was conducted to examine what brain areas are engaged by the two experimental factors. In this experiment, the counter-switching and stimulus-response compatibility tasks were wholly separate from one another. For both tasks, the stimuli consisted of a sequence of arrows presented one at a time, as in the behavioral experiment. The counter-switching manipulation was tested by having subjects keep track of two counters (left and right arrows) in two types of blocks. In one type of block, subjects had to switch between counters relatively frequently (70% of trials); in the other type, they had to switch relatively infrequently (20% of trials). On each trial in these blocks, subjects responded to each arrow with a double key-press using both left and right index fingers, so the responses to each arrow were identical, with no compatibility variation. The compatibility manipulation was tested in yet different blocks, contrasting a block of trials in which subjects responded compatibly to each arrow versus another block of trials in which they responded incompatibly, neither of which blocks involved any counting. Thus, this experiment examined the effects of each variable separately from the effects of the other, but within the same subjects.

One potential concern with the imaging data was that both experimental tasks might involve more overt or intended eye movements than their controls, and that mechanisms controlling these eye movements might produce activations that were not of interest. To rule out this possibility, a saccade-control task was included in the experiment. For this control task, we instructed subjects to execute saccades to a series of stimuli presented on a screen. Saccade-related activity was contrasted with a control condition in which subjects maintained fixation. In order to examine the areas of activation uncontaminated by the activations due to saccades, we subtracted out the saccade-related activations from those due to switching and compatibility in further analyses.

Having subtracted out the effects of eye movements, we proceeded to categorize the areas of activation observed in the switching and compatibility contrasts as being common to both task-switching and compatibility, or uniquely associated with one of these two variables. We created regions of interest consisting of all the activations due to both switching and compatibility, and determined which voxels within this ROI were active in both tasks (see Figure 8). These included bilateral superior parietal cortex, superior colliculus, anterior cingulate, left middle frontal gyrus and bilateral premotor cortex.. The bilateral parietal cortex and superior colliculus have been implicated in selective attention (Buchel et al., 1998; Casey et al., 2000), the dorsolateral prefrontal cortex is thought to be involved in maintaining contents of working memory that may need to be manipulated, while the anterior cingulate may be involved in detecting or responding to the conflict that arises from a competing dominant response (Gehring & Knight, 2000; Jonides, Badre, Curtis, Thompson-Schill, & Smith, in press; MacDonald, Cohen, Stenger, & Carter, 2000). The bilateral premotor cortex may be involved in the inhibition of a prepotent response in the response compatibility task. In the switching task, it is possible that subjects are actively delaying responses on switch-trials relative to non-switch trials since

on switch-trials they must complete the counter-switch and counter-updating processes before they can make their motor responses, which may necessitate inhibition of a response, indexed by premotor activation. Overall, then these activations reveal that there are certain processes, such as detection of conflict and inhibition of a prepotent response that seem to be common to these two tasks and that reflect the recruitment of common executive mechanisms.
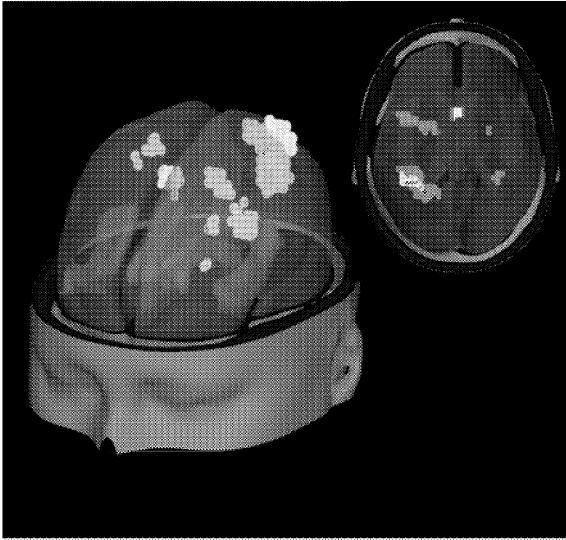
Figure 8. Regions of common activation in the switching and compatibility tasks superimposed on a the canonical structural brain drawn from the Montreal Neurological Institute as included in the SPM program. Note that two views of the activations are shown to make it clearer where they are localized.

In contrast to these regions of common activation, there were also areas of activation that were better described as being unique to each of the tasks. We discovered regions of activation distinctive to the switching and compatibility variables by comparing switch-related activations to compatibility-related activations in the same regions of interest we used to assess common activations across the tasks. Using paired t-tests, we found that the counter-switching task yielded significantly greater activation in bilateral extrastriate cortex, left posterior superior parietal cortex, superior colliculus, left dorsolateral prefrontal cortex, and anterior cingulate (see Figure 9a). Together with the analysis of common activations, this suggests that there is unique activation in the extrastriate and posterior superior parietal regions for the counter-switching task, and greater activation due to switching than response-inhibition in the other areas (even those these areas are active at a lower level in the stimulus-response compatibility task). The posterior superior parietal cortex appears to be involved in attention- switching (Dove, Schubert, Wiggins, & von Cramon, 2000), while the extrastriate activation may be a result of the use of mental imagery to represent the counters (see, e.g., Kosslyn et al., 1993, for evidence of the involvement of occipital cortex in mediating visual imagery). Supporting this hypothesis are the reports of several subjects who stated that their representations of the counters had a spatial quality to them (consistent with the left-right difference in the stimuli that mark the counters). These distinctive activations are an indication that the switching task recruits processes that are task-specific (such as the occipital activation that may reflect the recruitment of imagery

processes) and additional executive processes (such as may be reflected in the dorsolateral prefrontal activation) that are not recruited at all or as much by the compatibility task.
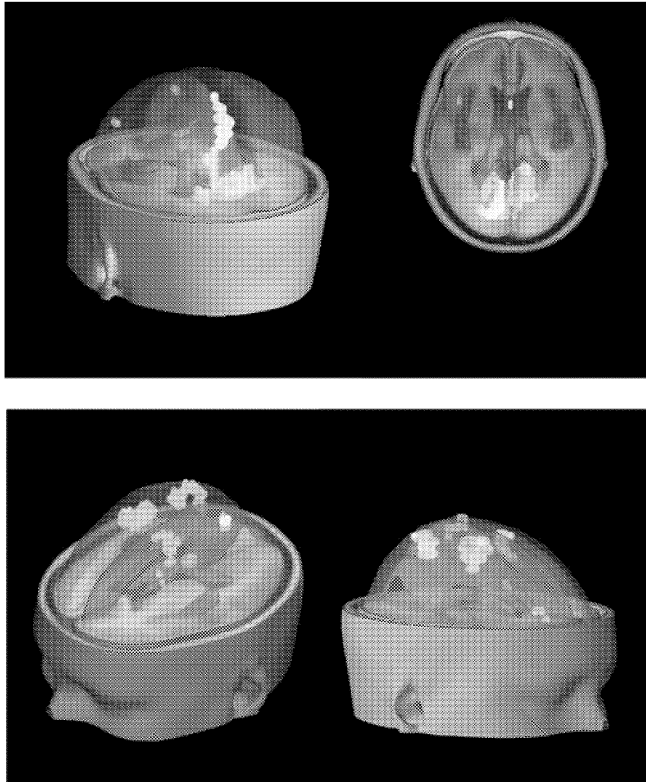
Figure 9. Panel a: Regions of greater activation in the switching than the compatibility task. Panel b: Regions of greater activation in the compatibility task than the switching task. For both panels, the activations have been superimposed on the canonical structural brain drawn from the Montreal Neurological Institute as included in the SPM program.

Areas of activation that were better described as uniquely associated with response incompatibility were the bilateral superior parietal and supplementary motor area, as well as the right frontopolar cortex (see Figure 9b). It is important to remember that the parietal and superior frontal cortex activation observed in this analysis are not a result of saccade-related activity in that we subtracted this out prior to comparing activation due to switching and compatibility. Rather, these areas may be involved with motor response inhibition and reponse selection (Rubia et al., 2000). The frontal area (BA 10) may be involved in the maintenance and monitoring of a subgoal (i.e. "respond opposite") before the correct response can be made (Braver & Bongiolatti, 2002). So, the activations that are uniquely emblematic of the compatibility task are those that may reflect motor-related processes, ones that would not be needed in the switching task.

What do these commonalities and differences between tasks tell us about executive processes? One suggestion is that there is, indeed, a common executive mechanism involved in the allocation of attention in both the counter-switching and response inhibition task. This common mechanism, which is parietal in location, controls the allocation of attention—whether to an internal representation or to a mapping-rule. However, attentional allocation alone cannot account for the execution of both task-switching and response-inhibition processes. There are also separable mechanisms that mediate the switching of attention and the inhibition of a pre-potent motor response. For the counters, this involves the actual switching of attention from one counter to another, and may be controlled by a region in superior parietal and dorsolateral prefrontal cortex. For the stimulus-response mapping, it involves the maintenance of a general task goal, controlled by frontopolar cortex, as well as motor programming operations regulated by supplementary motor and parietal areas that allow one to inhibit a prepotent motor response and select an alternative response.

Conclusion

When looked at in this way, the issue of whether executive mechanisms are unitary in nature or are composed of multiple types dissolves into the particulars of the mechanisms needed for any task. As models such as EPIC (Meyer & Kieras, 1997) suggest, what may prove to be the most productive exercise in understanding executive processes is a detailed modeling of what mechanisms are needed to yield behavioral performance. What our neuroimaging data suggest is that some of these mechanisms may be common to tasks that require executive control and others may be quite different. Further progress in understanding these mechanisms will come from mapping them in more and more tasks to understand when there are similarities among mechanisms and when there are differences.

We have come to understand a good deal about working memory by examining a combination of behavioral and neuroimaging data. What has emerged from this examination is a picture of a complex system with a modular organization. This organization appears, as originally proposed by Baddeley (1986, 1992), to be well-characterized by differentiating between processes responsible for maintenance and those responsible for information-manipulation. Maintenance appears to be mediated by sites in which information is stored and rehearsed. Storage and rehearsal processes, furthermore, are themselves not singular in form; they vary with the kind of code being maintained, and this variation is reflected in the brain mechanisms that are activated by different kinds of information as well as by the effects of brain lesions on particular deficits in working memory (see Jonides et al., 1996, for a discussion). Executive processes have multiple mechanisms underlying them as well. What appears to be a common thread among these mechanisms is the need to allocate or withdraw attention successively between alternative representations. How this is accomplished, though, depends on the particulars of the task in question. It may also depend on the type of information being processed (e.g., verbal versus spatial), although at this time, there is insufficient data to address whether this is so. With this sort of componential view of working memory developing, what is

now needed is more extensive research on the particulars of each component, working toward a comprehensive model of the multiple modules of working memory.

Acknowledgement

Section C

CONSOLIDATION OF MEMORIES

8

The Principle of Memory Consolidation and Its Pharmacological Modulation

Rainer K.W. Schwarting

Memory consolidation describes time-dependent processes that transfer physiological substrates of newly acquired information into rather permanently stable states. Specific neurobehavioral paradigms have been developed to study the substrates of such endogenous processes, and in psychopharmacological research, the `post-trial´ approach provides a powerful tool to manipulate memory processes during presumptive consolidation phases. This approach will be presented, emphasizing its behavioral details and major pharmacological findings. Finally, an example will be given which shows that cholinergic processes in the nucleus accumbens may play a role during memory consolidation.

The Consolidation Hypothesis and Its Origins

Learning can be defined as a change of behavior which is dependent on experience. Consolidation describes another theoretical construct, namely the transfer of experience into relatively lasting physiological substrates which allow later retrieval of the learned behavior. In other words, one assumes that memories are somehow produced physiologically after an initial experience. These memories are thought to exist initially in a rather fragile state from which they are strengthened over time, becoming less and less vulnerable to interference. Here, several consecutive or partly independent processes seem to take place. The processes critical for memory are thought to occur in the brain, and can include changes in activity, that is, electrical

and biochemical (see Paller this volume), and changes in anatomical connectivity (see Röder this volume). The emphasis of the present overview will be on chemical mechanisms and their modulation by pharmacological means, some of which will be outlined in more detail below.

In the early years of memory research, the idea of consolidation was grounded on clinical experience, that is on observations obtained from patients with memory disturbances. Later on, memory disturbances were also studied in experimental animals, for example, by using pharmacological manipulations. It was found that memory can not only be impaired, but also enhanced by specific pharmacological interventions. Another research phase has been characterized by the search for the presumptive physiological substrates of memory and their possible phases. Some of these critical historical aspects will be addressed below.

The history of the consolidation hypothesis dates back to the end of the 19th century to Ribot's work (1882) on retrograde amnesia after cerebral trauma. Ribot found that events which had been experienced immediately before a trauma were the most likely to be forgotten. Several years later, Ramon y Cajal (1893) formulated a theory of memory storage in which information is stored in the brain by anatomical changes of the connections between neurons. Müller & Pilzecker's work (Müller & Pilzecker, 1900) in humans showed that memory of newly learned information could be interfered with if a subject was required to learn other information shortly after the original learning. Based on these findings, they suggested that processes underlying new memories initially persist in a fragile state and consolidate over time. Hebb (1949) proposed a theoretical substrate for such consolidation, in his dual-trace theory of memory, assuming that the stabilization of reverberating neural activity underlying short-term memory produces long-term memory.

This hypothesis led to studies of retrograde amnesia in experimental animals. Rodents, especially rats and mice, were the main test subjects used for these studies and are still the preferred animal subjects in this area of research. Starting with the pioneering work on post-trial electroconvulsive shock (Duncan, 1949; Gerard, 1949), several treatments were found to be amnestic when administered after learning. These manipulations include hypoxia, hypothermia, inhibitors of protein synthesis, and various drugs. Furthermore, a common feature of these treatments was discovered, namely the temporal gradient of efficacy; shorter intervals between training and treatment were more efficient in terms of amnesia than longer intervals. The invulnerability of memory against these treatments after long intervals was taken as evidence that memory was now in a fixed, consolidated, and rather stable state (McGaugh, 1966).

Experimental Procedures for Post-Trial Designs

The research field dealing with the pharmacology of memory formation was pioneered by James McGaugh (McGaugh, 1966,1989, 2000). He propagated specific designs which still serve today as powerful tools for memory research, namely, the post-trial design and the use of simple learning tasks. Such studies were usually performed in the following way: Learning tasks were used which require only minimal experience (for example, one trial of learning) leading to relatively lasting behavioral changes (thus indicating memory). These tasks, which will be outlined in more detail below, were followed by post-trial treatments at various intervals after

the training trial. The rationale for post-training treatments was that they should be optimal with tasks that are learned quickly, so that drug effects could be timed and thus linked to the activity of specific underlying neuronal systems or molecular events during consolidation. Since the drugs are injected <u>after</u> the learning trial in such an experimental design, they are not present and effective when the critical behavior is being learned or when it is tested. Such an experimental procedure avoids or reduces several critical problems such as state-dependency, or drug effects other than on memory, and cognitive functions that are necessary during acquisition or retention.
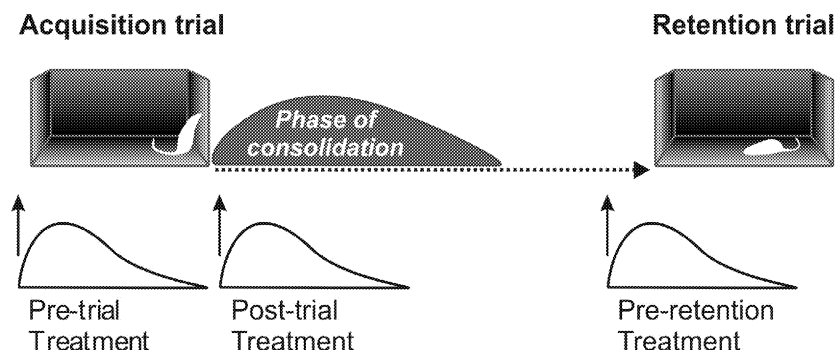
Figure 1: The rationale of post-trial drug studies exemplified by habituation of open-field exploration. The animal is exposed twice to an open-field. Exploration during the 2nd, that is, the retention trial (right) declines dependent on prior experience of the same environment during the 1st, that is, the acquisition trial (left). This experience is thought to be consolidated during a phase of several hours after the learning trial. Drugs injected during this phase (post-trial treatment, lower graph) can act on such processes. In contrast, pre-trial treatment also affects acquisition, whereas pre-retention treatment affects retrieval or expression of retrieved information.

Inhibitory Avoidance

In an inhibitory (or passive) avoidance paradigm, the subject (usually a rat or mouse) learns to avoid a noxious or aversive event by suppressing a particular behavior (Bures, Buresova, & Huston, 1983; Sahgal, 1993). This learning requires that the aversive stimulus be closely associated (temporally contiguous) with the behavior that is to be inhibited. The behavior, in turn, is usually simple, well-defined, reproducible and easily measured. The emotional and motivational impact of the stimulus and the simplicity of the behavior are probably the prerequisites which allow rapid (i.e. one-trial) acquisition of behavioral changes. Since the period of learning is short, the phase of presumptive memory consolidation can be defined, or at least the time of its initiation can be defined. Retention is usually tested within several hours to days after the learning trial; most often, an interval of 24 hours is used. The degree of retention is characterized by measuring latencies until the specific response is shown during the test trial. The increase in response latency is thought to reflect the strength of the memory trace of the previous aversive event. These response latencies are either compared to those during the

learning trial (within-group comparisons) or they are compared to test latencies of specific control subjects (between-group comparisons).

Step-in (step-through): Here, a testing box with two compartments which can be disconnected from each other by a door is used. One compartment is brightly illuminated, whereas the other is dark. Rodents typically avoid areas which are intensely lit. Thus, when placed into this compartment of the apparatus, they will soon enter the other, dark one. Immediately thereafter, the door is closed and mild electric footshock is applied (for example, 0.5mA for one sec). Thereafter, the animal is returned to its home cage. During the memory test, for example 24 hours after the learning trial, the animal is again placed into the well-lit compartment and the time until it enters the dark side is measured.

Step-down: The animal is placed on a small elevated platform which is situated in a specific testing compartment with an electrifyable floor. Typically, the animal rapidly descends from the platform - for which it is immediately punished by mild electric footshock. Retention is tested by placing the animal onto the platform again and by measuring the latency until it descends from it. No shock is given during the test trial. Both, during the learning and the test trial, the critical step-down behavior is defined by the latency until all four paws have been placed on the floor.

Up-hill-avoidance (step-up): This test employs the tendency of rats to undergo negative geotaxis: If the animal is placed on an inclined plane (for example 20^0) with the head facing the base, it will turn around and move up the incline (the `up-hill response´). Normal rats readily learn to suppress this response when punished immediately with an electric shock to the tail (Stäubli & Huston, 1979). Similar to the previous tests, retention is usually tested several hours after the learning trial.

Habituation of Exploration and Other Designs

In this paradigm, the decrease of exploratory activity as a function of repeated exposure to the same environment is taken as an index of memory (Cerbone & Sadile, 1994; Tomaz, Aguiar, & Nogueira, 1990). Typically, a simple but novel open-field is used to which the animal is exposed twice (for example, 10 min each time). For critical behavioral measures, locomotion, rearing (Gerhardt, Hasenöhrl, Hock, & Huston, 1993; Schildein, Huston, & Schwarting, 2000) and the latency to initiate exploration (Mello e Souza, Rohden, Meinhardt, Goncalves, & Quillfeldt, 2000) have been used. When comparing such measures, it has been found that rearing rather than locomotor behavior seems to be a superior index of habituation to the open-field, since rearing activity declines very reliably from the 1st to the 2nd experience (Gerhardt, Voits, Fink, & Huston, 1994; Schildein et al., 2000; Thiel, Huston, & Schwarting, 1998a, b). Such habituation of open-field behavior was found to be sensitive to post-trial pharmacological manipulations, for example systemic treatments with cholinergic agonists or antagonists (Platel & Porsolt, 1982). Furthermore, the paradigm can be used with direct intracerebral drug injections which will be addressed below (Gerhardt et al., 1993; Schildein et al., 2000; Schildein, Huston, & Schwarting, in press). Usually, only empty open-fields are used but in a modified procedure for mice, an open-field containing food has also been used (Ladner, Babbini, Davies, Parker, & Alkana,

2001). This has allowed researchers to use measures of approach and food consumption in addition to measures of open-field behavior.

In a simplified water maze procedure (Setlow & McGaugh, 1998), rats received one session of six training trials in which they had to find a hidden platform in a circular water tank. Learning and retention were determined using the time taken (latency) to reach the hidden platform. Similar to the habituation paradigm, the water maze procedure is strictly-speaking, not a one-trial, but a multi-trial test. Nevertheless, both paradigms also serve as useful tools for studying the pharmacology of memory formation since they can also be used effectively for post-trial manipulations (Cahill, Pham, & Setlow, 2000).

Specific Aspects of Post-Trial Designs

When designing post-trial experiments with the above-mentioned behavioral tests, several critical factors, which will be addressed below, have to be considered. If one uses aversive foot- or tail-shocks as the critical experience, these stimuli should be carefully pre-selected to eliminate ceiling effects. Thus, "intermediate" shock levels should be used for a basic design. Such shock levels should lead to increased, but not maximal step-in latencies in the retention test. Such procedures allow a given post-trial manipulation to impair or enhance consolidation. When using open-field exploration as the critical variable, the animals should not be habituated to the testing environment prior to the experiment, otherwise a floor-effect would be likely, that is, low levels of exploration during the acquisition trial which cannot be lowered further by the post-trial drug treatment.

Depending on the specific issue which is to be addressed in a given experiment, several of the following variations have to be used regarding the time-points of drug administration: 1) Post-trial: This is usually the major experimental approach, where a given drug is injected within a few seconds or minutes after the learning trial. Furthermore, the time of drug treatment can be delayed systematically, for example by one or several hours to compare the effectiveness of immediate vs. delayed injections. Such variations can be useful when trying to further determine possible consolidation periods, for example critical time windows. 2) Pre-retention: The drug is injected before the retention test (for example, 1 hour before). This approach is mainly used to test possible proactive effects of a given drug. 3) Pre-trial: The drug is injected already before the learning trial, so that it may not only affect consolidation but also acquisition.

Drug injections: Using such designs, drugs may be administered to experimental animals either systemically (intraperitoneal, subcutaneous, intravenous), or directly into the nervous system (into brain tissue, or intracerebroventricularly) using specific microinjection techniques. The important details of these pharmacological methods cannot be outlined here and the interested reader is referred to other sources (Bures et al., 1983). Nevertheless, at least two aspects should be addressed: 1) In a reasonable psychopharmacological experiment, a dose-response relationship should be addressed, typically by varying the dose of a drug in at least three steps. Furthermore, controls are necessary where the drug vehicle is administered instead of the drug solution. 2) In almost every study performed so far, the animals had to be handled in order to be injected. Although the animals are usually well habituated to being handled by the

experimenter, one still has to keep in mind that such handling can have substantial physiological effects (Thiel et al., 1998a,1998b), which should be considered in a given experiment, for example, by including control groups that are handled but not injected or sham-injected. 3) A further possible control is to inject animals that have not received a learning trial before. Using this approach one can test for possible unspecific lasting drug effects which may affect behavior in a certain paradigm.

What are the specific advantages of such psychopharmacological methods? First, one can use and compare systemic versus central injections, and here, one can even target specific brain nuclei. Besides varying sites of action, one can also vary the drug dose, and the time point of drug application, for example, in relation to the learning trial or the retention test. Furthermore, a wide range of drugs can be used, including specific agonists or antagonists of a given neurotransmitter under investigation. Even more, combinations of drugs may be used, for example, to test whether an agonist for transmitter X is effective when transmitter Y is blocked.

What are the possible drawbacks? It is generally assumed that a critical measure during a retention test, for example, the latency to step-in or the habituation of open-field rearing, reflects the strength of memory and that a change in this measure reflects the drug´s effects on consolidation processes. However, the possibility cannot always be excluded that a post-trial drug administration was effective due to cognitive and non-cognitive factors (motor, sensory, emotional, motivational; for detailed discussion see Carey, 1987). Such factors will also be addressed below. Finally, one should keep in mind that most post-trial experiments done so far have used inhibitory avoidance, since such behavior can be acquired with minimal learning experience allowing post-trial treatments to differentiate between acquisition and the onset of consolidation. Therefore, the available pharmacological evidence is largely based on aversively motivated behavior, and it remains to be determined whether similar patterns of results can be obtained with appetitively motivated behaviors, for which comparably useful tasks are still lacking today.

Pharmacological Manipulations of Consolidation

Using the methods mentioned above, it was found that memory formation can not only be prevented or impaired (amnesia), but that memory can also be enhanced when using specific pharmacological treatments. Thus, it is nowadays well established that several types of drugs acting on transmitter (or modulatory) systems can enhance memory consolidation when administered within minutes or hours after training (McGaugh, 1989; McGaugh & Izquierdo, 2000; McGaugh, 2000; Izquierdo, Medina, Vianna, Izquierdo, & Barros, 1999; Sara, 2000).

A number of transmitters, modulators, and brain sites have been found to play a role in the phenomenon of memory consolidation. Regarding the "anatomy of memory", sensitive sites that enhance or impair memory formation have been found, especially in the hippocampus, amygdala, septum, neocortex, entorhinal cortex, and striatum. The anatomical details of memory will not be addressed in great detail here (see Brand & Markowitsch this volume). It should be pointed out, however, that researchers nowadays do not assume that a certain "memory" can be

attributed solely to one specific brain area. Rather, it is currently thought that memory is the function of a network of brain sites and connections, and that -depending on the kind of memory- some or more of the abovementioned structures are critically involved within the brain´s circuitry.

With respect to role of specific transmitters, modulators and hormones, most evidence has been gathered for GABA, glutamate, acetylcholine, noradrenaline, histamine, dopamine, glucocorticoids, and several neuropeptides, especially opioids and substance P (McGaugh, 1989; McGaugh & Izquierdo, 2000; Hasenöhrl et al., 2000). Although it is difficult to briefly summarize the effects of these substances and to attribute `memory functions´ to them, one can cautiously state that increased opiate and GABA impact (especially via $GABA_A$ receptors) typically impairs memory, whereas glutamate, acetylcholine, dopamine, noradrenaline, substance P, and glucocorticoids seem to be beneficial for memory formation. Besides neurotransmitters, modulators and hormones, a number of other mechanisms have been studied pharmacologically, including second messengers (calcium functions, protein processing etc.), regulators of membrane function, or various intercellular interactions. Summarizing these fields of research would go far beyond the scope of this chapter; therefore, the reader is referred to other relevant work (Agranoff, Burrell, Dokas, & Springer, 1978; Abel & Lattal, 2001; Bourtchouladze et al., 1998; Nadel & Bohbot, 2001; Walz et al., 2000).

Furthermore, psychopharmacological and neurochemical studies of memory have provided evidence for different memory phases and for different temporal types of memory (Izquierdo et al., 1999). Thus, short- (STM) and long-term (LTM) forms have been suggested, where short-term memory usually refers to memories lasting seconds to hours, whereas long-term memory means memories that are thought to last hours to months, or longer. Intra- and extraneuronal molecules and biochemical processes seem to contribute differently to short-term and long-term memory. For example, protein synthesis is typically required only for consolidation of LTM. Further evidence for a temporal dissociation between different forms of memory is that some drugs can selectively block STM but not LTM (and vice versa). For example, it has been shown using post-trial designs that blocking NMDA-type glutamate receptors is effective immediately after training, but not after 2 hours, or that ß-receptor blockers are more effective in impairing memory when administered 1-2 hours after a learning trial, but not when administered either immediately or 5 hours or later after learning (Sara, 2000). Such findings support the hypothesis that NMDA receptors seem to be important during an early phase of memory consolidation, whereas second messengers (like those activated by ß-adrenergic receptors) are more critical during later phases. The issue of short- and long-term memory is not unequivocal, however, since there is a controversy of whether STM and LTM reflect independent and possibly parallel processes (McGaugh, 1966), or whether they are sequentially linked (Hebb, 1949; Gerard, 1949).

Besides the fact that some kinds of memory may be temporary and some lasting, both biochemical and neurobehavioral studies have repeatedly shown that many types of lasting memory require time to consolidate. This means that the persisting changes leading to substrates which are necessary for memory are not acquired immediately after a learning experience, but may take hours or even days to consolidate, and that activating or inhibiting neurotransmission and modulation during this period can impair or enhance the processes of consolidation. James

McGaugh (McGaugh, 2000) recently discussed this phenomenon that many forms of memory obviously require time to consolidate, that is, that (some) memories apparently consolidate rather slowly. The question arises, why this is the case? Why do many memories consolidate slowly? One obvious answer would be that the physiological processes of memory consolidation work slowly by nature. However, some forms of temporary memory are acquired almost immediately (short-term memory; working memory); therefore, it is at least thinkable that lasting memories could also be acquired rapidly. Alternatively, one could argue that a slow time course of memory consolidation serves an adaptive function, since it may enable other endogenous processes activated by an experience to modulate memory strength - for example, emotionally arousing experiences. Many of the known memory modulators may serve such a function, like epinephrine, histamine, corticosterone, substance P, and possibly others as well.

In the following, one specific psychopharmacological example will be presented in more detail. Experimental results will be presented which provide evidence that cholinergic, and especially nicotinic mechanisms of the nucleus accumbens seem to play a modulatory role in the consolidation of open-field memory.

An Example for a Pharmacological Post-Trial Approach: Cholinergic Manipulations in the Nucleus Accumbens of the Laboratory Rat

Brief Anatomy of the Nucleus Accumbens

The nucleus accumbens (NAcc) is a forebrain structure, located ventrally to the neostriatum (or caudate-putamen), that comprises the major portion of the ventral striatum. In the NAcc, afferent information converges from various sites, especially the prefrontal cortex, amygdala, hippocampus, thalamus, mesencephalon, and brain stem autonomic centers. Its efferents, in turn, reach the ventral pallidum, subthalamic nucleus, substantia nigra, ventral tegmental area, lateral hypothalamus, and brain stem autonomic centers (Fig. 2; for further details see Pennartz, Groenewegen, & Lopes Da Silva, 1994; Zahm, 2000).

The histochemical architecture and the profile of inputs and outputs suggest that this brain area (or parts of it) can be considered both as a part of the basal ganglia on the one hand, and of the extended amygdala on the other. Therefore, the NAcc is thought to be involved in motivational or limbic, as well as motor or basal ganglia functions, and may serve as an integrator of the two (the so-called `limbic-motor interface´; (Mogenson, Jones, & Yim, 1980; Willner & Scheel-Krüger, 1991). Furthermore, the NAcc can be divided into several sub-sites, called "shell" and "core"; however, these specific aspects will not be addressed here specifically (for further details see 3).

Transmitters in the Nucleus Accumbens

About 90% of neuronal cell bodies within the NAcc belong to projection neurons. These efferents use GABA as their primary transmitter, which is often co-localized with neuropeptides

like substance P, neurotensin, enkephalin or dynorphin. The remaining neurons within the NAcc are local circuit neurons which transmit with either GABA, acetylcholine, somatostatin, neuropeptide Y, or cholecystokinin. The majority of inputs to the NAcc is glutamanergic and originate from sites such as the prefrontal cortex, hippocampus, or amygdala. Furthermore, there is a dense dopaminergic innervation which stems mainly from the ventral tegmental area in the mesencephalon. In addition, the NAcc receives comparably smaller noradrenergic and serotonergic input from the brainstem.
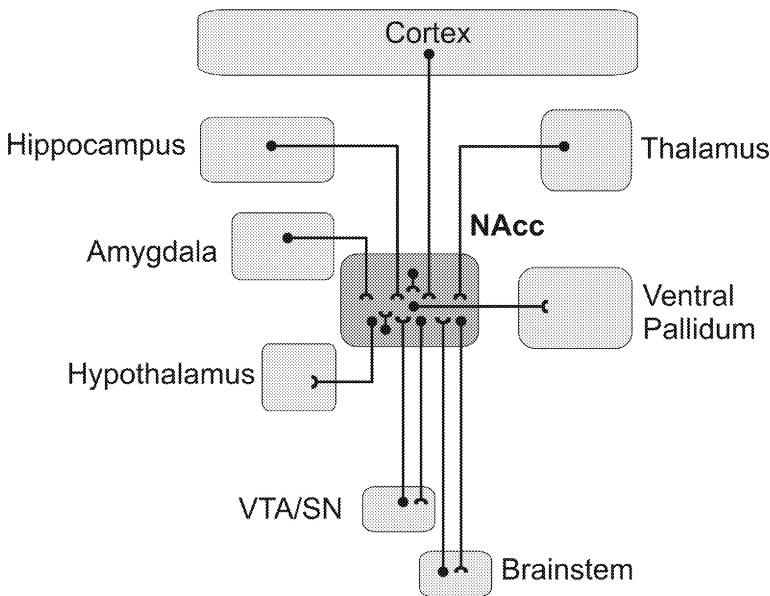
Figure 2: Simplified graph depicting the nucleus accumbens (Nacc, dark grey) and most of its major afferents and efferents. SN: substantia nigra, VTA: ventral tegmental area.

Given these typical inputs, interneurons, and outputs, an internal neuronal circuitry can be formulated within the NAcc: The glutamate input, for example that from the prefrontal cortex, directly innervates the GABAergic outputs in an excitatory way. These two neuronal elements can be considered as the main route of information transfer passing through the NAcc. This information transfer, however, can be critically and directly modulated by the mesencephalic dopamine input. Finally, the cholinergic interneuron is innervated by either input, and is able to regulate both, inputs and outputs. It is currently thought that its main function is to mediate the processing of input forward from the cortex to the GABAergic projection cells (Calabresi, Centonze, Gubellini, Pisani, & Bernardi, 2000). This important cholinergic regulation is mediated by nicotinic and muscarinic receptors, which are located on many pre- and postsynaptic sites within the Nacc.
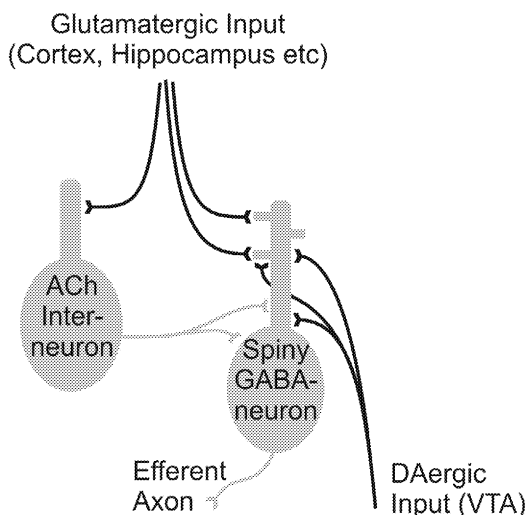
Figure 3: Simplified graph depicting critical circuitry elements within the NAcc. The two major neuron types of the NAcc, namely the spiny GABAergic projection neuron and a cholinergic interneuron (ACh), are shown in gray. Major afferents to the NAcc are shown in black, most of which are either glutamatergic or dopaminergic (DA). Nicotinic cholinergic receptors in the Nacc are typically situated at presynaptic sites, for example those of the DAergic and glutamatergic inputs.

Cholinergic Activity in the Nucleus Accumbens

To study ACh in the NAcc functionally, its extracellular activity has been studied by means of in-vivo microdialysis in awake, freely-moving rats. Such experiments have shown that extracellular ACh levels in the NAcc can increase in response to various stimuli and/or depend on factors such as food and water intake (Mark, Rada, Pothos, & Hoebel, 1992), presentation of an aversively conditioned taste (Mark, Weinberg, Rada, & Hoebel, 1995), intraperitoneal injections (Boix, Pfister, Huston, & Schwarting, 1994), electric footshock (Müller et al. unpublished data), handling, or exposure to an open-field (Thiel et al., 1998a). Thus, one can summarize that cholinergic activity, which is situated in a rather central position within the NAcc, is enhanced during many behaviorally significant situations. Given the physiological impact that such cholinergic activity can have on most others neuronal elements within this striatal brain structure (Calabresi, Centonze, Gubellini, Pisani, & Bernardi, 2000), one can assume that such cholinergic activations can critically affect the function of the Nacc.

Evidence for a Role of the Nucleus Accumbens in Mnestic Processes

In general, neurobehavioral research on the NAcc has focused on its role in psychomotor functions, motivation, and addiction (Willner & Scheel-Krüger, 1991). Meanwhile, considerable evidence is accumulating which indicates that the NAcc seems to play a role in learning and memory as well. Here, relevant data have been provided by means of behavioral, lesion and pharmacological techniques (Kelley, 1999; Setlow, 1997). For example, it has been found that lesions of the NAcc can impair passive avoidance behavior (Thompson, 1978; Taghzouti, Simon,

Louilot, Herman, & Le Moal, 1985; Schwarting & Carey, 1985). Such lesions can be selective for memory or the expression of learned behavior rather than its acquisition, since latencies to step-in were impaired during test, but not during the acquisition trial of a one-trial inhibitory avoidance task (Schwarting & Carey, 1985). In addition, pharmacological studies using a post-trial drug application design yielded impairments of inhibitory avoidance with post-trial injections of tetrodotoxin (Lorenzini, Baldi, Bucherelli, & Tassoni, 1995), or impaired memory of spatial water maze training with post-trial sulpiride (Setlow & McGaugh, 1998).

Furthermore, it has been shown that the striatal complex, including the NAcc, fulfills the electrophysiological criteria of cellular plasticity which are currently considered to be most relevant for learning and memory, namely long-term potentiation and long-term depression (Calabresi, Centonze, Gubellini, Pisani, & Bernardi, 2000; Boeijinga, Mulder, Pennartz, Manshanden, & Lopes da Silva, 1993; Kombian & Malenka, 1994). Further work suggested that the NAcc may be member of a distributed neural network participating in memory formation (Mulder, Arts, & Lopes da Silva, 1997). In addition, the known psychomotor functions of the NAcc have been incorporated into this framework. Thus, it has been suggested, for example, that the pathway from the hippocampus to the NAcc may serve not only to select, but also to "stamp in", that is, to consolidate, adaptive locomotor actions (Brown & Sharp, 1995).

Finally, cholinergic interneurons deserve specific attention here: Work in the monkey striatum has shown that electrophysiological activity in these interneurons increases in response to a learned cue that predicts a reward (Aosaki et al., 1994). Finally, there is interesting indirect evidence from human pathology: In Alzheimer´s disease (AD), there is not only the well-known loss of cholinergic projection systems inervating neocortex and hippocampus (Blokland, 1996; Fibiger, 1991), but there may also be a loss of cholinergic interneurons in the NAcc (Lehericy et al., 1989), indicating that a cholinergic deficit in the NAcc may also contribute to the cognitive deficits observed in this neurodegenerative disease.

Together, current evidence clearly shows that the NAcc not only serves as an "interface between motivation and action", but that it also plays a role in changes of action dependent on experience. Furthermore, cholinergic activity within the NAcc seems to be involved in such mnestic functions. In the following final section, some of our recent psychopharmacological evidence in favor of this relationship will be presented.

Post-Trial Manipulations of Cholinergic Function in the NAcc:

Given the evidence briefly summarized above, we recently asked whether pharmacological manipulations of cholinergic function during the presumptive period of consolidation following a learning phase might affect later retention of the previous experience (Schildein, Huston, & Schwarting, 2000, 2002). To test this hypothesis, we used the following post-trial drug treatments: tacrine, the muscarinic antagonist scopolamine (Schildein et al., 2000), nicotine, and the nicotinic antagonist mecamylamine (Hygge & Hugdahl, 1985). Tacrine is an unspecific acetylcholinesterase inhibitor, which can enhance cholinergic function in the brain. In animal models, including post-trial designs, tacrine has been found to be memory-enhancing (Flood & Cherkin, 1998). In Alzheimer´s disease, this drug has been used therapeutically to enhance

cognitive functions, however, with rather limited success (Flood & Cherkin, 1998). The muscarinic antagonist scopolamine, on the other hand, serves as a routine tool in psychopharmacological memory research, since it leads to profound amnesia when given systemically both, pre- and post-trial (Doyle & Regan, 1993; Toumane & Durkin, 1993). Finally, nicotine has been shown to enhance cognitive functions in animal models and in humans (Platel & Porsolt, 1982; Elrod, Buccafusco, & Jackson, 1988; Jones, G. M., Sahakian, Levy, Warburton, & Gray, 1992; Levin, 1992; Levin & Simon, 1998; Whitehouse & Kalaria, 1995). Promoting nicotinic mechanisms has also been suggested to be of therapeutic value in Alzheimer´s disease (Weinstock, 1995). Given such evidence, we expected that enhancement of cholinergic activity by means of tacrine or nicotine should be memory-promoting in the open-field habituation paradigm when given post-trial into the NAcc, whereas inhibition of cholineric impact by means of scolopamine or mecamylamine should be amnesic.

Methods: To test this hypothesis, we implanted male Wistar rats with guide cannula aimed unilaterally at the NAcc. After sufficient recovery from surgery and careful adaptation to the experimenter (termed `handling´), the animals were exposed singly to an open-field to which they had not been exposed before (1st exposure). After a 10min period of exploration, the animals were removed from this environment and received drug or vehicle injections into the NAcc. The interval between open-field exposure and drug injection were varied in several groups: We used either `acute´ injections, which were given immediately after open-field exposure, or `delayed´ injections, which were administered five hours later. The intracranial injections (0.5µl) were performed in the awake state using specific injection devices. On the following day (the test day), the animals were again exposed to the open-field for 10 min. Rearing behavior served as the index of open-field exploration, and a decrease of rearing during the test as compared to the 1st exposure served as memory index of this open-field.

Results: These experiments yielded the following main results (Fig. 4; for details see Schildein et al., 2000, 2002): During the critical test, that is the 2nd exposure to the open-field, control animals which had received post-trial injections of the drug vehicle saline, showed the expected pattern of habituation, that is, a decrease in the number of rearings as compared to the 1st exposure. This negatively expressed retention score was of higher magnitude, indicating enhanced memory, in animals which had received post-trial injection of the highest dose of tacrine (10.0 µg), but not with the two lower doses. Post-trial administration of scopolamine impaired retention with lower doses (0.1, 1.0 µg), but did not affect retention with the highest dose of tacrine (10.0 µg). The effects of the 10 µg-doses of tacrine and scopolamine were specific to immediate post-trial treatment, because they were not observed when these doses were injected after a delay of 5 hours. These delayed treatments even impaired retention, since unlike vehicle controls, there was no evidence for habituation in drug-treated animals.

Post-trial administration of nicotine (Fig. 5) also affected retention in a dose-dependent way. Here, a low dose was ineffective (8 µg), whereas habituation was enhanced in animals with post-trial injections of 40 or 80 µg of nicotine. In contrast, the nicotinic antagonist mecamylamine proved to be amnesic in a dose of 1.0 µg (Fig. 5). A lower dose (0.1 µg) showed no effect, whereas in animals with post-trial injections of 10.0 µg, rearing activity was even enhanced on the subsequent day. To test whether the effects of nicotine and mecamylamine were specific to the immediate post-trial phase, one effective dose of each drug was also tested when

given 5 hours after 1st exposure to the open-field. When given after this delay, nicotine (40 µg) was no longer memory-promoting as compared to vehicle controls, and the amnesic effect of mecamylamine (10 µg) was clearly reduced as compared to immediate post-trial injections.
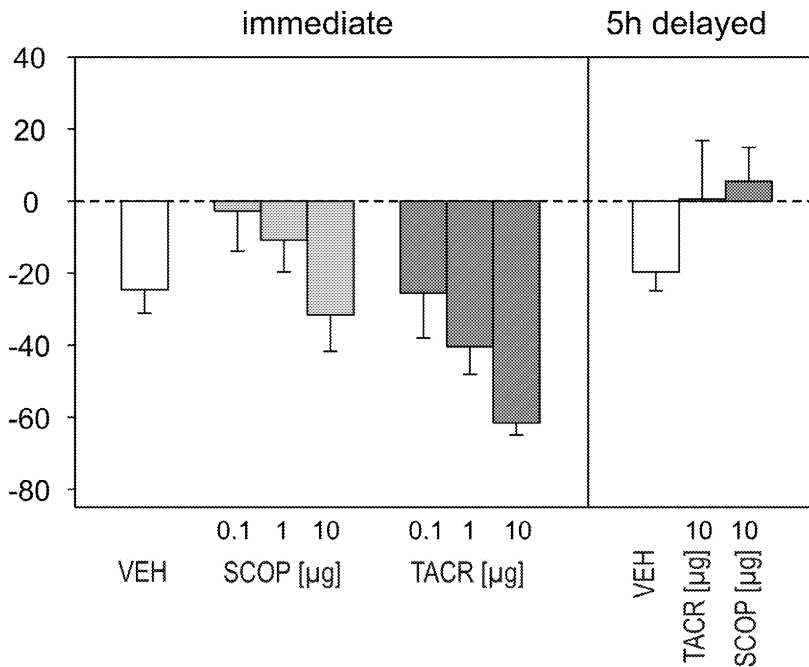
Figure 4: Effects of intraaccumbens injections of different doses of vehicle (VEH), scopolamine (SCOP), or tacrine (TACR) on habituation of rearing behavior during a retention test. Rearing during this test is expressed as mean (±SEM) percent of baseline during an acquisition test on the preceding day 1. Memory, i.e. decreased exploration during the retention test, is indicated by negative scores. Injections had been performed after the acquisition trial, either immediately post-trial (left) or with a delay of 5 hours (right).

Discussion

These experiments show that post-trial injections of pro-cholinergic and anti-cholinergic drugs into the NAcc can have pronounced effects in the habituation paradigm. These effects were dependent on the kind of drug, its dose, and the time of injection. Furthermore, other behavioral analyses provided further details which cannot be outlined here (see Schildein et al., 2000, 2002). In general, the data support the cholinergic hypothesis since the pro-cholinergic drugs tacrine and nicotine were dose-dependently effective in promoting memory, whereas the

antagonists scopolamine and mecamylamine were dose-dependently amnesic. The data obtained with scopolamine might appear puzzling at first sight, since only lower doses were amnesic, whereas memory was left unaffected with the highest dose. These latter effects might be due to
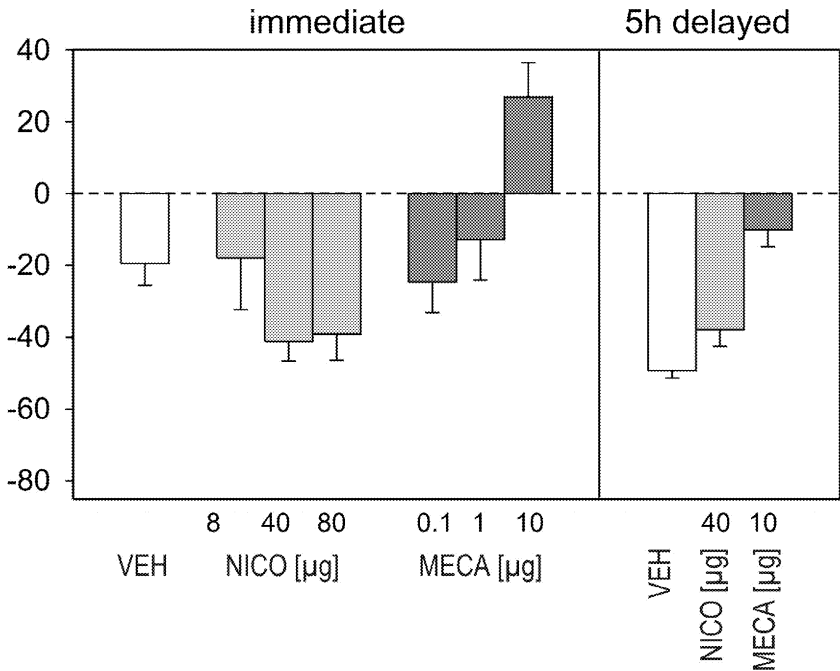
Figure 5: Effects of intraaccumbens injections of different doses of vehicle (VEH), nicotine (NICO), or mecamylamine (MECA) on habituation of rearing behavior during a retention test. Rearing during this test is expressed as mean (±SEM) percent of baseline during an acquisition test on the preceding day 1. Memory, i.e. decreased exploration during the retention test, is indicated by negative scores. Injections had been performed after the acquisition trial, either immediately post-trial (left) or with a delay of 5 hours (right).

a differential and dose-dependent action of scopolamine on pre- versus postsynaptic ACh receptors: Possibly, the lower doses acted mainly anti-cholinergic, and were thus amnesic, via a blockade of postsynaptic muscarinic receptors. The higher dose, on the other hand, might also have blocked presynaptic autoreceptors, which seem to have a lower sensitivity than the postsynaptic receptors (Szerb, Hadházy, & Dudar, 1977). Scopolamine-induced blockade of cholinergic autoreceptors can lead to enhanced ACh release which, in turn, can stimulate nicotinic ACh receptors, since these are not occupied by scopolamine. Therefore, the higher dose of scopolamine might have acted in a similar way like nicotine.

It should be pointed out, however, that the present data pattern cannot solely be interpreted in terms of memory modulation, that is, one has to consider whether some drugs affected more than just memory processes. In particular, the effects found with the highest immediate post-trial dose of mecamylamine cannot solely be explained in terms of amnesia, since amnesia should have led to a lack of habituation, but not to enhanced activity during testing on the 2nd day. Such data indicate that non-mnestic mechanisms also have played a role. Thus, one could argue that the present drug effects were due to post-trial motivational or emotional changes (Carey, 1987), which might be especially likely with treatments aimed at the NAcc. For example, manipulation of cholinergic systems in the NAcc might have affected the motivation to remember the open-field rather than directly modulating consolidation itself. Alternatively, the drug may have led to interference processes which unspecifically impaired consolidation processes. However, even such motivational, emotional or interference effects cannot explain why behavioral activity was actually increased on the subsequent day in animals which had received post-trial injections of mecamylamine.

Possibly, mecamylamine acted in a proactive way, and might have thereby affected behavioral activity on the next day (McGaugh, 1989; Mondadori, Ducret, & Borkowski, 1991). This could partly explain why the same dose of mecamylamine also reduced habituation when injected 5 hours after first exposure to the open-field. Thus, mecamylamine could have led to a proactive increase in rearing, which masked habituation or even increased activity on the subsequent day. We tested this assumption in another experiment (data not shown) where we injected mecamylamine in animals which had not been exposed to the open-field before. When exposing these animals to the open-field on the subsequent day, we did not find behavioral differences between animals with mecamylamine- versus vehicle pretreatments, which argues against such proactive effects. It should be noted, however, that the open-field environment was new in this test. Therefore, it is possible that behavioral activation, which is typically elicited by such a new testing environment (Thiel et al., 1998a, b), led to a ceiling effect which might have masked the potential proactive actions of mecamylamine.

Clearly, further psychopharmacological studies will be needed to demonstrate the specific role of cholinergic mechanisms in the NAcc for memory consolidation. Here, one should use different learning tasks, for example those for inhibitory avoidance, in order to test whether similar memory effects as seen here can also be observed with other behavioral domains for which the NAcc seem to be critical. In addition, one should test other and more specific agonists of nicotinic receptors, especially those of sub-classes which predominate within the NAcc. Furthermore, the role of muscarinic ACh receptor sub-types should be addressed, since based on electrophysiological and biochemical evidence one could suggest an amnestic action mediated via M2-receptors, but a pro-mnestic action mediated via M1-receptors (Calabresi, Centonze, Gubellini, Pisani, & Bernardi, 2000).

Despite the theoretical and methodological limitations of the current evidence, the available post-trial data may have relevance for mechanisms of consolidation. Thus, previous pharmacological studies have shown that memory consolidation can be affected optimally within about six hours after acquisition. During this period, memory consolidation can be enhanced or impaired in a drug-, dose-, and time-dependent way (McGaugh & Izquierdo, 2000). The present results are in line with this general pattern, since the memory-promoting effects of nicotine or

tacrine, and the amnestic effects of mecamylamine or scopolamine were observed only with specific doses. Furthermore, immediate and delayed injections were differentially effective, since, for example, nicotine improved memory only with immediate injections, whereas partly amnestic effects of mecamylamine were observed also with delayed injections.

Differential effectiveness of immediate vs. delayed drug treatments may reflect actions on different mechanisms which are necessary for memory formation. Neurochemical studies of the hippocampus, cortex, and amygdala have shown that the immediate post-trial phase seems to be characterized by a number of physiological changes, including transmitter release, stimulation of receptors, ion fluxes, and activation of protein kinases. Hours later, however, the activity of protein kinases seems to predominate (Bourtchouladze et al., 1998; Izquierdo et al., 1999; McGaugh & Izquierdo, 2000; Nadel & Bohbot, 2001; Walz et al., 2000). Given that such biochemical processes also occur in the NAcc, one can postulate that the delayed injections, given five hours after open-field exposure, were effective on the later stages of memory formation. Thus, one could argue that a certain degree of cholinergic impact is also necessary for these later stages; however, further enhancement of this impact does not then improve the efficacy of the relevant biochemical mechanisms of consolidation.

Nicotinic receptors, especially, may play an important role in modulating such memory mechanisms. Pro-mnestic effects have repeatedly been demonstrated with nicotinic agonism (Elrod, Buccafusco, & Jackson, 1988; Grigoryan, Hodges, Mitchell, Sinden, & Gray, 1996; Levin & Simon, 1998), for example with injections into the hippocampus or ventral tegmental area (Bancroft & Levin, 2000; Kim & Levin, 1996; Levin, Briggs, Christopher, & Auman, 1994). Our work adds the NAcc to this scenario. Interestingly, the hippocampus and VTA provide major inputs to this brain area. Regarding the potential mechanisms by which nicotine might have been effective, several factors may have played a role: nicotine has been termed a "secretagoge", since it stimulates the release of various neurotransmitters including acetylcholine itself (Toth, Sershen, Hashim, Vizi, & Lajtha, 1992). Electrophysiologically, nicotinic receptors are known to enhance excitatory synaptic transmission in the brain via pre- and postsynaptic sites of action. Furthermore, nicotine can facilitate the induction of long-term potentiation, at least in the hippocampus (Fujii, Ji, Morita, & Sumikawa, 1999). These effects can lead to lasting changes, which are required for learning and memory (Jones, S., Sudweeks, & Yakel, 1999). The present results provide evidence that nicotinic actions on mnestic processes can also be observed within the NAcc. These findings might possibly bear clinical relevance, since cholinergic drugs are considered as treatments in Alzheimer´s disease (Weinstock, 1995). In this neurodegenerative disorder, cholinergic neurons are severely affected in the brain. This cell loss does not only occur in cholinergic projections to the neocortex and hippocampus, but also in the NAcc, where cholinergic interneurons seem to be lost rather specifically (Lehericy et al., 1989). Furthermore, losses of nicotinic receptors in the striatal complex have been observed in several human neurodegenerative diseases which are associated with dementia, namely Alzheimer´s disease, dementia with Lewy bodies, and Parkinson´s disease with cognitive deficits (Court et al., 2000). From our data, one could hypothesize that striatal cholinergic deficits might critically contribute to the mnestic pathology of such diseases.

Conclusion

By combining specific psychopharmacological and behavioral techniques, experimental work in laboratory animals has provided evidence about the details of consolidation processes of memory. This neurobehavioral work supports and complements biochemical, electrophysiological and anatomical approaches which show that a number of extra- and intracellular processes and changes in the brain are required for lasting memories. Several neurotransmitters or modulators can affect such processes, that is, they may promote or impair memory when given during presumptive consolidation phases. Such actions can be achieved by systemical and by direct intracranial drug applications. The latter approach, in particular, helps to identify the possible anatomical substrates of suspected memory networks. One of the brain sites which more recently has come into the viewpoint of neurobehavioral memory research is the NAcc. Our work and the work of others indicates that cholinergic activity within this brain site seems not only to be critical during ongoing action and the acquisition experience, but also during the consolidation of experience. The data presented here illustrate part of the currently available evidence, and portray some of the advantages, but also the drawbacks of the methods used. In the future, such paradigms and other, even more refined psychopharmacological methods and designs will continue to serve as powerful tools in neuroscientific memory research.

Acknowledgments

9

The Principle of Cross-Cortical Consolidation of Declarative Memories

Ken A. Paller

Memory disorders due to neurological insult or injury can be highly selective. Impairments in remembering facts and events can arise while other memory functions remain intact. An explanation for anterograde and retrograde deficits in declarative memory is advanced that ascribes these deficits to a core defect in cross-cortical consolidation, a process whereby the components of a declarative memory are linked in an enduring manner. Through interactions between medial temporal and multiple cortical regions, a memory can repeatedly be accessed and associated with other information, during waking and during sleep. Connections among discrete cortical representations are thus strengthened, while a new representation of the essence of the declarative memory, gradually formed in the temporal lobe, provides enduring coherence to the dispersed neocortical representation of the memory.

A central challenge in memory research is to integrate conceptions of the cognitive structure of memory with our understanding of the neurophysiological events that support memory. Neural plasticity includes a wealth of phenomena whereby the functioning of networks of neurons can be put into place and altered with experience. Memory functions also comprise a huge category of phenomena whereby behavioral observations can be ascribed to influences of prior experience on the nervous system. Memory subcategories are subject to modification and expansion as new memory phenomena are described and categorized. Advances in understanding these subtypes of human memory, and their relationships to each other, arise from improved understanding of both the cognitive and neural substrates of memory.

Declarative Memory and Amnesia

The subtype of memory emphasized here is known as *declarative memory* and pertains to the recall and recognition of facts and events. The status of declarative memory as a distinct memory subtype is supported by strong evidence from cognitive and neural sources. Evidence from memory disorders, in particular, has provided many clues about the detailed organization of declarative memory in the brain.

Defining Declarative Memory

Observations of preserved and impaired memory in patients with amnesia indicate that the recall and recognition of facts and episodes is dependent on a particular subset of brain regions and can be disrupted selectively (Gabrieli, 1998; Squire, 1992; Squire & Knowlton, 2000; Squire & Paller, 2000). This selectivity implies both that these brain regions play a critical role in declarative memory and that they do not make a necessary contribution to other types of memory.

One preserved type of memory is *immediate memory*, which pertains to information that is maintained at the focus of attention and thus kept available in the immediate present. The concept of *working memory* is similar, although it is often specified in terms of specific rehearsal and control systems, and encompasses both maintenance and manipulation (Baddeley, 1998). Declarative memory entails immediate memory both when factual and episodic information is first encoded and when it is retrieved, so they are intimately related. The fact that amnesia can occur along with normal immediate memory abilities (Cave & Squire, 1992), nonetheless underscores the distinction between these two memory categories.

Declarative memory and several other memory subtypes can involve memory phenomena demonstrated after an extended delay from initial learning, beyond the span of immediate memory. In *The Principles of Psychology,* James (1890) referred to this as *secondary memory*, in contradistinction to *primary memory*. But declarative memory stands out from the others primarily in the type of information that can be stored — complex facts and personally experienced events — and also in the connection with *recollection*, the subjective experience of remembering. When people demonstrate other sorts of memory — such as conditioning, motor skills, cognitive skills, category learning, and priming — they need not be aware of remembering, but rather must merely perform a behavior and show altered performance as a result of acquiring a nondeclarative memory. Contrasts between declarative memory and *priming*, the item-specific facilitation or biasing of stimulus processing due to recent experience (Moscovitch, Vriezen, & Gottstein, 1993; Roediger & McDermott, 1993; Schacter, Chiu, & Ochsner, 1993; Shimamura, 1986; Verfaellie & Keane, 2002), may be particularly informative because information storage may rely on cortical networks in both cases. The category of *nondeclarative memory* includes a diverse set of memory phenomena that need not share similar neural mechanisms, but rather are grouped together because they are distinct from declarative memory.

In defining declarative memory, memory theorists can choose to consider several factors, including the behavioral characteristics of memory performance, the subjective characteristics, the cognitive structure, and the neural substrates. Determining precisely how each of these

criteria map onto the others is an important research goal for the future. Here is one example of how separate descriptions might correspond to the same phenomenon:

- memory supporting performance on recall and recognition tests for facts and episodes;
- memory that tends to be accompanied by the experience of conscious recollection;
- memory that depends on retrieving a conjunction of distinct informational fragments;
- memory that ultimately requires cross-cortical consolidation.

Despite widespread agreement about the selectivity of memory deficits in amnesia, a pervasive problem for research in this area is how to arrive at a generally agreed upon definition for the type of memory that is impaired in amnesia. Although terms such as *explicit memory*, *conscious memory*, and *aware memory* have been used in this context, sometimes synonymously, here I will rely on the term *declarative memory*. It should be acknowledged that definitions of declarative memory can be allowed to gradually evolve, such that as its unique characteristics become substantiated, they are folded into the definition. The definition would then freely include behavioral, subjective, cognitive, and neural characteristics. Whereas this scenario is reasonable, at present it seems advantageous to separate two steps of theory-building. The first step is to settle on a behavioral definition of declarative memory. The second step and primary research agenda is then to map neural, cognitive, and subjective facets of declarative memory onto each other and onto the behavioral definition, with the proviso that the definition may eventually need to be changed.

Behavioral Definition of Declarative Memory

Recall and recognition of facts and episodes

Isolated cortical networks linked with coherence ensembles formed via cross-cortical consolidation

Perceptual and conceptual information fragments combined by virtue of a superordinate representation

Biological Structure   Cognitive Structure
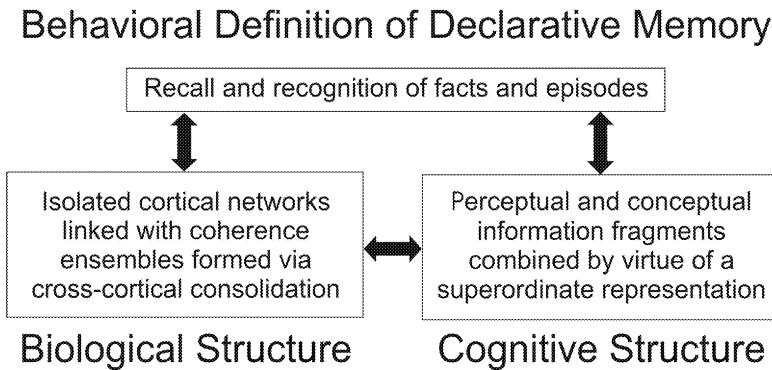
Figure 1. The three-way theoretical connections between behavior, biology, and cognition that are necessary for a comprehensive understanding of declarative memory. Declarative memory is defined behaviorally, and some aspects of a neurocognitive theory of declarative memory are depicted in terms of both biological and cognitive structure. (Reprinted with permission from Paller, 2002).

Figure 1 shows a scheme for relating descriptions of declarative memory at different levels. A complete understanding of disorders of declarative memory should describe the three-

way connections between the neural dysfunction, the cognitive dysfunction, and the resultant behavioral shortcomings. Likewise, the neural, cognitive, and behavioral realms must be bridged by a neurocognitive conceptualization of normal declarative memory. An explanation for the subjective experience of remembering with respect to declarative memories must also be sought.

A Neural Feature of Declarative Memory: Cross-Cortical Consolidation

The central hypothesis here is that the *long-term storage of declarative memories characteristically requires cross-cortical consolidation*, a process mediated by the confluence of cortico-thalamic and cortico-hippocampal networks. The information inherent in personally experienced events and complex facts is stored within a set of distinct zones of the cerebral cortex, each of which is dedicated to processing a specific type of information. Although gaps remain in our ability to describe how information is coded by neuronal connections within and between neocortical zones, it is clear that these zones are specialized for distinct functions. Autobiographical memories are re-creations of episodes that were originally experienced and understood via information processing in many different neocortical regions. Episodes generally entail a set of attributes (Underwood, 1969) such as a spatial layout of environmental features, sights, sounds, smells, motion, other people, goals, actions, emotional coloring, timing with respect to other events, and so on. Given that major aspects of an episode are represented at distant brain loci, storage of that episode must include new cross-cortical connections. Episodic memory storage depends on a memory trace corresponding to each of these attributes as well as connections between them. The cortical fragments must be linked together in order for the representation of the episode to survive as a unit to be remembered later.

In short, a memory for an episode inherently has a strong dependence on cross-cortical storage. Whether this applies to memory for facts may depend on how *fact* is defined. When complex information is learned — such as factual knowledge about the world expressed as a statement (Shimamura & Squire, 1987) — cross-cortical storage may be responsible. On the other hand, when minimal factual knowledge is acquired — such as simple three-word combinations (Tulving, Hayman, & Mcdonald, 1991) — information minimally sufficient to support that learning may be stored within a single neocortical zone responsible for specialized semantic information. Explicitly stating that this consolidation process is cross-cortical is also important given that other sorts of consolidation may occur for other sorts of memory and in other brain regions (Brashers-Krug, Shadmehr, & Bizzi, 1996; Gais, Plihal, Wagner, & Born, 2000). Although linking together separate representations in different cortical regions is considered an essential step in the creation of an enduring declarative memory, additional processing at the time of retrieval is also critical. Prefrontal contributions to declarative memory, in particular, come into play here (Knight & Grabowecky, 1995; Shimamura, 1995; Wheeler, Stuss, & Tulving, 1997). Retrieval requirements include conducting a systematic search for stored information, evaluating the products of retrieval and assessing relevance to the task at hand, escaping from the present moment to bring a prior experience to mind, maintaining and working with information in an active state, inhibiting the intrusion of irrelevant information, constructing a scenario within which retrieved information is put together, evaluating the likelihood of different scenarios, and so on.

Establishing long-lasting links between cortical fragments must, of course, be distinguished from establishing analogous but temporary bindings in the present moment, as occurs when an event is experienced. Patients with amnesia apparently experience events normally and are able to maintain that information while it stays at the focus of attention (Cave & Squire, 1992). Thus, this initial component of encoding can be normal in amnesia, and distinguished from a second component of encoding that entails storage (Paller & Wagner, 2002). Amnesic patients can form cross-cortical associations temporarily, such that factual or episodic information can be represented and effectively support immediate memory. The difficulty is in storing that information in an enduring way.

Cross-cortical consolidation proceeds when a set of neuronal ensembles in the neocortex is repeatedly activated, as has been assumed in computational models of consolidation (McClelland, McNaughton, & O'Reilly, 1995; Murre, 1997; Squire & Alvarez, 1995). A distributed cortical network ultimately represents the remembered information, but it starts out in an unstable form at the time of initial encoding. The memory generally includes representations of discrete components of an event at multiple levels of relevant perceptual processing streams. Consolidation produces a stable network of distributed cortical representations, but it is conceptualized here not as a passive or automatic process that inevitably runs its course. Rather, consolidation proceeds as the memory is actively used. Components of the network are loosely connected via interposed limbic connections such that partial information can cue the retrieval of the whole memory, as in *pattern completion* (McClelland, McNaughton, & O'Reilly, 1995; Treves & Rolls, 1994). These limbic connections are formed swiftly at encoding so as to unify the distinct cortical components, but the connections are not long-lasting and gradually become less effective with disuse. Importantly, these connections can be sufficient for retrieving a declarative memory shortly after learning, before cross-cortical consolidation has progressed significantly. Furthermore, each time these connections are used to reactivate the distributed cortical representation for a declarative memory, the process of cross-cortical consolidation is hypothesized to be moved forward in a particular way that involves the gradual formation of new neuronal ensembles in the cortex termed *coherence ensembles* (Paller, 1997).

Another Neural Feature of Declarative Memory: Coherence Ensembles

Whenever the network of neocortical neuronal ensembles is activated, one commonly proposed outcome is a strengthening of the cortico-cortical connections between parts of the network. In contrast, cross-cortical consolidation is here conceptualized as resulting from additional neural changes. Network reactivation can involve not only retrieval, but also associations between that memory and other memories, with concomitant changes to the declarative memory representation in question. The memory may lose some detail, and also gain new meaning in the context of the associations. It may be evaluated in comparison to other memories. It may come to be interpreted in a new way in the light of subsequent events. These associations can leave a trace and so come to constitute part of the network that underlies storage of the declarative memory.

Furthermore, consolidation proceeds whether or not the individual is intending to memorize or rehearse the memory; it proceeds in conjunction with any associative processing

that involves that memory. As the memory takes on additional meaning by taking its place in the context of other stored knowledge, other neurons come to represent this higher-order meaning or thematic information. These other neurons may be located in adjacent portions of the temporal lobe, such as entorhinal cortex, the temporal pole, and perhaps other areas such as orbitofrontal cortex, retrosplenial cortex, or posterior cingulate. I refer to these hypothetical neuronal ensembles as *coherence ensembles* (Paller, 1997) because they function to provide coherence to the set of neocortical fragments that comprise a declarative memory. At the same time, they take over the function of representing the central, superordinate meaning of the memory, the essence of the representation, including its relationship to other memories and its place within autobiographical and/or general semantic frameworks, akin to *thematic retrieval frameworks* (Hodges & McCarthy, 1995). When a coherence ensemble is activated and the gist of a memory retrieved, projections from the coherence ensemble can enable various details of the memory to be retrieved. Hippocampal neurons initially participate in this re-activation of a memory, whereas later the newly formed coherence ensembles are sufficient to accomplish this.

This conceptualization of cross-cortical consolidation has much in common with views from many other memory theorists (although it is not possible to describe each of these other theories here). The memory-indexing theory of Teyler & DiScenna (1986), for example, also suggested that the hippocampus was involved in connecting sets of neocortical ensembles while a cortically based memory is established incrementally. Squire, Cohen, & Nadel (1984) described a consolidation process in which neocortical activity was modified by input from the hippocampal region, leading to neocortical reorganization. Other important influences can also be listed (Damasio, 1989; Eichenbaum, 2000; Halgren, 1984; Marr, 1971; Mesulam, 1998; Milner, 1989; O'Keefe & Nadel, 1978; Wickelgren, 1979). Nonetheless, one distinctive aspect of the current conceptualization is that new representations, instantiated by neuronal coherence ensembles, are proposed take over the function of reactivating a network of distributed neocortical representations as a result of cross-cortical consolidation.

Retrograde Amnesia, Ongoing Hippocampal Contributions, and Sleep

What would happen if coherence ensembles were damaged while other medial temporal circuitry was left intact? This condition may constitute a description of damage to critical storage zones leading to focal retrograde amnesia (Kapur, 1993; Kopelman & Kapur, 2001; Markowitsch, 1995). Retrograde impairments could present along with a relatively preserved (though not entirely unaffected) ability to form new declarative memories. This impairment could make old memories inaccessible, because the fragments would be present in the cortex but not connected, so that the episode could no longer be re-assembled. Likewise, circumscribed damage to lateral temporal regions may lead to semantic dementia, with remote memories disrupted more than recent memories (Hodges & Graham, 1998). Differential loss of autobiographical versus general semantic information could also be explained if different sorts of coherence ensembles were not randomly scattered about but functionally clustered in different regions.

Heterogeneity of symptoms in amnesic patients, and dissociations between anterograde and retrograde impairments, may then be explained as follows. A core amnesia with retrograde

and anterograde deficits may result from brain damage to either cortico-thalamic or cortico-hippocampal networks. In severe cases, damage to major portions of the medial temporal region may disrupt cross-cortical consolidation entirely and also destroy previously established coherence ensembles. The extent of retrograde impairment may depend on the extent to which coherence ensembles are also destroyed. Retrograde memory loss for long time periods may result from extensive damage to cortical coherence ensembles. Retrograde deficits may be observed in a relatively pure fashion when a subset of established coherence ensembles is damaged leaving the major machinery for cross-cortical consolidation intact. Other retrieval problems with respect to search, organization, and evaluation may emerge and contribute to the memory disorder with additional prefrontal damage.

Whether hippocampal neurons continue to participate after cross-cortical consolidation produces a durable memory remains a question currently under active debate (Nadel & Moscovitch, 1997; Nadel, Samsonovich, Ryan, & Moscovitch, 2000). According to the present view, if an episode continues to be recalled periodically, as is the case for most significant life episodes, new associations will be formed with other events. If a memory is not totally isolated from the rest of an individual's ongoing experiences, it may continue to change rather than remain in a static state. In this sense, cross-cortical consolidation may continue indefinitely. Continued dependence on the hippocampus may be determined by the extent to which the fact or episode in question continues to be associatively processed with new information and to evolve accordingly. There may thus be two distinct means for long periods of retrograde amnesia to be produced. One cause would be significant damage to cortical storage zones, and in particular, to coherence ensembles essential for retrieving declarative memories. The other cause would be prolonged disruption of the hippocampus and related circuitry so as to disrupt continuing cross-cortical consolidation of remote memories that would otherwise be strengthened through recurring associations with other information, including subsequent episodes of retelling the story to others. Deficits in intentional retrieval such as those produced by prefrontal damage could also contribute to failures to consolidate and to retrieve declarative memories. Even in the absence of neurological dysfunction, memories of the contextual details of an episode tend to be difficult to maintain because they are so heavily based on the singular initial experience of the episode. As time goes by, contextual details of an episode are postulated either to be forgotten or to be represented in the neocortex and linked together with other recallable aspects of the episode by virtue of coherence ensembles. An episodic memory can become thoroughly integrated with other stored information and largely devoid of distinctive contextual detail, and can eventually come to constitute a semantic memory (Cermak, 1984).

Finally, it should be noted that the repeated activation of the neocortical network that is critical for cross-cortical consolidation occurs not only when the memory is retrieved intentionally, but also when it is retrieved unintentionally, and perhaps particularly when retrieval occurs during sleep. Indeed, a high proportion of dreams incorporate recent events of the day or the past several days, such that the consolidation of an episodic memory may progress significantly during the first few nights after the event occurs. Moreover, if dreams provide an opportunity for evaluating possible solutions to ongoing life issues, recent events can be related to long-term goals accordingly. The emotional coloring of a declarative memory can thus become influential in promoting consolidation over an extended period. Furthermore, consolidation will

continue to influence storage to the extent that related events occur on subsequent days. It may be difficult to observe cross-cortical consolidation during sleep, but several lines of empirical evidence can currently be assembled to support these ideas (Stickgold, Hobson, Fosse, & Fosse, 2001; Sutherland & McNaughton, 2000; Winson, 1985). Indeed, investigations of interactions between processing during sleep and the status of declarative memories are likely to gain prominence in memory research and comprise a exciting approach for understanding the basis of declarative memory in neocortical networks.

Beyond Declarative Memory: Questions of Definition

The memory dysfunction in amnesia is not strictly limited to declarative memory. Damage to medial temporal or medial diencephalic brain regions can produce both a deficit in storing declarative memories *and* deficits in certain other types of memory that fall near definitional borders, such as some variations on simple classical conditioning (e.g., Gluck, Ermita, Oliver, & Myers, 1997) and some types of new-association priming (e.g., Cermak, Bleich, & Blackford, 1988; Paller & Mayes, 1994; Schacter & Graf, 1986; Shimamura & Squire, 1989). New-association priming may be preserved when it is based on perceptual processing of a unitized element, but not when it is based on conceptual processing (Gabrieli, Keane, Zarella, & Poldrack, 1997; Verfaellie & Keane, 2002). Some memory phenomena that would normally fall within the category of nondeclarative memory but that are not preserved in amnesia should perhaps be reclassified within a new subcategory of nondeclarative memory — the category could be called "nondeclarative memory that depends on neocortical associations."

Would it be a good idea to choose to define new types of memory based on neurobiological criteria instead of behavioral criteria? If so, another possible category would be "cross-cortical-consolidation-memory," which depends on neocortical associations that require cross-cortical consolidation, and which includes both declarative and nondeclarative varieties. This neural distinction might be the best way to carve nature at the joints. And yet, it also risks the danger of circular definitions, given that we don't have an objective marker for cross-cortical consolidation. Future research should pursue this goal. In the meantime, should we continue using current definitions of declarative memory (or explicit memory, conscious memory, or aware memory), or should we define new memory categories in order to cover all the memory abilities impaired in amnesia?

Some researchers have advocated using cognitive criteria to define the type of memory impaired in amnesia. Qualities such as flexible, configural, relational, or dependent on complex associations can be emphasized (Cohen & Eichenbaum, 1993; Ryan, Althoff, Whitlow, & Cohen, 2000; Shimamura, 2002). But should these attributes be central to the definition of declarative memory? This approach might meet with the same circularity problems as would making the neural criteria central to the definition. Definitions of terms such as relational or flexible are themselves rather flexible in practice, though operational definitions are possible. Moreover, it is likely that attributes such as "relational" can apply to some memories that are not stored in the cortex and that should be considered nondeclarative, such as some complex motor memories and habits. When a new memory phenomenon is demonstrated using some novel behavioral

paradigm, objectively determining whether it depends either on cross-cortical consolidation or on complex associations of some sort may present a challenge.

Until ways to surmount these challenges are well established, it may be best to maintain the behavioral definition of declarative memory as referring to the recall and recognition of facts and episodes, while at the same time hypothesizing neurocognitive reasons for why declarative memory is different from all other types of memory. Cross-cortical consolidation is presumably necessary for normal declarative memory and it is here hypothesized to be the core defect in amnesia. Importantly, cross-cortical consolidation is also necessary for certain types of associative nondeclarative memory that likewise depend on dispersed neocortical representations.

Declarative Memory and Conscious Recollection

The approach outlined above provides a natural segregation between declarative memory and conscious recollection as follows. *Conscious recollection*, the subjective experience of remembering, appears to be contingent on declarative memory, and it tends to happen in concert with the recall and recognition of facts and episodes. Although recollection is central to definitions of aware memory, conscious memory, and explicit memory, it is not formally part of the definition of declarative memory advocated here. Rather, recollection is an additional phenomenon that depends on some of the same neurocognitive substrates as declarative memory. Cross-cortical storage is a necessary but not sufficient condition for the conscious recollection of a declarative memory. The retrieval of a declarative memory can be accomplished through cortico-hippocampal and cortico-thalamic networks shortly after learning, and recollection can accompany retrieval. Moreover, cross-cortical consolidation allows a set of isolated cortical networks to become more strongly linked together, and once linked in this manner, the composite set of networks corresponds to an enduring declarative memory. This memory can become accessible to conscious awareness when the distributed cortical representation is reactivated. Recollection is a metamemory function, in that it requires both retrieval of the declarative memory and an understanding of the source of the remembering experience.

Indeed, a central function of cortico-thalamic connections in declarative memory may be in the temporary activation of the distributed declarative memory. Speculatively, the thalamic neurons that are particularly relevant here may be the same neurons characterized neuro-chemically as calbindin cells that form a so-called *thalamic matrix* (Jones, 1998), given that they are found in all thalamic nuclei and project widely to superficial cortical locations. Medial thalamic connections to multiple cortical regions may be able to support the conscious experience of a remembered event, together with prefrontal networks that support working memory. Medial thalamic damage could thus indirectly disrupt cortical function, as suggested by neuroimaging findings in patients with Korsakoff syndrome (Paller et al., 1997). The medial diencephalic contribution to conscious recollection may also entail inhibiting other potential conscious contents, so as to facilitate the conscious retrieval of the memory. Although further evidence is needed on this point, it is conceivable that thalamic control networks are critical for consolidation because they can support both the retrieval and activation of a distributed declarative memory,

which thus sets the stage for consolidation to proceed through the action of cortico-hippocampal networks, as coherence ensembles are formed and strengthened.

Neuroimaging and Declarative Memory

Empirical tests of hypotheses such as those developed above can be expected not only from neuropsychological studies of amnesic patients but also from monitoring neural activity while memories are normally formed and expressed. Neuroimaging in humans may present many fruitful avenues for advancing theories couched at this level. The term *neuroimaging* is used here in the wider sense to refer to techniques that make it possible to observe neural activity or correlated hemodynamic changes, either in specific brain regions or with sufficient temporal resolution to monitor changes in neural activity as cognitive events unfold in time, or both. I will place particular emphasis on neurophysiological methods for recording *event-related potentials* or ERPs (Münte, Urbach, Düzel, & Kutas, 2000), which may be useful for charting the time-course of relevant memory processing and ultimately, in conjunction with other neuroimaging measures, for deciphering the dynamics of brain network interactions. Issues that arise in taking this approach will apply to multiple methods for monitoring brain activity (e.g., MEG, fMRI, PET, EEG responses in the frequency domain, optical imaging, and so on).

How can we begin to comprehend the neural events responsible for forming and remembering declarative memories? One useful approach is to make comparisons between declarative memory and other types of memory, to search for specific ways in which the neurocognitive structure of declarative memory is distinctive. The success of this approach, however, depends on the validity of presumed associations between neural measures and cognitive operations. Given that we can only specify the structure of cognition on the basis of our working hypotheses, inaccurate conceptualization of the component processes of memory may corrupt our observations, and so hamper our ability to test hypotheses. Fortunately, we can move forward on many fronts simultaneously. For example, attempts to specify precisely how information is represented in the neocortex (e.g., Mesulam, 1998) can have implications for how we think about the storage of declarative memories and lead to refined conceptualizations of the component processes of memory.

In order for neural observations of the encoding and retrieval of declarative memories to support continuing theoretical progress, a key step is for valid and specific associations to be made between neural measures and discrete cognitive events. Given that multiple cognitive events generally occur simultaneously and in the midst of complex interactions among processes, discrete memory functions can be difficult to isolate. Encoding and retrieval, in particular, do not occur *only* when an experimenter instructs a subject to store or recall information, respectively. A incremental approach is thus needed to build associations between neural measures such as those extracted from the EEG and memory functions. How tightly can such measures be associated with the neurocognitive events responsible for declarative memory?

To start to answer this question, we may first note that differential EEG responses to remembered items in recognition tests, as compared to responses to new items, constitute a robust electrophysiological phenomenon tied to declarative memory (for reviews see Friedman & Johnson, 2000; Mecklinger, 2000; Paller, 2000; Rugg & Wilding, 2000). ERPs recorded at the time of retrieval differ systematically between old and new items in both explicit and implicit memory tests. Presumably, these *ERP repetition effects* reflect several cognitive events potentially related to memory retrieval. Given the foregoing discussion, it is clearly appropriate to determine the extent to which observed neural activity specifically reflects component processes of declarative memory.

In recent experiments we have used several methods for gaining this specificity. Contrasts between responses to test items associated with different levels of memory performance have been particularly informative. For example, we have emphasized contrasts between two types of studied words that gave rise to perceptual priming effects of the same magnitude but provoked very different levels of recognition accuracy. We inferred that these contrasts could be recast in terms of high and low recollection, such that corresponding ERP differences (e.g., Figure 2A) could be interpreted as electrophysiological correlates of recollecting declarative memories, devoid of any confounding influence related to perceptual priming (Gonsalves & Paller, 2000a; Paller, Bozic, Ranganath, Grabowecky, & Yamada, 1999; Paller & Kutas, 1992; Paller, Kutas, & McIsaac, 1995).
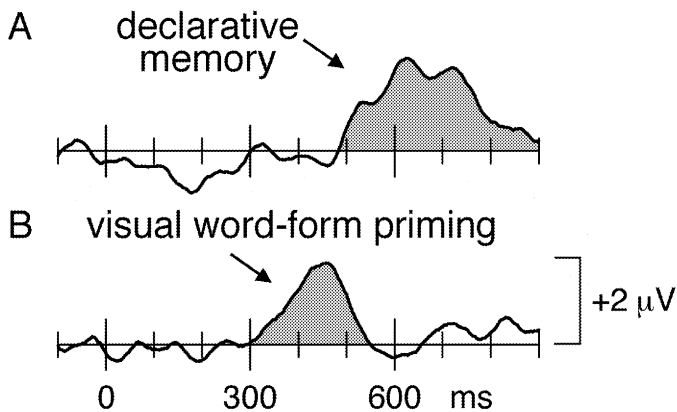
Figure 2. Brain potentials specifically associated with declarative memory and one type of nondeclarative memory, priming of visual word form. The difference wave form in **A** was computed by subtracting brain potentials elicited by words previously studied with emphasis on visual imagery versus orthographic processing; recollection was stronger in the former compared to the latter condition (data from Paller, Kutas, & McIsaac, 1995). The difference wave form in **B** was computed by subtracting brain potentials elicited by words previously viewed forwards or backwards; priming was greater in the former compared to the latter condition (data from Paller & Gross, 1998).

The same basic strategy in reverse was used in other experiments, such that conditions were set up to provide a contrast between words associated with similar levels of recognition but systematically different levels of perceptual priming. As a result, brain potentials were linked to neural events underlying perceptual priming restricted to the level of visual word-form (Paller & Gross, 1998; Paller, Kutas, & McIsaac, 1998). These electrophysiological correlates of visual word-form priming were most prominent at occipital scalp locations and occurred at a latency slightly earlier than that typically found for electrophysiological correlates of visual word recollection (Figure 2B). Neuroimaging studies using PET and fMRI suggest that perceptual priming may result from decreased neural activity following perceptual learning (Schacter & Buckner, 1998; Wiggs & Martin, 1998). Furthermore, magnetoencephalographic evidence concerning the timing of repetition-related changes implicates top-down influences onto earlier cortical regions rather than effects on initial stages of sensory information processing (Dale et al., 2000). Electrophysiological correlates of perceptual priming can also be revealed in recordings from single neurons in monkey visual cortex. In particular, some neurons in ventral temporal areas tend to show reduced responses during stimulus repetitions, a phenomenon termed *repetition suppression* (Desimone, 1996). Many questions remain concerning the events that support priming effects, but combining results from these different methods may lead to some of the answers as well as to a better understanding of how priming and declarative memory differ.

In addition, however, we will also need more thorough evaluations of neural correlates of declarative memory in order to disentangle the various factors responsible for recollection. In neuroimaging studies, one approach to this problem have been to manipulate the type of information that subjects retrieve during a recognition test (e.g., Johnson, Kounios, & Nolde, 1997; Ranganath, Johnson, & D'Esposito, 2000; Ranganath & Paller, 1999, 2000; Wilding, 2000). There is good evidence to distinguish between the active search processing necessary for retrieval in cases when the information is not immediately available, the evaluation of the products of retrieval for their suitability to the task at hand, and the successful access of the desired information. Many of these heavily strategic components clearly rely on prefrontal processing (e.g., Shimamura, 1995). However, much controversy currently surrounds our ability to empirically separate retrieval effort, retrieval success, and other processes relevant for retrieval (Rugg & Wilding, 2000).

Memory research using ERPs has not only focused on the retrieval phase, but also on neural events that take place at the time of encoding. Many studies have shown that both hemodynamic and electrophysiological measures can be predictive of later declarative memory (for reviews, see Paller & Wagner, 2002; Wagner, Koutstaal, & Schacter, 1999). These effects are sometimes termed *Dm* as a shorthand for neural *d*ifferences based on later *m*emory performance (Paller, Kutas, & Mayes, 1987). Dm studies can provide insights into memory formation by monitoring the events whereby the experience of an event is transformed into a declarative memory. For example, it appears that prefrontal and posterior neocortical computations are responsible for the representation and goal-directed processing of events, while medial temporal computations guide the storage of durable episodic traces whereby the elements of these representations are linked together (Paller & Wagner, 2002).

In a recent example of results showing electrical indications of the formation of declarative memories, ERPs were recorded in response to pictures of common objects and to corresponding words presented during a study phase (Gonsalves & Paller, 2000b). When the words were shown (as depicted in Figure 3A), subjects were instructed to generate a visual image of the object. On half of the trials, a picture of that object was also presented immediately after the word. On other trials no picture was presented. Nevertheless, when given a subsequent memory test (Figure 3B) subjects later claimed to remember some of the images that were never presented but only imagined — these can be considered *false memories* or *source-monitoring errors* (Johnson, Hashtroudi, & Lindsay, 1993; Schacter, Norman, & Koutstaal, 1998). ERPs in response to words differed according to whether the items would later be falsely remembered or not (Figure 3C). These ERP differences were interpreted as reflections of visual imagery generated in response to the words, given that similar ERPs in a prior experiment were shown to vary reliably as a function of the extent to which visual imagery was engaged (Gonsalves & Paller, 2000a). ERPs in response to pictures also differed systematically in amplitude according to whether the picture would be accurately recognized later. Neural activity observed at encoding
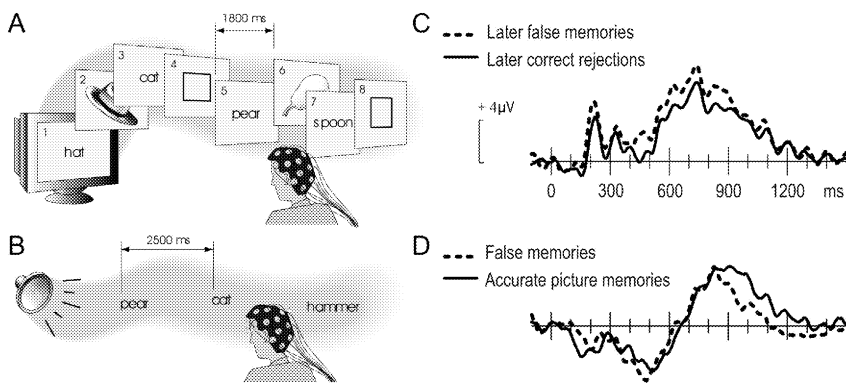
Figure 3. Behavioral paradigm and electrophysiological results from an investigation of false memories (Gonsalves & Paller, 2000a). A: In the study phase, subjects viewed a series of words and were required to make a size judgement for each one ("is the object larger or smaller than the video monitor?"). Half of the words were followed by a color image of the corresponding object and half were followed by an empty rectangle. B: In the test phase, subjects listened to a series of words and were required to decide whether the corresponding image had been viewed during the study phase. When a subject claimed to remember seeing a picture that was only imagined, these trials were designated *false memories*. C: ERPs recorded to words in the study phase (from the midline occipital scalp location) differed at 600-900 ms according to whether a false memory occurred in the test phase for that item. D: Midline occipital ERPs recorded to auditory words in the test phase differed at 900-1200 ms according to whether that trial constituted an accurate memory or a false memory. These potentials were interpreted as indications of visual imagery that was recapitulated at retrieval for pictures either perceived in the study phase or, to a lesser extent, imagined in the study phase. (Data in C and D from Gonsalves & Paller, 2000a) (Reprinted with permission from Paller, 2002.)

thus influenced the outcome of later recognition testing, both for accurate and for false memories. An analysis of ERPs recorded during retrieval (Figure 3D) showed that the amplitude of these ERP was larger for accurate picture memories than for false memories, suggesting that visual imagery was less vivid for false memories.

Thus, it is possible to monitor relevant neural activity both at encoding and at retrieval using ERPs. Yet, as stated above, the core defect in amnesia is postulated to be at storage rather than at encoding or retrieval. How should future theory-driven research attempt to promote advances in our understanding of consolidation? According to the views expressed above, storage and retrieval are intertwined, because cross-cortical consolidation entails retrieval. Therefore, one way to study consolidation would be to observe neural activity during a retrieval event wherein associations are made such that the memory in question is strengthened. It may also be helpful if distinct cortical networks can be monitored as consolidation proceeds. The configuration of crtical networks involved in an episodic memory might be expected to change over time in ways that implicate storage processes. For example, informative differences may emerge if comparisons can be made between declarative memories that are matched in strength but systematically differ in only the number of distinct types of information linked together to form the memory. There are also many open questions regarding the role of the hippocampus and whether this role changes over the lifetime of a memory. If hippocampal contributions decrease over time, one might expect that new activity corresponding to the formation of coherence ensembles might emerge in other brain locations. Although there is not currently an abundance of evidence that can be brought to bear on these and many other related questions about human memory, approaches utilizing scalp and intracranial ERP recordings and fMRI time-series analyses do hold promise for these issues.

Finally, a coming together of neuropsychology and neuroimaging can also be expected in studies with patients suffering from memory disorders (e.g., Eustache, Desgranges, Aupee, Guillery, & Baron, 2000; Olichney et al., 2000). It is important to note that structural neuroimaging in patients only tells part of the story, in that the pattern of cognitive deficits must be related not only to sites of anatomical damage but also to neural dysfunction that results from distant structural damage. Patients with alcoholic Korsakoff's syndrome, for example, have patterns of cortical glucose hypometabolism that suggest thalamocortical dysfunction secondary to direct thalamic damage (Paller et al., 1997). It will be critical for future neuroimaging research to search for other such indications of impaired cross-cortical consolidation and to monitor the temporal dynamics of the dysfunction.

Conclusion

Although much remains to be learned about how human memory functions are implemented in the brain, many insights into declarative memory have been gained from studies of patients with memory disorders. At the same time, neuroscience has clarified many physiological and molecular underpinnings of neuronal plasticity that may support human memory. Some mechanisms of plasticity may be common to many or even all memory functions. With the

categorization of subtypes of memory, however, it is clear that certain memory functions, such as some required for declarative memory, are supported by distinct neurobiological mechanisms. To elucidate the neurocognitive structure of declarative memory, neuropsychological studies of amnesic patients and neuroimaging studies in healthy and memory-impaired populations represent two powerful approaches that, together, will continue to provide insights into declarative memory. Speculations about memory couched at the level of neural circuits may have previously appeared impossible to address rigorously in humans. That limitation could certainly have applied to the hypotheses specified in the present chapter, such as:

- declarative memory storage accomplished initially through temporarily connected neuronal ensembles in the cerebral cortex;

- unitized representations in assorted cortical zones that comprise the discrete components of memories for complex facts and events;

- a linking process for these dispersed neocortical representations based on cortico-thalamic and cortico-hippocampal networks;

- retrieval and association over extended periods of time that strengthen connections between the components of a declarative memory;

- the gradual development of coherence ensembles that can ultimately take over the linking process to provide enduring coherence to the components of the memory.

Due to methodological advances in cognitive neuroscience, it is now easier to envision how hypotheses like these can be developed further and empirically tested using a range of techniques for studying the human brain in action. Electrical and hemodynamic measures of brain function, for example, are providing a wealth of new evidence that must be included in future accounts of declarative memory. In this way, the combination of neuropsychology and neuroimaging will be useful for understanding declarative memory when it is dysfunctional, when it is optimally functional, and when it is subject to the mixture of success and failure that people normally experience.

Acknowledgments

10

The Principle of Bottleneck Structures

Matthias Brand and Hans J. Markowitsch

Memory is one of the most complex and important human brain functions. It can be subdivided along dimensions time (e.g., short and long-term-memory) or contents (e.g., episodic and semantic memory), and according to the stages of information processing (encoding, consolidation, storage, and retrieval of information). It is assumed that in different memory processes specific brain structures, so called 'bottleneck structures' (e.g., Markowitsch, 1995b), are primarily involved. Amnesic syndromes can therefore occur as a consequence of widespread brain damage, such as in Alzheimer's disease, as well as after tiniest lesions or functional alterations of the brain.

This paper addresses the following questions: What are the bottleneck structures for different memory aspects? And accordingly: What kind of brain damage will lead to specific memory impairments, such as anterograde or retrograde amnesia?

Classification of Memory

Traditionally, memory is divided along the dimension of time, for instance into short-term, intermediate and long-term memory (Rosenzweig, Bennett, Colombo, Lee, & Serrano, 1993). In the last decade of the 20th century a further classification of memory – along the contents of memory systems – was introduced by Tulving (1995). Four different, long-term memory systems are postulated: episodic memory, semantic memory, procedural memory, and priming (see Markowitsch, 1995a; Tulving, 1995, Fig. 1). The episodic memory system represents events and

episodes of a person with respect to time and locus. The knowledge system consists of facts without personal reference (e.g., arithmetical rules, world knowledge). Skills are the components of procedural memory (e.g., riding a bike, playing tennis), and priming describes the improved recognition or reproduction of information that was already experienced before. Retrieval of episodic memories occurs explicitly or intentional, while the other forms of memory retrieval are incidental (Tulving, 1995).
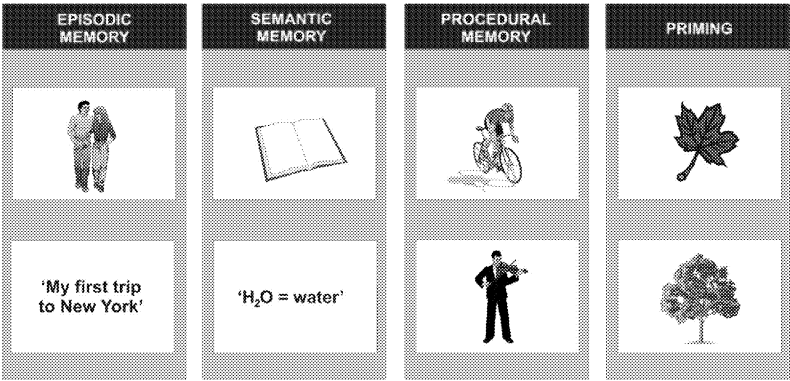
Figure 1. The four long-term memory systems (modified from Markowitsch, 1996)

Our knowledge of interdependencies between brain regions and memory aspects has increased in the last years. An expansion of different methods to study brain functions and their combination (e.g., neuroimaging methods and neuropsychological investigations) as well as studies on brain lesioned animals substantiate the growth of information on brain-memory interactions. Nevertheless, most of our knowledge stems from detailed descriptions of brain damaged patients.

When drawing inferences from brain damaged patients, the time period between lesion acquisition and testing is of crucial importance (Barbizet, 1970, Fig. 2) as is that of distinguishing between anterograde and retrograde amnesia (Fig. 3).

Amnesic Syndromes

Medial Temporal Lobe Amnesia

Case H.M. constitutes probably the most extensively studied patient, who became persistently anterograde amnesic after bilateral resection of major portions of the medial temporal lobes (Scoville & Milner, 1957). Preoperatively, he suffered from a pharmacologically intractable

epilepsy, and brain surgery was conducted to reduce the frequency of his epileptic attacks. However, following the intervention, he lost his ability to store new information long-term. Intellectual impairments as well as emotional or behavioral changes were not observed. Furthermore, his working memory capacity and other cognitive abilities like reading, writing, and calculating remained intact, and also his recall of remote autobiographical memories was not affected. H.M. has been extensively examined from 1955 to the present. It was obvious that his acquisition of information is not completely devastated, as he is still able to learn some bits of new information, particularly in an implicit way. A static brain imaging investigation (magnetic resonance imaging, MRI) revealed that his brain damage comprised bilateral lesions of the amygdala, the parahippocampal-entorhinal cortex, and the anterior hippocampus (Corkin, Amaral, Gonzalez, Johnson, & Hyman, 1997). The description of H.M. demonstrates the importance of the medial temporal lobes – primarily the hippocampal formation – for learning and storing new information. However, the investigations on the hippocampus and its role in memory processes have been continued up to this day. A special role of the hippocampus itself in the acquisition of episodic memory had been pointed out by Vargha-Kadem et al. (1997). They described three patients with early hippocampal damage and found that these patients were severely impaired in the acquisition of episodic, but not of semantic memory. Consequently, they proposed that only episodic memory acquisition depends on the hippocampus.
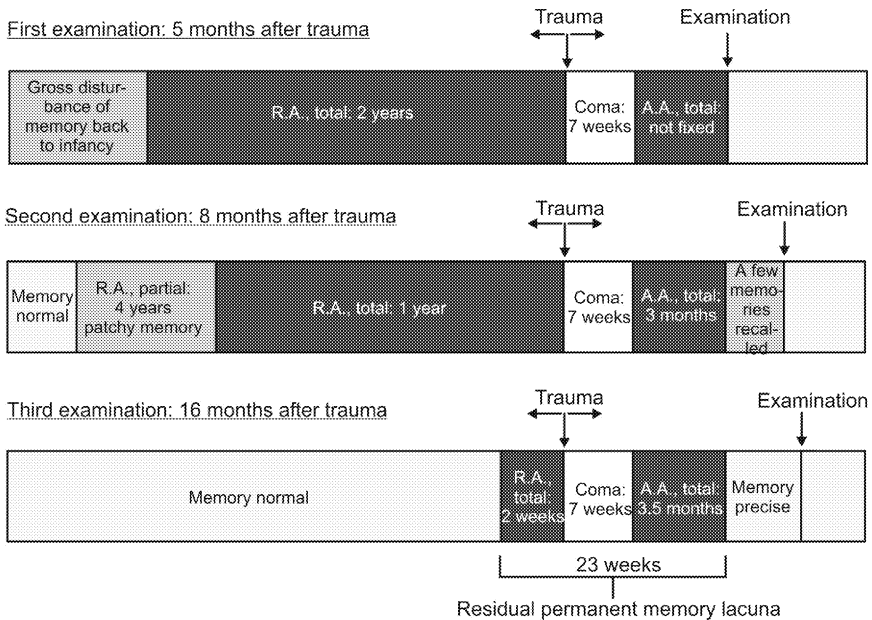
Figure 2. Relations between duration of recovery after brain damage and recovery of anterograde and retrograde memory (after Figure 9 of Barbizet, 1970)

Medial Diencephalic Amnesia

Studies of patients with alcoholic Korsakoff syndrome revealed that damage of medial dien-cephalic structures such as the mammillary bodies, the mediodorsal and anterior thalamic nuclei, as well as of nonspecific medial thalamic nuclei, and the medial pulvinar may lead to remarkable memory impairments comparable to those after bilateral medial temporal lobe damage. The intelligence of alcoholic Korsakoff patients may remain unchanged.
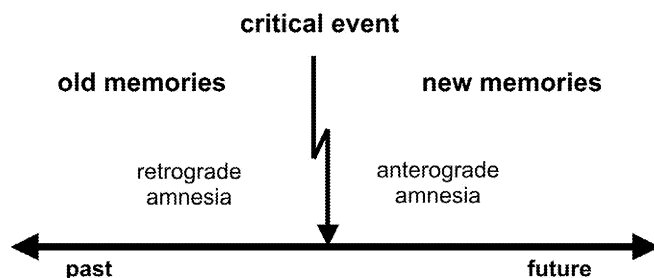
Figure 3. Possible consequences of criti-cal events or brain injury on new and old memories (modified from Markowitsch, 1995).

The relevance of damage of different diencephalic structures for the Korsakoff syndrome has been discussed controversially. From a detailed neuropsychological description and post mortem pathological analysis, Mair, Warrington, & Weiskrantz (1979) concluded that the mammillary bodies as well as anterior and medial thalamic nuclei (e.g., the paratenial nuclei), but not the medial dorsal nuclei, are involved in Korsakoff amnesia. Harding, Halliday, Caine, & Kril (2000) attempted to unravel the importance of various diencephalic structures for Wernicke encephalopathy, the first phase of the Wernicke-Korsakoff syndrome, and of those of the later and chronic Korsakoff state. In their eyes the principally different damage is that of the anterior thalamic nuclei in the Korsakoff state.

Although Korsakoff syndrome is one of the most common causes for diencephalic amnesia, other etiologies, such as thalamic infarctions (e.g., Graff-Radford, Tranel, Van Hoesen, & Brandt, 1990; Markowitsch, von Cramon, & Schuri, 1993), can also lead to memory disturbances.

Due to the severity of learning impairments in patients with diencephalic amnesia, anterograde amnesia is described consistently in many studies. Additionally, retrograde amnesia is observed in Korsakoff patients as well, but to a more variable degree (Kopelman, Stanhope, & Kingsley, 1999; Mayes, Daum, Markowitsch, & Sauter, 1997; Shimamura & Squire, 1991).

Similarities between medial temporal lobe and medial diencephalic amnesia are widely preserved intellectual functions and mostly unimpaired short-term, priming and procedural memory functions. The main discrepancy between the two concerns the different degrees of the patients' awareness of their own deficits. Patients with medial temporal lobe amnesia, such as H.M., are often able to describe their memory problems, whereas amnesic patients with medial diencephalic damage prevalently negate any deficits or are unaware of their intensity (see Markowitsch, 1999b, for a review).

Basal Forebrain Amnesia

Another brain region whose damage can cause memory disturbances and amnesia is the basal forebrain. The basal forebrain consists of various structures and interconnecting fibers. The nuclei involved in memory processes comprise the septal nuclei, the nucleus accumbens, the nuclei of the diagonal band of Broca, and the nucleus basalis of Meynert. The most common etiology for basal forebrain lesions is rupture of aneurysms of the anterior communicating artery (ACoA) (see De Luca & Diamond, 1995). The resulting hypoperfusion of the basal forebrain causes the so called ACoA syndrome with symptoms of amnesia as well as confabulation and personality changes. Basal forebrain amnesia is characterized by impairments in explicit memory tasks, both recall and recognition, but there may be a disproportionate disturbance in recall compared to recognition mainly due to additional frontal lobe damage (see Rajaram, 1997, for a review). Implicit memory seems to be widely intact in those patients (e.g., Rajaram & Coslett, 2000; von Cramon, Markowitsch, & Schuri, 1993). Connections between cortical and subcortical memory relevant structures also contribute to basal forebrain amnesia. The case description of von Cramon & Schuri (1992) is an example, demonstrating that lesions of the septum and of pathways between septum and hippocampus can lead to anterograde as well as retrograde amnesia (cf. also the review of von Cramon & Markowitsch, 2000).

Amygdala Damage and Memory

The amygdala, viewed as an important structure for emotional processes (LeDoux, 2000), consists of various nuclei and is localized within the anterior medial portion of the temporal lobe. The amygdaloid region is strongly interconnected with the hippocampal formation and many other cortical and subcortical structures (e.g., orbito-frontal, cingular and insular cortices, hypothalamus, basal nucleus of Meynert, and medial thalamic nuclei; see Sater & Markowitsch, 1985, for a review). A few cases with selective (bilateral) damage of the amygdala have shown that specific aspects of memory may depend on the amygdaloid complex. Most of these patients with selective amygdala damage feature Urbach-Wiethe disease (UWD) (also known as lipoid proteinosis). The UWD is an autosomal recessive disease characterized by various skin abnormalities and on the neurological level by calcifications in the region of the anterior temporal lobes, mainly within the amygdaloid region.

Tranel & Hyman (1990) described a patient with bilateral amygdala mineralizations due to UWD who exhibited significant deficits in the new formation of nonverbal memories as well as in executive control. Cahill, Babinsky, Markowitsch, & McGaugh (1995) examined a female UWD patient with a story consisting of a set of pictures accompanied by a narrative. The story begins with neutral contents (phase 1) followed by an emotionally arousing part (phase 2) and a neutral end (phase 3). They found that in contrast to healthy subjects the patient did not profit from the emotionally arousing material during encoding. The study supports the view that the amygdala is a critical structure for the enhancement of memory for emotionally arousing material. Markowitsch et al. (1994) studied two UWD patients and summarized that the amygdala influences memory performance by structuring, selecting and filtering information of different relevance to the individual.

Bilateral damage of the amygdaloid complex may also cause the Klüver-Bucy syndrome (Klüver & Bucy, 1937) which is characterized by agnosia, amnesia, hypersexuality, hyperorality, hyperphagia, tameness, and hypermetamorphosis. These symptoms, originally observed in monkeys and more recently also shown in humans, comprise memory disturbances (primarily features of anterograde amnesia), but also emotional dysfunctions. In summary, the amygdaloid region can be viewed as a structure important for emotion-dependent memory functions, such as encoding of episodes.

Damage of Non Limbic Structures and Amnesia

Compared to the role of limbic structures, the importance of non-limbic regions in memory processing is far more ambiguous. For instance, neocortical lesions may lead to quite restricted forms of amnesia, such as impairments in remembering names and faces (Reinkemeier, Markowitsch, Rauch, & Kessler, 1997). On the other hand, neocortical damage can cause widespread cognitive and memory disturbances, as seen in Alzheimer's disease. The symptoms of the Alzheimer type dementia consist of several memory impairments (Morris, 1996) affecting episodic (e.g., Beatty, Salmon, Butters, Heindel, & Granholm, 1988; Bondi, Salmon, & Butters, 1994) and semantic information (e.g., Hodges, Salmon, & Butters, 1992; Lambon Ralph, Patterson, & Hodges, 1997; Nebes, 1989). Priming deficits can occur (Salmon, Shimamura, Butters, & Smith, 1988; Shimamura, Salmon, Squire, & Butters, 1987) but are usually less prominent. Additionally, short-term and working memory deficits (Collette, Van Der Linden, Bechet, & Salmon, 1999; White & Murphy, 1998), and further symptoms, such as agnosia (Fujimori et al., 2000), apraxia (Travniczek-Marterer, Danielczyk, Simanyi, & Fischer, 1993), as well as attention and executive dysfunctions (Perry & Hodges, 1999; Perry, Watson, & Hodges, 2000) can be observed in Alzheimer's disease. Though Alzheimer's disease is viewed as a 'cortical dementia' it has to be mentioned that a number of limbic and subcortical structures are affected as well (Braak & Braak, 1997). Therefore, the various memory impairments in Alzheimer's disease may not be caused by cortical damage alone. For instance, procedural memory deficits in Alzheimer patients are also shown by Huntington and Parkinson patients and depend primarily on subcortical damage (e.g., basal ganglia, portions of the cerebellum). Uni- and polymodal neocortical areas are associated with the fourth long-term memory system - priming. The study of Nielsen-Bohlman et al. (1997) gives support for this assumption. They examined patients with temporal-occipital lesions (occurring as a result of infarction of the posterior cerebral artery, surgical resection of an arterial venous malformation, or as a congenital defect) with a word-stem completion task. They found that this kind of priming is impaired in patients with temporal-occipital lesions, even though the patients showed lesions extending to medial temporal lobe regions. Nielsen-Bohlman, Ciranni, Shimamura, & Knight (1997) argued, that priming deficits are typically not observed in patients with medial temporal lobe amnesia and therefore the disturbances in their patients had to be caused by the tempero-occipital lesions.

Psychogenic and Functional Amnesia

There is a wide variety of types of psychogenic or dissociative amnesias (see Loewenstein, 1996, for a review). The classical state of psychogenic amnesia consists of a sudden loss of retrograde autobiographic episodes including the patient's own identity. When patients in addition travel away from their home – formerly described as a state of *Wanderlust* (wandering) – this is referred to as psychogenic fugue condition. Upon recovery from the fugue there is usually an amnesic gap (see Kopelman, 2000). Markowitsch, Fink, Thoene, Kessler, & Heiss (1997) described a 37-year-old patient who sustained a fugue. He left his house in the morning to buy bread for breakfast and did not return home, but continued cycling for five days along the River Rhine. Neuropsy-chological testing revealed persistent amnesia for personal events prior to fugue. Neurological and neuroradiological examination, including magnetic resonance imaging (MRI), failed to detect any abnormalities. A positron emission tomography (PET) investigation (episodic-autobiographic memory activation task) revealed increased regional cerebral blood flow in memory related regions only within the left, but not within the right hemisphere. The right hemisphere is normally activated during the retrieval of autobiographical memories (Fink et al., 1996), while the left one is related to 'neutral', semantic memory retrieval (world knowledge) (Markowitsch, Calabrese, Neufeld, Gehlen, & Durwen, 1999).

Psychogenic amnesia can be viewed as a mechanism of blocking the awareness of previous traumatic events (Markowitsch, 1996). In line with this definition, a patient (AMN) was reported by Markowitsch et al. (1998). AMN had seen a man burning to death at the age of four. 19 years later, at the age of 23, the patient experienced a fire in his house and immediately after that event, he became anterogradely amnesic and developed a retrograde amnesia concerning the period of the last six years. While conventional neurological diagnostics (including MRI) did not reveal any clinically relevant changes, a positron emission tomography (PET) investigation showed severe reductions of regional cerebral glucose metabolism, primarily in memory associated brain regions of the medial temporal lobe and the medial diencephalon (Fig. 4).

One year later and after pharmacological and psychotherapeutic interventions, his brain metabolism returned to normal levels and his amnesia improved.

The psychic causation of amnesia was described for a long time (e.g., Breuer & Freud, 1895). In recent years, it has become more obvious that the manifestation of post traumatic stress disorder (PTSD) may also result in memory and cognitive impairments (Barrett, Green, Morris, Giles, & Croft, 1996; McGrath, 1997; Silver, Rattok, & Anderson, 1997). Some of these disturbances are transient or affect memory to a minor degree, but others can affect the total biography or can lead to anterograde amnesia (Markowitsch et al., 1998).

So far, the neurobiological processes of psychogenic amnesia are only imperfectly understood. A possible explanation of the phenomenon may be that psychological stress causes morphological and functional alterations of limbic structures especially in medio-temporal regions, due to the release of stress-related hormones (glucocorticoids) (Lupien & McEwen, 1997; Sapolsky, 1996). Evidence for this hypothesis comes from patients with PTSD who are especially vulnerable to depression as well as to memory deficits. In PTSD a dysregulation in the release of stress-related hormones may cause alterations of neural function (van der Kolk, 1997). In line with this, some studies revealed a stress related reduction of hippocampal volume (e.g.,

Gurvits et al., 1996; Stein, Koverlola, Hanna, Torchia, & McClarty, 1997). A recent study of Knutson, Momenan, Rawlings, Fong, & Hommer (2001) with healthy subjects has found a negative relation between brain volume ratio and personality variables related to stress reactivity, primarily neuroticism. They argued that also in healthy subjects individual stress reactivity is involved in brain volume reduction.
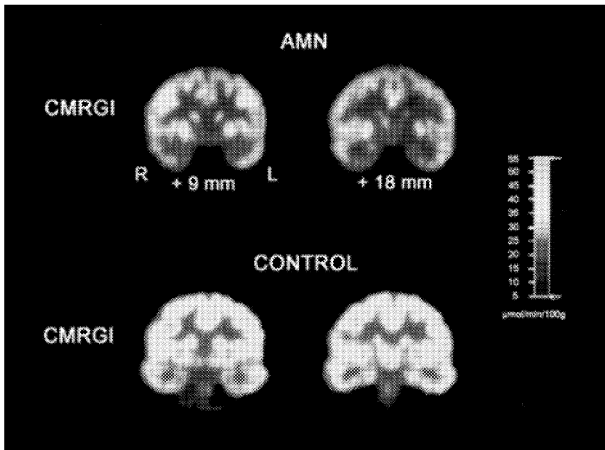
Figure 4. ^{18}F-2-fluoro-2-desoxy-D-glucose PET-based coronal sections from anterior (left) and posterior (right) through the brains of a patient (AMN) with trauma caused amnesia (top row) and a healthy control subject (modified from Markowitsch et al., 1998). More glucose utilization is reflected by more lumi-nosity.

To define amnesias without manifest brain correlates or psychiatric causation, De Renzi, Lucchelli, Muggia, & Spinnler (1997) introduced the term 'functional amnesia'. The most frequently reported etiology of functional amnesia is minor head trauma. Markowitsch (1999a) reviewed several cases with functional amnesia and proposed the term 'mnestic block syndrome' to bridge the former division of organic and psychogenic memory disturbances.

Anatomical Bases of Memory

After this line of evidence, we come back to the main question of this chapter: What are the bottleneck structures for different memory aspects? Various memory systems are probably represented in specific brain regions. These so called 'bottleneck structures' are well described for the episodic memory system and contain primarily the bilateral medial temporal lobe, the medial diencephalon and the basal forebrain as well as prefrontal regions (see Markowitsch, 2000).

A short overview of the structures relevant for encoding and consolidation, storage, and retrieval of information along the four long-term memory systems is shown in Table 1.

Table 1. Structures relevant for the four long-term memory systems and the different memory processes (modified from Markowitsch, 1999a)

	Episodic memory	Semantic memory	Procedural memory	Priming
Encoding and consolidation	Limbic system, Prefrontal cortex (?)	Limbic system, cerebral cortex	Basal ganglia, cerebellar structures	Cerebral cortex (uni- and poly-modal areas)
Storage	Cerebral cortex (mainly association areas) Limbic regions (?)	Cerebral cortex (mainly association areas)	Basal ganglia, cerebellar structures	Cerebral cortex (uni- and poly-modal areas)
Retrieval	Temporo-frontal cortex (right)	Temporo-frontal cortex (left)	Basal ganglia, cerebellar structures	Cerebral cortex (uni- and poly-modal areas)

? = no consistent evidence

As pointed out before, amnesia can be caused by various diseases and therefore by widespread areas of brain damage. This fact implies that the neural basis of memory is not a single brain structure but instead a distributed network of structures and fiber connections. In addition, memory depends on a wide range of sensory, perceptual, attentive, emotional, and motivational processes and their neuroanatomical correlates. Therefore, Chow's caveats (Chow, 1967) on interpreting interdependencies between brain and behavior have to be mentioned. He suggested that if a brain lesion fails to affect a learning task, it cannot be concluded that this part of the brain is not participating in that function. Further, if the lesion influences performance on this task, it does not necessarily mean that it is the only structure involved. The aim of ablation methods to clarify the functions of damaged brain regions is in a way never attainable, for it is based on observations in patients without the region of interest. These are important statements for interpreting and integrating results from both patient studies and neuroimaging investigations.

The following sections give an overview of assumptions and evidence for the involvement of specific structures in different memory processes.

Encoding and Consolidation

For encoding and consolidating newly acquired information (before this is transferred into the long-term store), two interconnected limbic circuits are proposed to act: the Papez circuit and the amygdaloid (basolateral limbic) circuit.

The Papez circuit consists of structures around the hippocampus (hippocampal formation, fornix, mammillary bodies, mammillothalamic tract, anterior thalamus, thalamo-cortical pedunculi, [cingulate cortex, cingulum] hippocampal formation [subiculum]) (cited in Markowitsch, 2000, Fig. 5). Even if Papez himself (Papez, 1937) viewed this circuit as

principally engaged in the analysis of emotions, recent studies have shown that this circuit is involved in the transfer of all kinds of information into long-term memory (see Markowitsch, 1998).

The amygdaloid circuit includes the amygdala, the mediodorsal nucleus of the thalamus, the subcallosal area of the basal forebrain (and closely associated regions), as well as interconnecting fibers: the ventral amygdalofugal pathway, the anterior thalamic peduncle and the bandeletta diagonalis (Fig. 5). This circuit is related to emotional processing and is also involved in encoding the emotional valence of experiences. Damage of the structures of both pathways usually causes severe memory impairments. The limbic structures, primarily the hippocampal formation (hippocampal-entorhinal complex) and the limbic thalamic nuclei are most closely related to episodic memory encoding and consolidation.
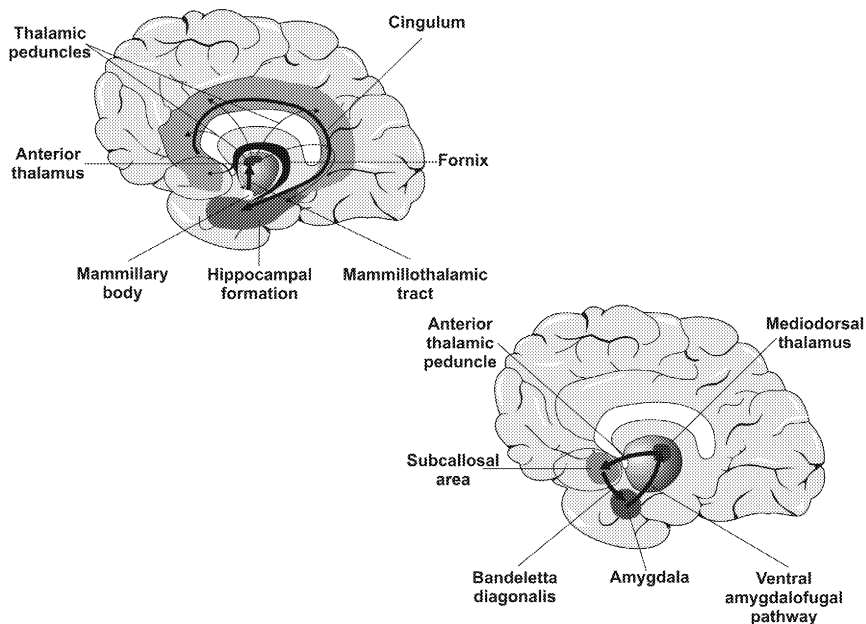
Figure 5. **Top:** The Papez circuit consisting of structures around the hippocampus. **Bottom:** The baso-lateral limbic circuit containing the amygdala, the mediodorsal nucleus of the thalamus, and portions of the basal forebrain as well as various interconnecting fibers.

The assumption of different underlying neural correlates for initial encoding into episodic memory and the successive consolidation of information is supported by the description of a 30 year-old female patient of Markowitsch, Kessler, Kalbe, & Herholz (1999). The patients' severe memory disturbances occurred after a whiplash trauma. She was quite superior in intelligence

and verbal and non-verbal functions, but lost the ability to retrieve her newly acquired information within 30-120 minutes. Both static and functional brain imaging investigations detected no specific brain damage, but she had sustained hearing deficits after injury.

A patient with temporal lobe epilepsy, studied by Kapur et al. (1997), showed intact long-term memory encoding and recall for days but exhibited a disability to remember information 40 days after learning. A comparable report of a patient with temporal lobe epilepsy and paraneoplastic limbic encephalitis, who could recall information after hours and days but showed an abnormal high rate of forgetting thereafter, was given by O'Connor, Sieggreen, Ahern, Schomer, & Mesulam (1997).

Observations like those suggest a dissociation of initial encoding into long-term memory and the subsequent and more stable consolidation of information. They also speak for the engagement of different brain structures at different periods of the memory process.

More recent functional neuroimaging studies have revealed an involvement of frontal regions during encoding (see Fletcher & Henson, 2001, for a review). Consistent activation was found in the left frontal cortex, mainly in the dorso-lateral and the ventro-lateral prefrontal cortex. Fletcher, Shallice, & Dolan (1998) presumed that the left prefrontal cortex plays an important role for organizational processes during encoding. In their PET investigation they detected an activation of the left prefrontal cortex (above the inferior frontal gyrus) only in the task condition which required a generation of semantic organization. They concluded that the left dorsolateral prefrontal cortex is a critical region for creation of an organizational structure during encoding while more ventral and anterior frontal regions may reflect a less specific component of episodic memory encoding. The degree of activation of different prefrontal and temporal regions during episodic memory encoding may depend on the depth of processing. Otten, Henson, & Rugg (2001) found greater activation of prefrontal and temporal areas for semantically than for alphabetically encoded words using event-related functional MRI. The importance of both (left) medial-temporal as well as (left) prefrontal cortex for memory encoding was already reported by Dolan & Fletcher (1997). They showed that activation of both regions are dissociable with hippocampal formation being sensitive to the novelty of information and prefrontal cortex being sensitive to establish semantic associations. The study of Fletcher, Shallice, & Dolan (2000) supports the view that the left prefrontal cortex is necessarily involved in optimal encoding of material by inhibiting the inappropriate and identifying the appropriate semantic features to form meaningful associations. Using functional MRI, Killgore, Casasanto, Yurgelun-Todd, Maldjian, & Detre (2000) revealed activations of the left hippocampus and the left amygdala during associative encoding. The critical role of the hippocampus for episodic memory encoding was already reported by Vargha-Kadem et al. (1997), whose findings are discussed by Tulving & Markowitsch (1998).

Storage of Information

The most common assumption for information storage is that wide areas of association cortices are involved. There is evidence for alterations in synaptic conjunctions within the cerebral cortex (e.g., Baily & Kandel, 1995) but it seems to be unclear how these changes perpetuate lifelong

engrams (e.g., Schuman, 1997). Besides the main role of association cortices in storage of information, it is proposed that limbic regions are necessary for binding information (see Markowitsch, 2000). Various studies revealed an amygdala activity dependent modulation of long-term memory storage (see Cahill, 2000), whereby right and left amygdala are not equally involved. With regard to that right-left distinction, gender differences may play an important role. Cahill et al. (2001) found increased activity of the right, but not left, amygdala related to better recall of emotional compared to neutral material only in men, whereas in women increased activity of the left, but not the right, amygdala associated with increased recall of the emotional stimuli was observed. Thus, Cahill et al., (2001) suggest sex-related differences in participation of the amygdala in emotionally influenced memory. Reasons for these divergent amygdala activations in men and woman are still unresolved.

Retrieval of Information

For retrieval of information stored in the long-term memory systems a more distinct localization is assumed to exist. In the retrieval of episodic memories the right hemisphere is viewed as to be primarily engaged, while in semantic memory retrieval the left hemisphere seems to play a critical role (Markowitsch, 2000; Tulving, Kapur, Craik, Moscovitch, & Houle, 1994). Within both hemispheres the prefrontal cortex is a primary region for retrieval of information. Brain imaging investigations with healthy subjects as well as studies with brain damaged patients revealed that infero-lateral frontal and antero-lateral temporal cortical areas are necessarily involved in successful retrieval (e.g., Markowitsch, 1995b). The retrieval of context-rich information and contents with emotional connotation may be supported by limbic structures of the medial diencephalon and medial temporal lobe regions (Markowitsch, 2000).

In their recent review, Fletcher & Henson (2001) conclude that there are three stages of memory retrieval: specification of search parameters, verification and monitoring of the products of memory searches, and a control processing supervising the switching between specification and monitoring, all probably depending on different regions of the prefrontal cortex. They suggest that the higher-level control processes, which optimize memory retrieval, are associated with the anterior prefrontal cortex. Fletcher, Shallice, Frith, Frackowiak, & Dolan (1998) hypothesized an important role of the right prefrontal cortex during retrieval of episodic memories because of its mediation of monitoring processes necessary for optimal recall. Their PET investigation revealed an increased activation of the right dorsal prefrontal cortex when monitoring during retrieval was demanded, while the right ventral prefrontal region activity was greater when no monitoring (external cuing) was required. In their eyes, one can interpret this result as a functional specialization within the prefrontal cortex during episodic memory retrieval. Furthermore, Nyberg, Habib, McIntosh, & Tulving (2000) suggested that cortical regions activated during encoding are reactivated during retrieval. In their PET study they used a task consisting of a visual word encoding paired with sounds. In the retrieval condition, activation of auditory brain regions was also detected, though the retrieval of auditory information was not demanded. They assumed that portions of a stimulus complex are able to evoke the whole experience.

A special case of episodic memory is that of autobiographical memory concerning memories for the experiences of one's own life, mostly connected with an emotional connotation. Widespread cortical regions seem to be involved in the retrieval of autobiographical memories, primarily within the right hemisphere. Such structures within the right hemisphere are the temporomedial (including hippocampus, parahippocampus, and amygdala) and temporolateral cortex, posterior cingulate areas, insula and prefrontal regions (Fink et al., 1996), even though Conway et al. (1999) found additional activation within the left frontal lobe during retrieval of autobiographical memories, suggesting that these regions are engaged in the control of what is remembered and how.

The involvement of the hippocampal formation in episodic memory retrieval is still unclear. Conway et al. (1999) did not find substantial differences between the activation of the hippocampus in recent and remote memory, whereas in a recent study of Haist, Bowden Gore, & Mao (2001) it has been revealed that the participation of the hippocampal formation in human memory is probably time limited. In their eyes, successful retrieval of remote memory is probably processed independently from the hippocampal activity, whereas the entorhinal cortex seems to be more involved in remote memory functions. A reason for the divergent findings of the participation of the hippocampus in encoding and retrieval of memories may lie in the necessity to segregate different hippocampus portions. Lepage, Habib, & Tulving (1998) proposed that encoding is associated with activation of rostral portions of the hippocampus and retrieval is related to activation of the caudal hippocampal regions. Dolan & Fletcher (1999) would agree with this suggestion. In a functional MRI study with healthy subjects, they confirmed the anterior-posterior functional segregation of the medial temporal lobe.

Conclusion

An illustration outlining the various brain structures and processes, described in this chapter and considered to be relevant for information processing, is given in Figure 6.

As had been presumed for a long time, a division into short- and long-term memory provides only one of the more simple facets of memory. Mnestic functions comprise many components, which can be classified according to time, content, involved process, and modality. Accordingly, various brain structures are involved to a variable degree. There is general agreement that most information is distributed along broad cerebral cortical networks (see McClelland & Rumelhart, 1986). Subcortical regions support specific memory functions (e.g., emotional memory, procedural memory). Amnesic disturbances occur after very heterogeneous forms of brain damage as well as after various functional (psychic, psychiatric) alterations.

Importantly, however, the concept of a disconnection syndrome, introduced since long in neurology, is of high importance for a proper understanding of lesion-induced amnesia. As damage to an individual link of a chain makes the chain as a whole useless, damage to certain bottleneck structures in the brain may lead to permanent amnesic states. The concept of bottleneck structures has to be seen together with Chow's (1967) caveat that it is invalid to

conclude from the failure of functioning after damage to a given brain structure to the exclusive representation of this function in exactly this structure in the non-damaged brain (cf. above).
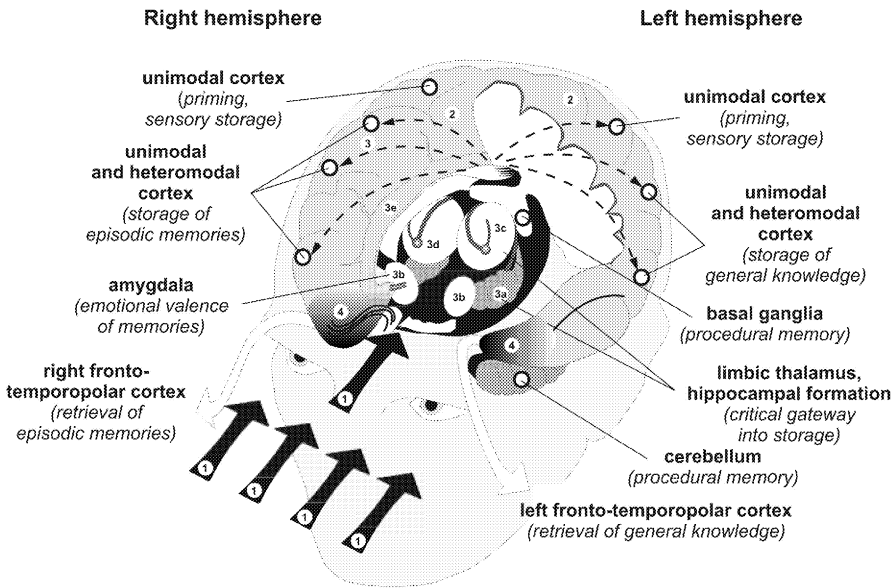
Figure 6. View of the brain structures involved in long-term memory encoding and consolidation, storage, and retrieval. 1= sensory input, 2= cerebral cortex, 3= limbic system: 3a= hippocampal formation and parahippocampal cortices, 3b= amygdala, 3c= limbic thalamus, 3d= mammillary bodies, 3e= cingulate gyrus and other paralimbic cortices, 4= fronto-temporopolar cortex interconnected by the uncinate fascicle (modified from Markowitsch, 2000).

While early researchers in the field of memory were inclined to adhere in a dichotomous way to either a narrow localizationist's or to a strict anti-localizationist's view, present-day theories attempt to follow a converging strategy. Nevertheless, enough further questions remain unsettled. Among them the kind of organization of episodic and semantic memory (e.g., hierarchical, connective) and its brain correlates. The continuously increasing methodological repertoire and theoretical polishing and refinement will improve our understanding of brain-behavior interactions exponentially in the field of information processing. We are, however, still dependent on traditional methods, techniques, and species to which we can add the recently established ones.

Section D

CONTROL
OF
MEMORIES

11

The Principle of Controlling Neuronal Dynamics in Neocortex: Rapid Reorganization and Consolidation of Neuronal Assemblies

Matthias H. J. Munk

The neuronal substrate for information processing in the neocortex consists of a highly divergent and sparsely connected network of neurons. In order to cope with the complexity of real-world information in time and space, the operations of neuronal circuits have to include both processes of rapid reorganization as well as the generation of stabilized representations. The brain has to find its equilibrium between these two seemingly antagonistic modes of processing, adaptivity and consolidation. Most synapses in the cortex cannot change their strength within a few seconds. On the one hand, rapid changes in functional connectivity need to be implemented by dynamic and reversible neuronal operations. On the other hand, some of the information once represented by dynamic neuronal operations is needed for future processing. Therefore, a trace has to be formed in the cortical circuitry that can be instantaneously re-activated upon occurrence of the same or a similar input pattern. This chapter will describe the neuronal mechanisms for dynamic grouping of cortical responses by means of millisecond-precise synchronisation and discuss whether neuronal assemblies provide a suitable concept to understand the equilibrium between cortical adaptivity and consolidation.

Problems in Understanding Cortical Information Processing

At first, problems in understanding information processing can only be overcome by considering the properties and specific features of the neocortex. While the ultimate test of our understanding will consist of implementing neuronal algorithms in computer models and compare their performance to that of the biological system, this chapter is confined to the conceptual level and the discussion of compatible experimental results. One of the central questions in this context concerns the *neuronal coding* of information. Conventional concepts of neuronal function quickly reach there limits of processing capacity when *complexity* and *processing speed* are considered. Beyond the computational problem of coding, the functional organization of cortical circuits needs to be considered. An important parameter for all brain functions is the *state of the system*, which not only determines what kind of input can reach central processing structures like the cortex, but also influence neuronal function within the cortex. Because neuronal processing in the neocortex is highly distributed within and across multiple areas, *local and global mechanisms* are required that can dynamically control the *flow of information*, including feedback and lateral interactions. These issues raise questions concerning the timing of neuronal operations that are responsible for behavioral performance.

Neuronal processes underlying cognitive function have to cope with combinatorial complexity. Combinatorial complexity arises from the fact that perceptual objects and the majority of behavioral processes consist of a number of persistent features that occur in uncountable configurations and combinations. If all configurations and combinations were unique and occurred often enough, the optimal strategy for neuronal systems like the neocortex would consist of using hardwired detectors. As the latter is not the case, coding the relations among individual features has to be organized in a more versatile fashion. As an example, the features of visual objects are numerous and huge numbers of cortical neurons in primary visual areas serve as detectors for elementary features like color, luminance contrast and the orientation of edges. If all possible combinations of features had to be implemented as individual detectors, the number of available neurons in the brain would be too small and, such highly specialized cells would rarely be used. In analogy, in the motor system arm-hand movements consist of elementary features like extension, flexion and rotation of individual joints, however, a well co-ordinated movement like pronation, grasping or reaching is a highly complex combination of elementary features that is highly context-dependent and therefore quite different each time it is executed. Similar arguments hold for processes that are less directly related to sensory or motor events, like the storage of information in memory or decision making based on more abstract rules.

Neuronal coding of information about stimuli is traditionally assigned to changes in firing rate (Barlow, 1972; Richmond & Optican, 1990). This coding strategy has been investigated for almost any brain region, describing neuron populations with highly selective response properties in cortical areas that are not directly fed by sensory systems. Such neurons have been termed 'smart neurons' to refer to their high degree of functional specialization, which is indeed impressive, if information from multiple modalities expresses in the response properties of individual neurons (Galletti, Battaglini, & Fattori, 1993) or predict the position of a receptive field after a saccade (Duhamel, Colby, & Goldberg, 1992). However, these studies typically employed successive recordings from many single cells, which questions the generality of

observing highly selective responses in dedicated cells, because their contribution to the representation of the respective stimulus material may have changed over time. The process of extracting stimulus information from firing rates of their afferent input is often too slow (Thorpe & Imbert, 1989), because decoding of frequency-encoded signals in serial chains of neurons requires temporal summation (Fig.1A) of successive signals (Munk, 2001). If the same information that is anyway distributed among huge populations of cortical neurons would be transmitted as coincidence-encoded signals, each of the transmitting neurons only needs to contribute a single action potential and the target neurons could decode the message by spatial summation which is as fast as the postsynaptic membranes can react (Fig.1B).
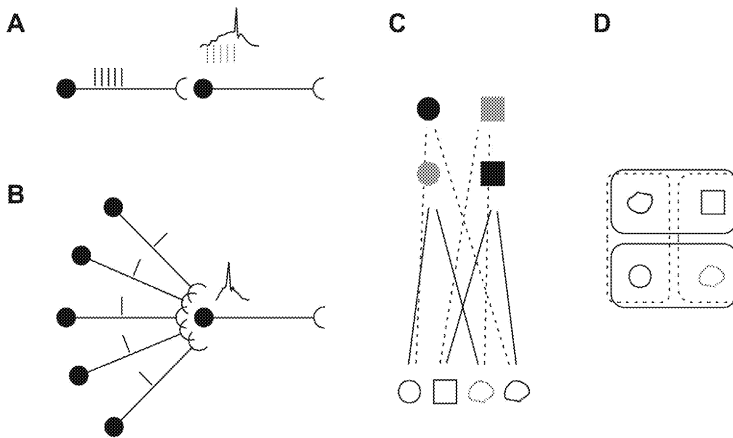
Figure 1. Mechanisms of neuronal signal integration. (**A**) Postsynaptic integration by temporal summation and (**B**) spatial summation. The curve in the inset represents the postsynaptic membrane potential. (**C**) Hardwired detectors that integrate via converging connections and (**D**) distributed code representing feature combinations by synchronizing assemblies.

       The neuronal architecture underlying the classical coding scheme of neuronal 'firing rates' or 'response strength' is assumed to consist of a hardwired convergence of elementary feature detectors that serves to construct more complex response properties (Fig.1C). Given the huge combinatorial space of features that needs to be covered, this strategy would require more cells than the cortex contains and would thus seriously limit the processing capacity. It has been proposed that an alternative to integration by converging inputs could consist of groups of neurons ('assemblies') that are defined by temporal relations among their members (Fig.1D). Each of the members would carry information about elementary features or subsets of features that belong to a perceptual object, but the entire object would only emerge if all members synchronize their firing. With assemblies, representations can be generated that could employ the same neurons for different purposes. Such a mechanism would permit to represent varying

content with a considerably smaller number of neurons by using the same neurons for different purposes (Singer, 1993; Singer et al., 1997).

Beyond these more basic computational aspects of cortical processing that could serve as pre-processing for cognitive operations, operations that require higher level integration and access to memory are highly dependent on the state of the brain. The range of brain states during which cognitive processes can occur is not entirely determined, however, higher levels of vigilance during waking are usually associated with cognitive processes. It is not yet understood how much brain states have to differ in order to support or impede cognitive processes. This is also reflected by the fact that the action of general anaesthetics remains elusive beyond the cellular level. This is not to say that only higher cognitive functions like e.g. abstract thinking require more complicated neuronal processes which are not accessible with current methods. It would already be useful to identify those brain processes underlying functions like simple sensations or sensory awareness. As has been proposed before (Engel & Singer, 2001), several elementary neuronal processes seem to be required for awareness: arousal, segmentation, selection and short-term memory. Arousal refers to the state of the system which one could consider as unspecific attentional mechanisms, while the more specific forms of attention serve to select those neuronal populations that provide information about the most salient or behaviorally relevant features. Component processes that serve the identification and maintenance of perceptual objects comprise segmentation in the first place and short-term memory in the second. Although some of the neuronal mechanisms for these different processes have been identified, their precise nature and their interactions are largely undefined.

At a more global level, cortical information processing is characterized by multiple simultaneously occurring processes. These can be analyzed by observing the flow of information through the cortical architecture consisting of multiple areas and layers. Feed-forward transmission in sensory systems primarily serves the supply with new information about the environment. Lateral exchange between simultaneously active sites within an area or among areas at the same level is needed to determine the relatedness of information that is available about the parts of a scene or object. Feedback is for example needed to extract the relevant information under sub-optimal conditions, i.e. when noise or occlusions impede a simple feed-forward analysis based on the integration of local features (Bullier, 2001). One possibility could be that higher areas project a neuronal hypothesis about the sensory input onto lower-level areas and thus help to determine the most likely combination of elementary features. It can be expected that such a complex operation requires well timed interactions between the different levels of processing (for review see Engel, Fries, & Singer, 2001). Local and global mechanisms need to interact efficiently in order to integrate these different aspects of processing fast enough to influence the decisions taken at the behavioral level. A unifying concept for most of these functions could consist of neuronal assemblies, because multiple assemblies can operate at the same time and in different connections, but always provide their ability to integrate or segregate based on the compatibility of their relative timing. Assemblies can only be formed if neurons can interact and change their activity pattern such that their relatedness can be detected by subsequent processing stages. The emergence of interactions critically depends on the type and structure of cortico-cortical connections.

Features of the Cortical Wetware

Cortico-cortical *connections* are the basis for neuronal interactions that enable neuronal processes to analyze relations among elementary features that may constitute an object and to use internal hypotheses to extract ambiguous information from a cluttered environment. Patterns of cortical connections suggest the degree of freedom with which cortical neurons may interact. Properties of cortical *synapses* provide some insight on how the cortex can restrict its adaptivity to neuronal signals that reflect a high degree of cooperativity and thus to signals that are related. Neuronal activity in the cortex always has a *spatio-temporal structure*, however, not all kinds of structure are necessarily a candidate mechanism for integration. In particular, temporal dependencies of neuronal activity that have their origin outside the brain have to be distinguished from internally generated correlations that reflect the cooperativity of the cortical network. Intra-cortically generated correlations of neuronal responses exhibit different degrees of *temporal precision* which can be assigned different cortical *circuits*. Among these different types of interactions, millisecond-precise synchronisation originates from mono-synaptically coupled populations of cortical neurons.

Three major types of cortico-cortical connections have been isolated and characterized functionally. Based on the pattern of their origin and termination, cortico-cortical connections have been classified as feed-forward, lateral or feedback connections (Felleman & Van Essen, 1991). Feed-forward connections serve the transmission and distribution of afferent activity that causes neurons to respond to a stimulus and determine the basic properties of their receptive fields (region in the sensory surface from which a cell can be activated). The information cortical connections convey exhibits topological or in the case of the visual system retinotopic selectivity. This topological selectivity has been shown to correspond between the source and target cells of feed-forward projections (Salin, Bullier, & Kennedy, 1989). For example in the visual system, feed-forward connections that arise from neurons in V1 transmit information from the same sector of the visual field to neurons in V2 that is actually represented by the responses of the target neurons of this projection in V2 (Salin & Bullier, 1995). This is not the case for lateral and feedback connections. They violate topographic correspondence, which clearly indicates that they serve functions other than generating primary response properties or receptive fields. Lateral and feedback connections appear to be involved in the organization of correlated firing (Munk, Nowak, Nelson, & Bullier, 1995) and feedback connections may play a role in the modulation of receptive field surround (Hupe et al., 1998). The topographic aspect of neuronal interactions suggests that lateral and feedback connections primarily serve to mediate contextual information (Phillips & Singer, 1997).

In addition to their different functional topography, cortico-cortical connections differ in their susceptibility to modification during different developmental stages (see Singer, 1995, for review). Feed-forward connections in the visual system are largely determined by genetic information and retain only very limited susceptibility to induction of long-term plasticity. Changes of receptive field properties have only been achieved experimentally with invasive conditioning procedures or extensive training. In contrast, lateral and feedback connections seem to preserve considerable capacity to change in later developmental stages. These observations

also suggest that feed-forward on the one hand and lateral and feedback connections on the other hand serve quite distinct functions.

The majority of cortico-cortical connections is reciprocal. A connection is considered to be reciprocal if the neurons that send their axons to a different population of cells either in the same or another cortical area will also receive projections from their targets. What does this mean in functional terms? In a feed-forward/feedback system, given that this projection is topographically organized, the cells in the higher area can control the cells in the lower area that provide their excitatory drive. In a horizontal direction, i.e. through intrinsic long-range or lateral inter-areal connections, interactions may support the generation and fine-tuning of response selectivity. However, it has been shown that these connections are also necessary to mediate synchronized firing (Engel, König, Kreiter, & Singer, 1991; Munk, Nowak, Nelson, & Bullier, 1995).

There is another important property of cortical connectivity that has consequences for the coding of information and the modulation of synaptic efficacy. In a network with a high degree of divergence and convergence, it is not only the spatial spread of axonal arborization and the number of postsynaptic target cells that determine the functional consequences of divergence, but the overall probability of contacts between any two neurons determines the number of synaptic contacts between two given cells. This feature of cortical connectivity is referred to as sparseness. Anatomical investigations have revealed that except for very local connections the probability for synapses between two neurons is below 1 (Braitenberg & Schüz, 1991; Martin, 1994). Given that the synaptic efficacy of cortical synapses is comparatively low (Mason, Nicoli, & Stratford, 1991), this implies that any reliable transmission of a signal between any two given neurons never works without the co-operative support of a significant number of other neurons, so-called 'helper cells' (Abeles, 1982). A very similar insight comes from the discussion of transmission speed through the cortical network. In short, the response latencies of cortical neurons in higher visual areas like infero-temporal cortex cannot be explained by a transmission process based on firing rates, because each processing stage has not enough time to de- and re-encode the signal. Again, if converging inputs of an individual cell are well co-ordinated in time, i.e. by synchronisation, each cell along a pathway can very efficiently integrate the activity by means of spatial summation. This mechanism of synchronous transmission has been further developed into an elaborate model of cortical transmission, the so-called 'synfire chain' (Abeles, 1991; Abeles, Prut, Bergman, & Vaadia, 1994), which has more recently been studied in a quantitative fashion (Diesmann, Gewaltig, & Aertsen, 1999). The crucial parameter for tuning a neuronal network to initiate and maintain a certain kind of interaction is the efficacy of its synapses, which can be modified in a use-dependent way.

It is well established that the connections between neocortical neurons can increase or decrease their efficacy in a lasting fashion which is referred to as long-term potentiation (LTP) and depression (LTD), respectively. Although coincident activation of pre- and postsynaptic membranes has long been postulated to be the relevant signal to initiate synaptic modification (Bienenstock, Cooper, & Munro, 1982; Hebb, 1949; Sejnowski, 1977), it has only recently been demonstrated for neocortical connections. The temporal contingency of presynaptic activation with postsynaptic depolarisation or hyperpolarisation can cause lasting changes of synaptic efficacy in opposite directions, whereas random temporal delays between pre- and postsynaptic

events have no effect (Frégnac, Burke, Smith, & Friedlander, 1994). Synaptic efficacy is increased if presynaptic actionpotentials precede a postsynaptic spike by a few milliseconds and vice versa (Markram, Lübke, Frotscher, & Sakmann, 1997). The critical interval for synaptic change has more recently been refined to include intervals up to ±15 ms (Froemke & Dan, 2002). In the cortical network with its numerous collaterals and reciprocal connections, precisely timed co-ordination of activity in pre- and postsynaptic neurons will be able to adjust synaptic gain continuously.

In feed-forward architectures, changes in synaptic gain can be expected to result in modified response strength, if the same set of afferent connections is modified, and in modified response specificity, if previously weak connections are strengthened and or previously strong inputs are weakened. The synaptic changes depend on the degree of postsynaptic depolarisation which determines the intracellular calcium concentration. As described above, the latter can be boosted by coincident pre- and postsynaptic activation. These mechanisms have mostly been studied by testing postsynaptic responses to single presynaptic test stimuli. However, under in-vivo conditions, neurons often fire trains and bursts of action potentials. It has recently been demonstrated that the time course of a postsynaptic response to a regular 20Hz burst of presynaptic action potentials can be modified without changing the net efficacy of the involved synapse, after the connection was exposed to repeated synchronous activation of the pre- and postsynaptic cell (Markram & Tsodyks, 1996). This redistribution of response amplitude is due to a modification of the frequency attenuation of the postsynaptic response. If synchronous activation of the pre- and postsynaptic cells can cause a systematic shift of the response maximum in time without changing the average level of activation in a broader time window, the exact latency of a neuron's response can be modified so that the time at which a cell participates in an assembly can be adapted by neuronal mechanisms. If the timing of synaptic responses can change independently of their strength, two different algorithms for synaptic modifications can be conceived of. Changing the strength of postsynaptic responses may be the mechanism by which the cortex can select the cells that respond to a certain input pattern, whereas the modification of the response timing could determine or at least bias the participation of a given cell in neuronal assemblies.

Coherent neuronal activity can have many sources, but only certain kinds of coupled neuronal activity can be regarded as the signature of neuronal assemblies (Singer et al., 1997). If a sensory stimulus activates two neurons at the same time, they might discharge action potentials in a highly synchronous fashion. However, if they do not interact via neuronal connections, the coupled activity is considered as firing rate covariation. The same logic applies to neurons in the motor system that are only co-active during the planning, preparation or execution of movements. Although in most cases the temporal precision of neuronal interactions is in the millisecond range and therefore much higher than that of coherent signals based on other sources, there are statistical methods (Palm, Aertsen, & Gerstein, 1988) that allow for a secure differentiation. When applied systematically, different types of neuronal synchronisation can be detected in the visual cortex (Nowak, Munk, James, Girard, & Bullier, 1999; Nowak, Munk, Nelson, James, & Bullier, 1995), but also in auditory (Eggermont, 1992; Eggermont, Smith, &

Bowman, 1993), infero-temporal (Freiwald, Kreiter, & Singer, 1998; Gochin, Miller, Gross, & Gerstein, 1991) and frontal (Aertsen et al., 1991) areas.

The temporal precision of synchronisation could be shown to reflect the type of mediating connections. Horizontal and lateral connections are necessary to maintain temporally precise synchronisation as its incidence is most affected by destroying direct connectivity, whereas the experimental manipulation of those cell populations from which feedback connections arise has a greater effect on temporally disperse correlations (Munk, Nowak, Nelson, & Bullier, 1995). This means that horizontal (intra-areal) and lateral (inter-areal) connections sustain mutual neuronal interactions with high temporal precision as can be observed during the synchronisation of gamma oscillations, whereas the reciprocal connections based on feed-forward and feedback projections may not only control the excitatory drive from afferents, but may also modulate interactions within and between lower order areas (Munk, 2001; Nelson, Nowak, Chouvet, Munk, & Bullier, 1992). The most intriguing observation in these studies on the functional connectivity was that neurons in primary visual cortex of opposite hemispheres continued to synchronize, though with low temporal precision, when all the monosynaptic callosal connections were absent. It is therefore quite likely that under normal conditions cortical neurons can interact over very large distances through polysynaptic pathways, which is an important prerequisite if assemblies should also serve as a mechanism for global integration across modalities or with motor and memory systems.

Dynamical Organization of Large Neuronal Populations: Synchronisation of Oscillations in the Gamma-Frequency Band

Millisecond-precise *synchronisation* can co-ordinate neuronal responses across large distances, can rapidly occur and cease or persist for periods of several seconds. The *dynamical aspects* of response synchronisation become evident with their dependence on the *level of cortical activation* and the global configuration 'Gestalt' of the sensory input pattern. In states of higher vigilance, response synchronisation which is increasingly based on fast neuronal oscillations becomes more stable. More importantly, response synchronisation depends on the global outline of visual stimuli which suggests that the temporal co-ordination of neuronal responses is part of the processes that integrate information that is distributed among large populations of neurons. This stimulus-dependence of response synchronisation is a dynamic property of cell populations that are co-activated by the same stimulus and it can change from trial to trial and thus within a few seconds. A very similar kind of stimulus-dependence was observed in neuronal *mass signals* like the *human* EEG. Synchronized oscillations appear to accompany processes that require *attention* or need to maintain or reconstruct *internal representations* of information like e.g. during short-term memory. In contrast to the highly dynamic emergence and decay of synchronized neuronal assemblies, storing information in memory requires more stabilized representations.

Synchronisation of neuronal activity with millisecond precision has been observed within and across many cortical areas in cats, monkey and man. Of course, the methods and

experimental conditions have not been the same, but there is growing evidence that synchronisation could be a mechanism for perceptual and sensorimotor integration and also seems to occur without direct relation to external events, whenever an active representation of sensory information is needed to take a decision (Tallon-Baudry & Bertrand, 1999). The reason why synchronisation is an attractive candidate mechanism for neuronal assemblies is its dynamical behavior. Presumably the most basic aspect of this dynamical behavior is the state-dependence of millisecond-precise synchronisation that can be observed among groups of neurons in the visual cortex during anaesthesia (Herculano-Houzel, Munk, Neuenschwander, & Singer, 1999) or the transition between different behavioral states (Roelfsema, Engel, König, & Singer, 1997). Both in cats and monkeys, neurons in visual areas become increasingly engaged in response synchronisation if the level of cortical activation is increased. In animal experiments, the level of activation can be increased by stimulation of the reticular activating system, e. g. at the level of the midbrain (MRF). In such experiments, the strength of oscillatory patterning at frequencies
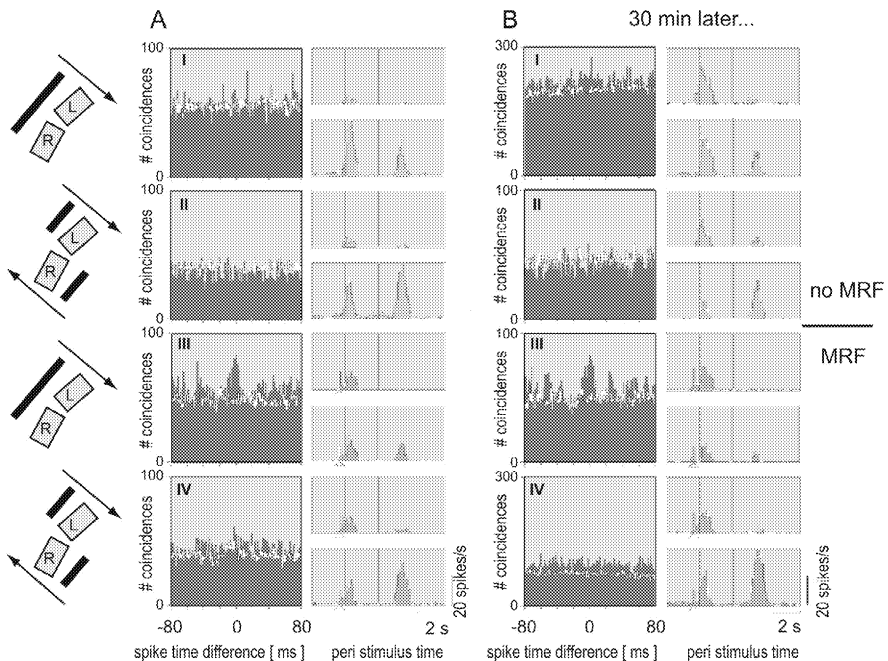
Figure 2. Stimulus-dependence of response synchronisation in primary visual cortex of the cat. Left panel: receptive fields (white boxes with letters) and visual stimuli (black bars, arrows indicate direction of movement). Visual responses were averaged over 10 consecutive repetitions and are presented as peri stimulus time histograms (right half of each column) and cross-coincidence histograms (left half of each column). In the upper half, the reticular formation is stimulated in each trial (arrows indicate artefacts).

above 20 Hz (gamma-frequency range) increased with more central activation which suggests that a functional relation could exist between the occurrence of oscillatory firing patterns and the ability to express strong synchronisation.

The most important observation, however, is the dependence of synchronisation on the global structure or 'Gestalt' of a visual stimulus. This dependence demonstrates that synchronized firing does not only reflect the existence of cortical connections, but can change from moment to moment when a different input pattern contains related or unrelated features. The simplest experimental test for stimulus-dependence of cortical synchronisation in the visual system is illustrated in figure 2. If two groups of neurons in the visual cortex of the cat are co-activated by a single stimulus (1st and 3rd row) they can synchronize (3rd row), if the level or cortical activation is high enough. They never synchronize when they are co-activated by separate stimuli moving in opposite directions (2nd and 4th row), independent of the state. This and similar experiments have been performed in various experimental paradigms (Engel, König, & Singer, 1991; Gray & Singer, 1989; Munk, Roelfsema, König, Engel, & Singer, 1996). A very important result however was that in the awake monkey, neurons in area MT expressed the same kind of dynamical changes in synchronisation patterns (Kreiter & Singer, 1996).

It is much more difficult to investigate neuronal synchronisation with non-invasive methods in humans. A first approach was using visual stimuli like the Kanizsa triangle to test whether high-frequency components (30-60 Hz) of the human EEG would reflect increased synchronisation in response to stimuli that had to be integrated across visual space (Tallon-Baudry, Bertrand, Delpuech, & Pernier, 1996). Because of the poor spatial resolution of the non-invasive EEG recordings, increased strength of oscillatory signals is always confounded with increased synchronisation. However, for synchronisation of mass signals across larger distances like for signals recorded at different surface electrodes, synchronisation of signal components with different frequencies can be investigated by phase locking statistics (Lachaux, Rodriguez, Martinerie, & Varela, 1999). It was the synchronisation of activity in the gamma-frequency range which discriminated between trials in which human observers could perceive or not perceive a blurred face (Rodriguez, E. et al., 1999, see Fig. 3). The dynamic character of cortical synchronisation even over very large cortical distances is particularly evident in the time course of phase-locking. In the first 400 milliseconds after stimulus presentation, synchronisation increases, presumably to integrate the distributed information of the image, the latency being fully compatible with stimulus-induced synchronisation observed in experiments with cats and monkeys (Munk & Neuenschwander, 2000; Rols, Tallon-Baudry, Girard, Bertrand, & Bullier, 2001). While the behavioral response is generated (around 500 ms), synchronisation sharply decreased and recovered around the time of the actual motor response (reaction time being 640 ms and 760 ms for the two conditions). The long-range character of the phase locking indicates that synchronisation of gamma-activity may be viewed as a mechanism that subserves large-scale cognitive integration, and not just local visual-feature binding.

Although most of the research on cortical synchronisation has been carried out in the visual system, there is a considerable number of studies that has investigated integration in other sensory modalities and the motor system. In the motor system highly dynamic synchronisation of oscillatory neuronal activity has been shown, both in monkey (Baker, Spinks, Jackson, &

Lemon, 2001; Murthy & Fetz, 1996) and man (Kilner, Baker, Salenius, Hari, & Lemon, 2000; Kilner et al., 1999), to correlate with the compliance in solving difficult motor tasks. In visual and parietal areas of behaving cats, long-range synchronisation could be shown to increase during epochs of increased attention (Roelfsema, Engel, König, & Singer, 1997). In secondary somatosensory cortex of monkeys, synchronisation between units was decreased when the monkey performed a visual task while somatosensory stimuli were still present to activate neurones (Steinmetz et al., 2000). Intrinsic synchronisation of gamma-frequency oscillations in monkey area V4 has recently been shown to be higher in attended positions of the visual field (Fries, Reynolds, Rorie, & Desimone, 2001), suggesting that response selection may make use of a bias that is at least supported by synchronisation.
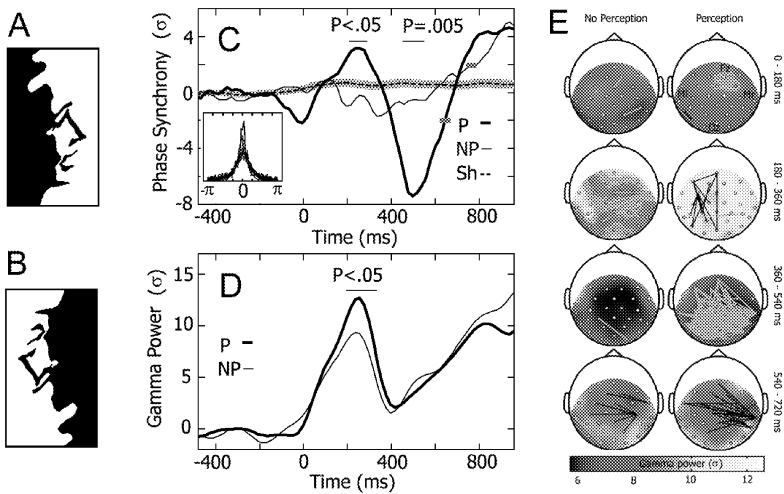
Figure 3. Phase-locking of EEG activity in the gamma-frequency range. **A, B** Visual stimuli used were 'moony faces' which are much more difficult to perceive if presented upside down (**B**). **C** Time course of the phase locking for the trials in which a face was perceived (P) and not perceived (NP). The dashed line and grey shade indicate the distribution phase-locking expected in a random sample. **D** Time course of the strength of gamma-activity that occurred in both conditions. **E** Average scalp distribution of gamma-activity (grey scale) and phase-locking (increases and decreases of synchronisation in black and white lines, respectively, modified from Rodriguez, E. et al., 1999).

A very interesting example of neuronal processes that require dynamic coding is short-term memory (STM). The storage of information in STM is a highly dynamic process because it requires the retention of items and their mutual relations that change from moment to moment. Therefore, the neuronal processes that organize STM need to employ strategies that allow for rapid reorganization of memory contents. This, in turn, depends upon a fundamental capacity of neural systems to preserve the relations among multiple features in a highly dynamic fashion, as the conjunction of the particular sets of features can change from trial to trial, and therefore

cannot be learned in advance. If synchronisation serves to associate the rapidly changing relations, one could expect to see periods of enhanced oscillatory patterning during the memory delay. In human EEG recordings of subjects that performed a visual short-term memory task, an oscillatory network centered on prefrontal and visual areas that could serve the rehearsal of the visual stimuli in memory had been observed (Tallon-Baudry, Bertrand, Peronnet, & Pernier, 1998). A direct proof for neuronal synchronisation as a basis for dynamic coding during short-term memory is still missing.

Mechanisms and Putative Functions of Gamma Oscillations

Thus far, millisecond-precise synchronisation has been described as a physiological correlate of assemblies which could serve as a mechanism for coding and integration of distributed information. But what are the neuronal mechanisms of synchronisation? The fact that stimulation of the reticular formation strengthens cortical synchronisation of *gamma-oscillations* suggests that synchronisation could provide a mechanism of unspecific *attention*, as MRF activation is behaviorally associated with increased vigilance, attention and better behavioral performance. There is growing evidence that the brain systems responsible for vigilance and attention are involved in the generation of fast neuronal oscillations in the cortex. A recent pharmacological investigation has shown that the *cholinergic system* controls the strength of visually induced oscillations. However, this does not mean that oscillations are solely the result of interactions between the basal forebrain and the cortex. Apart from defining a temporal window for synchronisation, oscillations might be directly relevant for *plasticity*.

Ever since electrical brain activity was investigated, signals have been described to contain oscillatory waves that have been classified into numerous different frequency bands (Niedermeyer, 1987). From the very beginning, changes in the frequency distribution of the EEG have been related to changes of the functional state of the brain. The concept of synchronized and de-synchronized EEG activity were based on the following ideas. If huge populations of neurons engage in the same rhythm, their synaptic potentials summate and therefore generate a signal strong enough to be measured on the surface of the brain or scull. Conversely, if input from sensory organs arrived or the subject became mentally involved, then many neurons operate in different modes and at different times and therefore would cause a low amplitude signal of higher frequencies on the surface. This classical observation of a reproducible shift of the dominant frequency was first described for the occipital alpha rhythm (8-13 Hz) that was replaced by the faster and smaller beta (14-30 Hz) waves (Berger, 1929). The term gamma frequency band was introduced to designate frequencies above 30 Hz (Jasper & Andrews, 1938) and originally described as superimposed on the occipital alpha-rhythm.

Shortly after the discovery of brain potentials and their state dependency, the mechanisms responsible for the dramatic changes in the EEG were investigated. Electrical stimulation of the mesencephalic reticular formation (MRF) was shown to cause an arousal reaction accompanied by a reliable increase of the dominant frequency of the EEG in cats (Moruzzi & Magoun, 1949).

An important observation was that the modulatory systems in the brainstem not only regulate wakefulness but also modulate brain performance in the alert state. Stimulating the MRF in awake behaving monkeys that performed a haptic discrimination task, resulted in improved sensorimotor processing as reaction times shortened and error rates decreased (Fuster, 1958, 1962).

Combined studies of EEG and single unit activity in the olfactory system revealed for the first time that defined neuronal circuits involved in sensory processing are responsible for the generation of gamma oscillations (Freeman & Skarda, 1985). In the neocortex, gamma oscillations were discovered in the local field potential of visual areas in anaesthetized cats (Gray & Singer, 1987). During light anaesthesia, responses of cortical neurons to moving visual stimuli were accompanied by a strong periodic modulation of the local field potential (Eckhorn et al., 1988; Gray & Singer, 1989). These gamma-oscillations could be readily detected in multi-unit responses, whereas single unit responses would only participate in about a third of the investigated cells (Eckhorn & Obermueller, 1993; Gray & McCormick, 1996). Oscillations in the gamma-frequency range synchronize across large and remote populations of neurons that respond to the same or a related stimuli (Eckhorn et al., 1988; Engel, König, & Singer, 1991; Gray & Singer, 1989) and can be quickly attenuated if the continuity of stimulus motion is reduced by superposition of a random motion (Kruse & Eckhorn, 1996). In the awake cat the incidence of gamma-frequency oscillations during visual responses is higher (26%) than during anaesthesia (17%) (Gray & Viana, 1997).

In the awake macaque monkey, response- related oscillations have originally been described to occur either in extrastriate areas (Kreiter & Singer, 1996), or with higher frequencies (Eckhorn et al., 1993; Frien, Eckhorn, Bauer, Woelbern, & Kehr, 1994) than described for the cat or in V1 of squirrel monkeys (Livingstone, 1996). It has been shown that gamma oscillations occur in a large proportion (46%) of single cells in V1 of the awake macaque (Friedman-Hill, Maldonado, & Gray, 2000) and structure the responses in many other areas of the neocortex, in the infero-temporal cortex during passive viewing of complex visual objects (Freiwald, Kreiter, & Singer, 1998), in parietal cortex during the preparatory period of a visually guided reaching movement (MacKay & Mendonça, 1995) and in sensorimotor (Murthy & Fetz, 1996) and motor cortex (Sanes & Donoghue, 1993).

Numerous proposals have been made of how gamma oscillations may be generated (Ritz & Sejnowski, 1997; Traub, Whittington, Stanford, & Jefferys, 1996). In many visual cortical neurons, oscillatory modulation of membrane potentials seems to originate from synaptic inputs (Bringuier, Frégnac, Baranyi, Debanne, & Shulz, 1997; Bringuier, Frégnac, Debanne, Shulz, & Baranyi, 1992). This finding is compatible with the observation that some pacemaker cells generate the rhythm by intrinsic properties and entrain the network transsynaptically. In visual cortex of anaesthetized cats, about one third (25:73) of the neurons have been shown to generate oscillations upon progressive depolarization and visual stimulation. These cells were later identified as superficial pyramidal neurons called 'chattering cells' (Gray & McCormick, 1996).

There is accumulating evidence that acetylcholine can induce rhythmic firing in neocortical neurons (Lukatch & MacIver, 1997; McCormick, 1993; Wang, Z. & McCormick,

1993) that may be able to entrain the entire network or at least parts of it. Studies of the temporal structure of neuronal activity in the hippocampus (Buzsaki & Chrobak, 1995) and more recently in-vitro and simulation studies of the neocortex (Whittington, Traub, & Jefferys, 1995) suggest that apart from pacemaker cells networks of connected inhibitory interneurons may also be able to generate oscillations in the gamma-frequency range. It is however not yet clear which of the numerous candidate mechanisms is relevant under realistic conditions of brain function.
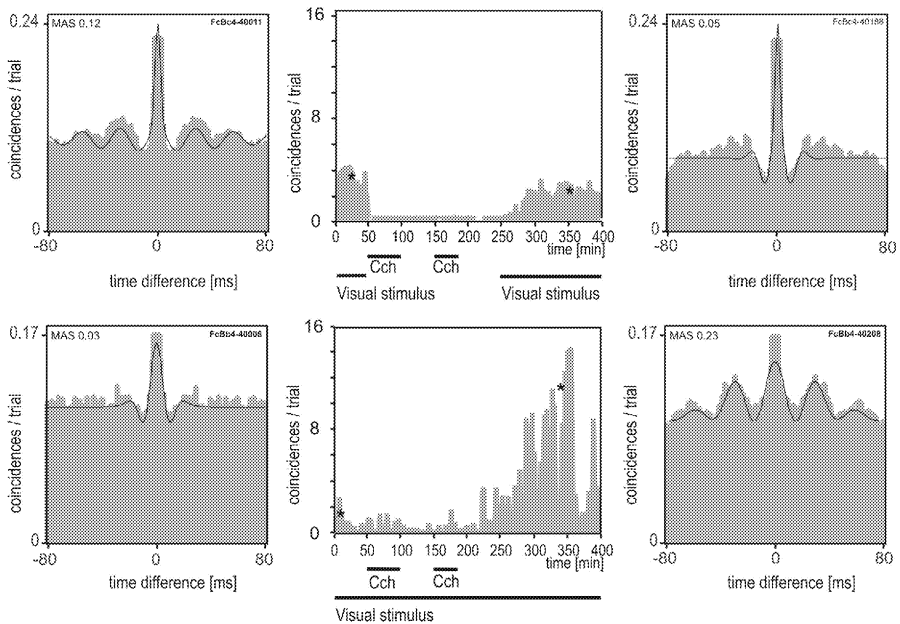
Figure 4. Cholinergic control of visually-induced gamma-oscillations in cat cortex. The temporal fine-structure of visual responses is shown as auto-coincidence histograms (ACH). These histograms provide information about the recurrence of intervals between action potentials that could constitute an oscillation. In the upper row, the left ACH shows a weak gamma-oscillation of 12% modulation (MAS), while the right ACH shows no significant modulation in the gamma-frequency range. In the lower row, the left ACH shows no modulation, while after pairing of a visual stimulus with a cholinergic agonist (Cch) a strong oscillation of 23% modulation was observed. The time courses for oscillation strength shown in the middle column show that cholinergic stimulation without contingent visual stimulation (upper row) did not induce oscillations, while continued visual stimulation caused a strong increase.

More recently we have performed experiments to directly test whether visually-induced gamma-oscillations in the cat are controlled by the cholinergic system. We used micro-iontophoresis to activate or block cholinergic receptors in the visual cortex of the cat directly. The effect of applying cholinergic agonists into the cortex while it responds to visual stimuli is shown

in Fig. 4 (Rodriguez, R., Kallenbach, Singer, & Munk, 2000). If cholinergic receptors are activated while the neurons respond to visual stimuli, gamma-oscillations are induced or strengthened. In complementary experiments we facilitated oscillatory visual responses by stimulation of the MRF and applied antagonists into the cortex (Rodriguez, R., Kallenbach, Singer, & Munk, 2001), which reduced or suppressed gamma-oscillations. The delay with which oscillations could be induced in this pharmacological experiment and the observation that cholinergic stimulation had to be contingent with the visual responses suggests that plastic changes are needed to set up oscillatory firing in cortical circuits.

Another important aspect in the search for the mechanisms of oscillations is to identify the circuits that are involved. The example of the motor cortex is of particular interest, because its main output, the pyramidal tract (PT) to the spinal cord can be manipulated without direct interference with the cortical tissue. With electrical micro-stimulation of the PT it is possible to determine whether PT neurons (PTNs) are part of the circuit that generates beta-frequency (15-30 Hz) oscillations (Jackson, Spinks, Freeman, Wolpert, & Lemon, 2002). If antidromic PT stimulation causes a phase-resetting of the cortical rhythm, then PT neurons are part of the circuit, while no effect of electrical stimulation would support the hypothesis that the generator only imposes the oscillation onto the PT neurons (Fig. 5). As the study shows, PT neurons are part of the circuit, which means that the neurons responsible for long-range interactions are not only passive elements for transmission. This seems to imply that activity patterns on long-range connections can directly influence the oscillatory processes at the origin and target locations of a projection.

Apart from defining a temporal window for synchronisation, oscillations might be directly relevant for plasticity. The repetitive activation of synapses involved in a synchronized oscillation could be responsible for imprinting synchronisation patterns into the cortical circuitry by triggering the cellular mechanisms of synaptic plasticity. If distributed representations employ synchronized activity, all the synapses that receive synchronized inputs are likely to change their transmission characteristics and thus control the composition of a memory trace. This adaptive process has to be restricted to behaviorally important situations, in which learning is required. In behaviorally significant situations, vigilance and attention are increased by modulators like acetylcholine and norepinephrine which are also known to directly facilitate synaptic plasticity (Bröcher, Artola, & Singer, 1992; Rasmusson, 2000) and oscillatory firing patterns in the gamma-frequency range. Neuro-modulators are therefore a factor that can strengthen synchronized neuronal assemblies on the one hand and drive synaptic plasticity in a context dependent manner on the other hand. If millisecond-precise synchronisation of gamma-oscillations provides a mechanism to control attention and if gamma-oscillations are controlled by the same neuromodulators (like acetylcholine) which are a prerequisite for learning and memory, then gamma-oscillations could be an important link between attention and memory formation. Because the cortex maintains a massive reciprocal connection to the basal forebrain, which is the main source of ACh in the cortex (Everitt & Robbins, 1997), the processes in the cortex could signal back to the basal forebrain when a cortical representation needs to be adapted or consolidated.

A

B

PT Stimulus
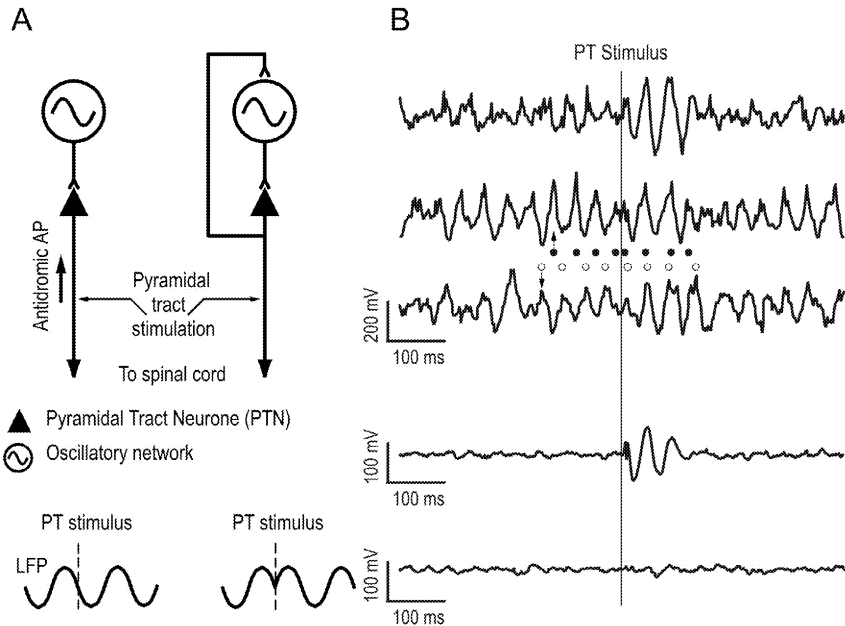
Figure 5. Phase-resetting of cortical oscillations in motor cortex help identifying the generating circuitry. **(A)** Schematic diagram of mechanisms for oscillatory locking in motor cortex. Either the rhythm is generated by circuits independent of PTN activity, which drive the PTNs into phase with the rhythm (left), or the PTN activity is itself involved in the generation (right). These two possibilities are distinguished using PT stimulation to set up antidromic action potentials (APs) in PTNs. If PTNs are not involved in generating the rhythm then the stimulus should have no effect on the phase of the oscillation (lower left). If PTNs lie within the rhythm-generating networks, then stimulation may reset the phase of on-going rhythms (lower right). **(B)** Stimulus-triggered averages of local field potentials (LFP). The upper three curves show sample traces aligned to the PT stimulus, recorded during three different trials. Single stimuli were delivered to the PT ipsilateral to the recording site during the hold period. Note that a complex wave was evoked by the PT shock, irrespective of whether there was on-going oscillatory activity before the stimulus (2nd and 3rd trace) or not (1st trace). Resetting of the ongoing activity is demonstrated by rhythmic activity in the 2nd and 3rd trace, being out of phase before the stimulus, but in phase after it. 4th trace: average of 110 trials with phase locking of LFP for 100–150 ms after the stimulus. 5th trace: stimulus-triggered average for contralateral PT stimulation (150 mA, 110 trials) showed no effect. Modified with permission from Jackson et al., 2002.

Adaptivity versus Consolidation

Neuronal processes underlying perception and behavior have to adapt constantly to cope with the ever changing environment. The time scale for neuronal adaptivity ranges from fractions of a

second during which changing sensory input patterns need to be integrated up to lifelong changes in behavior that for example account for the changing physical properties of the organism. Although a high level of adaptivity is generally desirable, continuity and constancy of some neuronal operations is needed to ensure reliability and compatibility of processing. To provide this reliability, the mechanisms of sensory input need to be stabilized as much as possible and a certain fraction of the perceptual and behavioral experiences need to be stored in memory. For the latter, information encoded by transient neuronal activity needs to be passed to more stable forms of neuronal representations that may not change after they have been consolidated. Certain basic elements of the underlying neuronal mechanisms like transient changes of neuronal discharge or long-lasting changes of synaptic transmission as the basis for memory have been identified. Between the two however, mechanisms have to exist that determine when and what kind of information is stored. Because neuronal assemblies are self-organizing processes that can be influenced both by local and global processes in the cortex, they appear to provide a solution for finding a balance between adaptivity and consolidation.

Synchronisation patterns that can change from moment to moment constitute a type of representation that can adapt to practically any constellation of features. This flexibility in coding is required for coping with the combinatorial complexity to begin with, but is at least as important for the search of new constellations and learning. An existing set of hardwired detectors would simply not be able to discover new feature combinations, because none of the integrating higher-level cells would respond. A set of synchronized groups of neurons would be able to represent a new constellation, without identifying its novelty. But due to the massive divergence of cortico-cortical connections, the synchronized activity will reach a large number of other synaptically connected neurons. If the respective pre- and postsynaptic neurons are synchronously activated in the presence of plasticity-enabling neuromodulators, these connections will increase their efficacy and thus learn to respond to the new constellation. This process does not yet include the detection of novelty, which might be contributed by feedback connections (Bullier, 2001). They could provide internally generated hypotheses which could be back projected onto the representation of the input (Mumford, 1992), compared to the new activity patterns (Siegel, M., Körding, & König, 2000; von Stein, Chiang, & König, 2000) and the respective difference or error signals (Ahissar, E., 1998; Ahissar, E., Haidarliu, & Zacksenhouse, 1997) used to activate mechanisms of adaptation.

Because of the huge number of feature combinations occurring in real life, the generation of new units, perhaps of smart neurons by synchronized activity will require a large number of cells. This might go beyond the capacity of primary sensory areas and could be incompatible with their function to provide a stable and reliable representation of the actual input patterns. The response properties of neurons in subsequent areas in the hierarchy of for example the visual system become more and more complex with increasing distance from the primary representation. Psychophysical studies suggest that learning processes may actually start in higher areas (see reverse-hierarchy model of perceptual learning (Ahissar, M. & Hochstein, 1997), because simpler and more basic aspects of a task improve before the more specific and more difficult aspects can be trained, at least if the latter require a modification of the more detailed peripheral representations. This does however not mean that primary areas are not capable to express changes in

response to perceptual learning as several studies in the visual (Gilbert, Sigman, & Crist, 2001; Schoups, Vogels, Qian, & Orban, 2001), auditory (Recanzone, Schreiner, & Merzenich, 1993) and somatosensory (Recanzone, Merzenich, Jenkins, Grajski, & Dinse, 1992; Wang, X., Merzenich, Sameshima, & Jenkins, 1995) systems have demonstrated (see also the chapter by Röder and Rösler in this volume). As can be expected from the reverse-hierarchy model, changes in early areas are more subtle and occur only for high performance in difficult tasks.

If different areas of the cortex are differently involved in learning processes, areas with relatively stable response properties could generate neuronal assemblies that are of shorter lifetime and stability so that they can quickly regroup and test out the different feature relations. In contrast, areas on the next level in which cells depend on the input cooperativity of the previous stage and thus get activated less frequently, the thresholds for plasticity could be lower or be more readily reduced by modulatory inputs. If feedback signals that provide information about expectation and context support the storage of new patterns, they could be stored by dedicating smart units or the formation of more persistent assemblies. A final consolidation would presumably require processes of competition for the finite neuronal circuitry. Much research on memory consolidation has revealed that sleep seems to be important for behavioral improvement in learning (Buzsaki, 1998; Stickgold, 1998), see however Siegel, J. M., (2001). During sleep, assemblies may be reactivated that rework and fine-tune the synaptic pathways that had been modified the day before.

Conclusion

The concept of neuronal assemblies based on millisecond-precise synchronisation seems to be compatible with the following experimental observations: information about the global structure ('Gestalt') of sensory stimuli is represented by dynamic grouping of neuronal population responses which is expressed in changing patterns of synchronisation (stimulus-dependence). Cortical processing based on synchronisation is modulated by "unspecific" cortical activation and attention, which could either be induced by experimental manipulation of the reticular formation or by cholinergic stimulation of the cortical circuits (state-dependence). Synchronisation patterns can be modified and stabilized through repeated stimulus presentations during activated states (adaptation and consolidation of synchronisation). The advantage of using a distributed code is to be able to store and recall large amounts of complex information in an efficient way. When a representation is reactivated by the same or a similar input pattern, identical features will activate the same neuronal machinery as in the first place. The comparison with stored information is therefore as fast and efficient as the original encoding process. When new synchronisation patterns emerge, the input composition of subsequent processing stages will be modified. Downstream neurons will therefore express altered response properties. When new response properties emerge, the balance of adaptivity and consolidation is shifted towards consolidation. Conversely, a high degree of adaptivity is maintained if the representation of feature combinations is kept flexible through reversible synchronisation of large neuronal populations. Regulating this balance needs to incorporate both local and global factors. Neuronal assemblies could be

instrumental for this regulation, because assemblies have access to local information processing and depending on their size and distributivity can be part of global processes. Future experiments will have to show whether synchronisation is indeed the physiological correlate of neuronal assemblies and how assemblies can shape the functional properties of the cortex.

12

The Principle of Inhibition

Dale Dagenbach and Aycia K. Kubat-Silman

The appeal of invoking inhibitory processes to explain successful cognitive and behavioral performance in a variety of domains becomes readily apparent when one considers a situation such as the following: Subjects are presented with multiple stimuli, and are required to respond to one of them while not responding to the others. Furthermore, at least one of the unselected stimuli has a strong automatic response associated with it or has recently been a target item itself. The ability to specifically inhibit the processing of the nontarget items in that context, or at least their access to response mechanisms, would seemingly allow for a degree of flexibility in behavioral and cognitive control that might otherwise be difficult, although not impossible, to achieve.

Appealing to inhibition to resolve such conflict is not a new theoretical insight: Inhibitory mechanisms were invoked to explain how we are sometimes able to exert voluntary control over involuntary behaviors well over a century ago (Sechenov, 1965), and early accounts of selective attention were often couched in terms of inhibition as well as facilitation (Pillsbury, 1908). However, systematic research into the actual contributions of inhibitory processes was relatively sparse for many decades after that.

That clearly is no longer the case. In recent years, the possible contributions of inhibitory processes to cognitive and behavioral performance have received extensive scrutiny. This interest was sparked in part by demonstrations of the apparent role of inhibition in a number of seemingly tractable experimental paradigms (Dagenbach & Carr, 1994; Dempster & Brainerd, 1995), the development of a theoretical perspective in which the development and decline of inhibition provided a basis for explaining important aspects of cognitive development (Dempster, 1991, 1992; Harnisfeger & Bjorklund, 1993; Hasher & Zacks, 1988), and the linkage of inhibition to specific neural regions (Fuster, 1998). Not surprisingly, the extensive ensuing research has

changed our understanding of the role of inhibition. In some cases, this research has borne out the importance of inhibitory processes, but in other cases the role of inhibitory processes is either in doubt or less straightforward than it once seemed. Thus, this seems to be a good point in time to take stock of the role of inhibitory processes in memory.

What Constitutes Inhibition?

One fundamental challenge is determining whether *inhibition* is really necessary to explain the observed data. Inhibition is frequently invoked to explain successful performance in the face of potential interference. Thus, successfully naming the color of ink and ignoring the word name in the color word Stroop task might be explained in terms of inhibiting the reading pathway (MacLeod, 1991). Correspondingly, deficits in inhibition may be invoked to explain observed interference such as the greater susceptibility of older adults to misremember an erroneous interpretation of a story that was set up by the initial sentences but disconfirmed in subsequent text (Hartman & Hasher, 1991). However, as noted below, alternative mechanisms to inhibition for overcoming interference must be considered, so observing either successful or unsuccessful resolution of interference does not by itself constitute evidence for inhibition. A stronger case would seem to exist when inhibition is invoked to explain slower or less accurate processing of information subsequent to its occurrence in a setting in which it had the potential to cause interference.

The negative priming paradigm provides a good illustration of this. In a typical negative priming experiment, a target and distractor appear simultaneously, either adjacent to or overlapping with each other. The target is generally designated by some salient quality such as color. Effective responding on a given trial requires processing the target, and not the distractor item. A hint to how this is achieved is provided by trials in which the ignored distractor becomes the target item on the subsequent trial. In such cases, responding is actually slower -- hence the term negative priming. One interpretation of this effect invokes inhibition, assuming that the slowed responding reflects the lingering consequences of active suppression of the item's representation from the previous trial on which it was the distractor (Tipper, 1985).

Although the negative priming paradigm may provide an example of inhibition following an item's occurrence in a situation in which it had the potential to cause interference, this interpretation has been contested. An alternative episodic retrieval account of negative priming has been proposed that suggests it stems from the retrieval of a "don't respond" tag attached that is attached to the distractor on trial *n*. That tag is automatically retrieved when the distractor is the target item on trial *n + 1*, and results in the observed slower responding (Neill, Terry, & Valdes, 1994). One might conceive of this as a form of representational inhibition (Henik & Carr, in press), but it clearly is quite removed from the simple suppression account of inhibition suggested by many cognitive models.

Most cognitive models that invoke inhibition implicitly suggest that it corresponds to a state of active neural suppression that might be produced by an inhibitory neurotransmitter such as GABA, but the range of situations in which inhibition might be observed is actually quite complex, and the mechanisms that might produce inhibition, or inhibition-like patterns in data, are diverse (Anderson & Bjork, 1994; Anderson & Neely, 1996; Taylor & Klein, 1994). It may be important to distinguish between lateral inhibition, wherein units within a single system are mutually inhibitory, and various types of inhibition between different systems. Inhibition between systems may further vary as a function of whether it is mutual or asymmetric, and as a function of whether it is absolute or graded. Apparent inhibition might be mediated by one process using all available resources (attention) at a given time, rendering the other process unable to function, or by reduced activation of or within pathways (Taylor & Klein, 1994). Given these many possible sources of apparent inhibition, only some of which involve active suppression of the type that a simple inhibitory account might imply, the ensuing confusion over the extent to which inhibitory processes are really needed to explain the observed data is understandable. In the remainder of this chapter, we will consider various demonstrations of inhibition in working and long term memory, and attempt to evaluate them in terms of the issues noted above.

Generalized Inhibitory Theories

As noted earlier, one reason for the current interest in inhibitory processes was the possibility that they would provide a parsimonious account of a wide range of phenomena. A number of seemingly disparate phenomena could be explained by associating the efficacy of inhibition with frontal lobe functioning (Dempster, 1991, 1992). The frontal lobes are the last area of the brain to develop in humans, with a pronounced increase in volume from birth to 2 years and slower increases through the teenage years. Myelinisation of the frontal cortex also proceeds at a slower pace, continuing until the early teenage years. Conversely, the frontal lobes also are among the first brain areas to decline (Haug & Eggers, 1991). This decline occurs in terms of volume, which seems to seems to reflect a decline in cellular volume rather than a loss of neurons per se. The decreased cellular volume may stem from a decrease in the number of synapses, a decline in dendritic processes, or a decline in mechanisms associated with the synthesis and transmission of neurotransmitters. The frontal lobes also show a greater occurrence of senile plaques. Finally, some measures of cerebral blood flow suggest that a disproportional decline occurs for the frontal cortex, and in particular the prefrontal cortex, in older adults (Gur, Gur, Orbist, Skolnick, & Reivich, 1987).

This pattern of frontal cortex development corresponds roughly with both the emergence and decline of behavioral competencies that may be related to the efficacy of inhibition. For example, in studies of reaching behavior by infants, the A, not B reaching error made by infants has been attributed to a lack of developed inhibitory processes (Diamond, Cruttendon, & Neiderman, 1994). In the A, not B task, a toy is placed in one well in plain sight of the infant and then covered, and the infant is able to successfully retrieve it. If the location of the toy is then

switched to a different well, once again in plain sight of the infant before it is ultimately covered, infants ranging in age from approximately 7 to 12 months will tend to persist in reaching for the toy at the earlier location. This is true even though other measures such as visual habituation suggest that the infant knows the toy is now in the other location. The A, not B, error is even obtained when the covers used are transparent and toy is clearly visible. The ultimate mastery of this task may reflect maturation of frontal cortex, with one resulting competency being inhibitory control over behavior.

At the other end of the developmental spectrum, cognitive aging effects have been attributed specifically to decline of the frontal lobes (West, 1996), and some specific deficits have been linked to a decline in the efficiency of inhibitory processes. For example, declines in working memory associated with aging have been linked to failures of inhibition. This was initially suggested by research indicating that older adults were more likely to misremember an inference induced by initial text that was nullified by subsequent information in the passage (Hasher & Zacks, 1988). Subsequent research showed apparent inhibitory deficits in older adults in negative identity priming (Hasher, Stoltzfus, Zacks, & Rypma, 1991; McDowd & Oseas-Kreger, 1991), a stop signal task (Kramer, Humphreys, Larish, Logan, & Strayer, 1994), Stroop tasks (Houx, Jolles, & Vreeling, 1993; Salthouse & Meinze, 1995), directed ignoring (Zacks & Hasher, 1994), and language processing (Hartman & Hasher, 1991).

The evidence reviewed thus far seems to suggest that the efficacy of inhibitory processes improves during early development, and then begins to decline with aging, and that these changes may be related to changes in frontal cortex functioning. Converging evidence comes from consideration of the deficits shown by individuals with frontal lobe lesions: While focal lesions of prefrontal cortex can give rise to a variety of impairments of attention, memory, and planning (Duncan, 1995), among the hallmark symptoms are perseveration and heightened susceptibility to distraction. Perseveration is manifested in sustained responses toward prepotent stimuli even when that response is no longer appropriate, such as when the categorization rule is changed in the Wisconsin Card Sort Task. Susceptibility to distraction is demonstrated when task-irrelevant stimuli capture behavior (Knight & Grabowecky, 1995). Thus, it is possible to view some of the more profound impairments from frontal lobe lesions as a consequence of impaired inhibition, although, as noted below, other accounts of this pattern need to be considered.

Problems for Generalized Inhibitory Accounts

The generalized inhibitory account described above is appealing because of its potential to explain a variety of findings, but it is not without problems. One potential problem is that many of the findings presumed to reflect inhibitory processes also can be explained without recourse to inhibition. The existence of an inhibitory module in prefrontal cortex can be argued against on this basis. The resolution of interference in the Stroop task, Wisconsin Card Sort Task, a go-no go task, the antisaccade task, and the A, not B task has been demonstrated in simulations that use no specific inhibitory connections (Kimberg & Farah, 2000). Instead, response activation is determined by working memory activation, priming activation, baseline activation, and noise activation. It is primarily the degree of activation in working memory that permits resolution of

the interference, and damage to working memory connections in the model produces the same patterns of impairments as a presumed lack of inhibition might be expected to produce in patients with prefrontal cortex damage. According to this account, damage to working memory per se, rather than damage to an inhibitory module, underlies the various deficits observed in patients with prefrontal damage. Presumably, the developmental changes that others have explained by invoking the rise and decline of inhibitory functions also would stem from changes in working memory according to this view.

Another potential problem for a generalized inhibition account is the apparent lack of correlation between purported measures of inhibition. For example, correlations between performance on the Wisconsin Card Sort Task, the stop–signal paradigm, negative priming, and a flanker test of selective attention examined in one study were weak and more consistent with the existence of a number of discrete inhibitory processes rather than an overall inhibitory mechanism (McDowd & Oseas-Kreger, 1991). While a generalized inhibition account does not necessarily have to predict correlation between all measures of inhibition in all domains, it would seem that it should at least provide a systematic basis of accounting for where such correlations should be observed.

Still more problems for a generalized inhibitory account arise from challenges to some of the specific supporting findings. As reviewed earlier, part of the evidence for a failure of inhibitory processes in older adults is based on their failure to show negative priming effects (Hasher, Stoltzfus, Zacks, & Rypma, 1991; McDowd & Oseas-Kreger, 1991; Stoltzfus, Hasher, Zacks, Ulivi, & Goldstein, 1993; Tipper, 1991). However, a number of studies have failed to observe age differences in negative priming (Kramer, Humphreys, Larish, Logan, & Strayer, 1994; Schooler, Neumann, Caplan, & Roberts, 1997; Sullivan & Faust, 1993; Grant & Dagenbach, 2000). One attempt to resolve these contradictory findings suggests that whether age differences are observed might be a function of whether negative priming effects are being driven by inhibitory attentional processes or episodic retrieval, with older adults showing negative priming when episodic retrieval processes were used (Kane, May, Hasher, Rahhal, & Stoltzfus, 1997). In those studies, the probability of episodic retrieval occurring was manipulated by degrading probe displays, varying the duration of prime and probe trials, and occasionally repeating target stimuli. College students showed negative priming under conditions that would foster either episodic retrieval or attentional inhibition, while older adults showed negative priming only under the episodic retrieval conditions. But some studies that meet the criteria for conditions associated with negative priming stemming from attentional inhibition still find evidence for intact negative priming in older adults (Grant & Dagenbach, 2000).

Finally, the search for the neural correlates of an inhibitory module has been less than completely satisfactory. While some studies have found results associating inhibition with specific prefrontal regions (Jonides, Smith, Marshuetz, Koeppe, & Reuter-Lorenz, 1998; Jonides et al., 2000), other studies have not (Bunge, Ochsner, Desmond, Glover, & Gabrielli, 2001), and there is support for an alternative view of the functions of prefrontal cortex that allows for control without an inhibitory module (Miller & Cohen, 2001). This evidence is reviewed in more detail below.

Although the evidence for some form of generalized inhibitory model, at least in the form of a special inhibitory module that enables inhibition across a range of behaviors and processes, has been challenged, that does not imply that there is no role for inhibition. For example, there is clear neurophysiological evidence that suppression of reflexive saccades in the antisaccade task does involve inhibition acting through the substantia nigra, although simulation results are consistent with the notion that the impaired control of saccades observed in prefrontal patients stems from impairments of working memory rather than a disruption of that inhibitory mechanism (Kimberg & Farah, 2000). Other possible specific instances of inhibition in working memory and long term memory are reviewed and evaluated below.

Inhibition and Working Memory

It has been suggested that inhibition acts as a gate-keeper, controlling access to working memory, deleting information from it, and providing restraint by preventing prepotent stimuli from seizing control of thought and action (Hasher & Zacks, 1988; Hasher, Zacks, & May, 1999). This process is assumed to be impaired in older adults, rendering them more susceptible to interference in a variety of situations. Although the variability in negative priming results with older adults noted earlier may be problematic for this account, along with the apparent lack of correlation between performance on negative priming and working memory (Earles et al., 1997; Grant & Dagenbach, 2000), considerable evidence consistent with an inhibitory deficit related to working memory has been amassed outside of the negative priming paradigm. For example, one study had subjects generate word endings for sentences. After each word was generated, a target word appeared that either matched the generated ending or was a plausible, but less probable ending. In a subsequent implicit memory test, subjects were required to complete sentences with the first word that came to mind. Younger adults completed significantly more of these with the target words than the generated but disconfirmed items, whereas older adults were equally likely to complete the sentences with disconfirmed items (Hartman & Hasher, 1991). Older adults also tend to erroneously remember a greater proportion of incorrect endings to passages set up by a garden path structure that encourages an initial misinterpretation before it is resolved (Hasher & Zacks, 1988), and are less successful in deleting information from memory following directed forgetting instructions (Zacks, Radvansky, & Hasher, 1996). Older adults also seem more susceptible to interference effects in a variety of classic learning and memory paradigms. This includes proactive interference, wherein learning A-B and then A-C associations results in poorer retrieval when A serves as a retrieval cue compared to a condition where there is no overlap of cues, and the fan effect wherein retrieval time and accuracy are hindered as a function of the number of items associated with each other. Older adults show larger fan effects (Radvansky, Zacks, & Hasher, 1996), and more proactive interference (Kane & Hasher, 1995). Moreover, it has been argued that certain aspects of these data can only be accommodated by inhibition. For example, in studies looking at the effects of circadian rhythms on inhibitory control, younger adults show below baseline priming for disconfirmed items in a sentence processing task (Hasher, Zacks, & May, 1999).

The Inhibition-Resource Model

An alternative to the gatekeeper view of inhibition and working memory is the resource-inhibition model (Engle, Conway, Tuholski, & Shishler, 1995). According to this model, a specialized inhibitory process does not control the contents of working memory, but rather it is the ability to control attention in working memory that underlies the ability to suppress goal-irrelevant information. The inhibition-resource theory gains support from individual differences studies comparing people with large working memory capacity, "high spans", to those with smaller working memory capacity, "low spans", on tasks that might require inhibition. For example, on a proactive interference task, high and low span participants studied and recalled three lists of 10 words each, with all words coming from the same semantic category (e.g., animals). Typically on this type of task, proactive interference is observed across lists, with the number of words recalled decreasing because of interference from words on the earlier lists. When high and low span participants were compared on this task, they demonstrated equivalent recall performance on the first list but the low span participants subsequently showed more proactive interference effects than did high span participants. Furthermore, this difference in susceptibility to interference seems to be related to a difference in controlled attention: When participants were given a secondary task that would demand attention (finger-tapping) to perform simultaneously at either study or recall, the difference between the two groups disappeared. High span participants performed the same as the low span participants without a secondary task, suggesting that working memory capacity is related to the ability to suppress information (Kane & Engle, 2000).

Attention, Inhibition, and Working Memory

The two inhibition accounts presented thus far differ in their description of how inhibition operates in working memory. One view suggests that inhibition controls access to working memory, while research on individual differences in working memory capacity suggests that controlled attention and inhibition are intrinsically linked. Still another view comes from studies investigating how selective attention acts to ensure goal-directed behavior (Lavie, 2000). This account proposes that there are two mechanisms for attentional control, a passive one that excludes irrelevant information from perception, and an active one that is used when irrelevant information can not be excluded from perception and must be suppressed from working memory. When there is a high load in the perception of relevant stimuli, there is reduced perception of the distractor stimuli because there is insufficient working memory capacity to process them all. In contrast, when there is a low load in the perception of relevant stimuli, both the relevant and irrelevant information gain access to working memory and active suppression is needed to reject the irrelevant information.

In one test of this dual-inhibition theory, a selective attention task was interleaved with a working memory task. First, the participant was presented a memory set (digits) to remember. To manipulate the working memory load, the memory set load was either low (1 digit) or high (six digits). After the memory set, the selective attention task was presented. Participants were asked to make a speeded discrimination judgment about a target letter accompanied by a second

distractor letter. Finally, a single memory probe appeared and participants had to indicate whether it had been present in the memory set. When there was a high working memory load, there was a greater effect of the distractor in the selective attention task than when there was a low working memory load, suggesting that capacity used for the larger memory set was not available for efficient suppression of the irrelevant information in the selective attention task.

Backward Inhibition in Working Memory

Other research suggesting a compelling role for inhibition in working memory has come from studies of backward inhibition in task-switching (Mayr & Keele, 2000). In a task-switching paradigm, subjects alternate performing two or more tasks, and a typical finding is that there is some cost associated with switching that is reflected in increased response times, especially just after the switch. Successful cognitive control in this situation may in part involve the suppression of information at the level of the abstract task-set. The task-set representation is the assemblage of attentional, perceptual, and mnemonic processes relevant for a goal-directed behavior.

Evidence for inhibition at the level of the abstract task-set during switches from one task to another is based on the following assumption: If inhibition is involved in the transition from one task to another, there should be larger switch costs upon returning to a task that has been recently abandoned compared to one abandoned less recently. The additional switch costs would reflect the lingering inhibition applied to the task-set representation. In studies bearing on this, subjects were required to switch between perceptual tasks. Subjects observed displays containing a grid with four objects that differed from each other in shape, color, size, and movement. Each of these dimensions had a standard and a discrepant value - for example, a stationary stimulus might be the standard value for the movement dimension, and a moving one the discrepant value. The subjects' task was to indicate the location of the stimulus with the discrepant value on the dimension cued prior to each trial. The relevant dimension changed with each trial, providing the task-switching component. Thus, subjects might be required to locate the stimulus with the deviant shape on one trial, the deviant color on the next trial, the deviant motion on the next trial, etc...

The basic finding observed consistent with inhibition was slower responding to the second trial on a given dimension (A) in a sequence of trials involving dimensions A, B, A compared to type C in a sequence of trials involving dimensions A, B, and C. For example, responding was slower in the second shape trial in a shape, movement, shape sequence, compared to responding to orientation in a shape, movement, orientation sequence. This slower responding was attributed to the lingering effects of the inhibition applied to the task-set representation upon the initial switch away from it. Further experiments suggested that the observed backward inhibition was not due to some form of negative priming, and that it was specifically due to an executive control process since it only occurred following top-down selection of task set. Moreover, it occurred even when subjects had sufficient time to reconfigure task settings. This backward inhibition may be a means of resolving a stability-flexibility paradox, wherein representations that are strong enough to resist incompatible actions are needed, but these same representations also need to be abandoned when the goal shifts.

While the observed backward inhibition could in principle be generated by either high level control or by some form of local triggering conditions, the failure to eliminate backward inhibition even with ample time to prepare for the next task set argues against the high level control account. The local triggering conditions might be a form of lateral inhibition that results indirectly from activation of the subsequent relevant task set. Consistent with that possibility, backward inhibition was stronger when the lag-1 trial contained a deviant distractor associated with the task set abandoned in the previous trial and which reappeared in the lag 2 trial.

Inhibition and Long Term Memory

Inhibition in Episodic Memory

A striking illustration of the possible use of inhibition to resolve potential interference in long-term memory comes from explorations of retrieval-induced forgetting (Anderson, Bjork, & Bjork, 1994; Anderson & Spellman, 1995). In these studies, subjects initially study exemplars from several semantic categories. They subsequently practice retrieval repeatedly for a subset of the exemplars from half of the categories based on category - exemplar stem cues (for example, fruit - or____). This is followed by a final recall test in which the category names are presented and subjects are asked to recall all the exemplars associated with that category in the experiment. As might be expected, recall is high for the practiced exemplars. More interestingly, recall is impaired for unpracticed members of the categories that received retrieval practice compared to recall for exemplars from categories that did not receive recall practice.

A variety of arguments have been presented in support of an inhibition-based account of that impaired recall. The inhibition-based account assumes that unpracticed members of a practiced category are likely to produce interference during the retrieval practice phase. This interference will be more pronounced for high-frequency exemplars, and is resolved by active suppression of them, generating the subsequent recall deficit. In keeping with this interpretation, impaired recall is observed for high-frequency unpracticed exemplars from practiced categories, but not for low frequency exemplars (Anderson, Bjork, & Bjork, 1994). A classic interference based explanation such as occlusion would not predict this distinction.

Based on results obtained using an independent probe method, it has been argued that the suppression that occurs during retrieval practice applies to the unpracticed exemplar's representation rather than to its association with the category (Anderson & Spellman, 1995). Categories with exemplars were learned, followed by retrieval practice on a subset of those categories. The retrieval practice involved only half of the exemplars from the categories receiving practice. The critical manipulation involved having exemplars in the unpracticed categories that had strong pre-experimental associations to the practiced categories. For example, one category might be RED, with practiced and unpracticed exemplars in it – light, tomato, blood, etc... Another category might receive no retrieval practice, but one of its exemplars might be associated to the word RED – for example, FOOD - bread, chicken, radish, etc... Radish is

associated with the category RED as well, and might generate interference during retrieval practice of that category's exemplars. Thus, the inhibition account predicts that it might be subject to active suppression during retrieval practice for the category RED, resulting in impaired retrieval of it when subjects are recalling the FOOD exemplars. Interference accounts assuming that the effects of retrieval practice are a result of changing the properties of associative links would not predict an effect on radish when tested using the FOOD link. Significant cross-category inhibition was observed (impairment of radish as a FOOD exemplar), in keeping with the assumption that suppression was directed at the item's representation.

Findings of retrieval induced forgetting consistent with this inhibitory account have now been reported in a variety of memory situations, including memory for visual-spatial information (Ciranni & Shimamura, 1999), eyewitness testimony (Shaw, Bjork, & Handal, 1995), and fan effects in the retrieval of propositional information (Anderson & Bell, 2001). These studies of retrieval inhibition suggest that retrieval may be thought of as conceptually focused selective attention, facing some of the same computational obstacles that selective attention must overcome, although the object of selection is a conceptual code rather than a perceptual code, and that some of the same mechanisms that accomplish selection of perceptual information may apply to selection of conceptual information as well (Anderson & Neely, 1996).

Another possible demonstration of inhibition comes from an examination of executive control and memory retrieval in a different sort of paradigm that may provide an experimental model of repression (Anderson & Green, 2001). In these studies, subjects first learn a set of word pairs. Subsequently, they are asked to learn to respond to some by producing the second word when the first appears, and not respond to others in a variant of a go-no go paradigm. Following extensive practice in responding to the "think" and "no-think" trials, recall of the no-think items is impaired. More interestingly, cued-recall also is impaired even when an independent cue is used. Thus, subjects might study ordeal-roach, and then receive a retrieval cue for roach such as insect r____. Observing impaired retrieval under these conditions seems less explicable in terms of some kind of blocking or interference account, and more consistent with the operation of an inhibitory process.

Inhibition in Semantic Memory

A role for inhibition in retrieving information from semantic memory when accessing semantic codes is difficult also has been proposed. The evidence for this account was first developed in studies of masked semantic priming that examined priming effects under various thresholds (Dagenbach, Carr, & Wilhelmson, 1989). Two thresholds were initially determined for each subject: One was a detection threshold based on presence-absence judgments, while the second was one of three informed-choice thresholds that varied between subjects. The critical result came from subjects whose informed-choice judgment required making decisions about the semantic content of the masked word – was the word presented related to *bird* or *lamp*? In a subsequent series of lexical decision trials with primes presented at the detection threshold, these subjects were significantly slower to respond on trials in which the prime was semantically related to the target. It was suggested that the observed inhibition might be a consequence of a failed semantic

retrieval attempt that resulted from a carryover of the strategy of trying to extract semantic information from the masked prime learned during the threshold-setting procedure.

In order to test this idea in a more tractable paradigm that was less subject to the vagaries of masked priming, further work looked at the consequences of failed semantic retrieval using a vocabulary word acquisition paradigm (Dagenbach, Carr, & Barnhardt, 1990). Subjects initially learned a relatively large set of real, but obscure, words and their definitions – *accipiter: a hawk*, with just enough study time so that successful recall of the meaning of the word was possible for some, but not all, of the items. The newly learned vocabulary words then served as primes in a lexical decision task. Following the lexical decision task, recall and then recognition tests for the meanings of the new vocabulary words were given. Analysis of the lexical decision data was conditionalized on the final recall performance, resulting in conditions with related and recalled, related and unrecalled, unrelated and recalled, and unrelated and unrecalled primes. Significant facilitation was observed in the related and recalled condition. More importantly, significant inhibition was observed in the related and unrecalled condition, consistent with the notion that failed attempts to retrieve semantic information might be associated with interference.

Masked priming effects from repetition and semantic primes were then compared in an attempt to address the functional properties of the previously observed inhibition (Carr & Dagenbach, 1990). The inhibition in the preceding experiments might have been due to some general refractory period in memory stemming from an unsuccessful search in a semantic neighborhood, impairing further searches in that same neighborhood. Alternatively, it might have reflected the operation of center-surround attentional mechanism used to aid in the access of weakly activated codes surrounded by codes with higher activation. If the former were true, one might predict inhibition for the object of the failed retrieval attempt – the prime itself, while the center-surround theory would predict either facilitation or at least a lack of inhibition for the prime. Two experiments were performed to address this question. In a baseline experiment, masked repetition and semantic priming in lexical decision were compared following threshold setting using detection judgments, and approximately equal amounts of facilitation were observed. In a second lexical decision experiment, a threshold was set using semantic similarity judgments. After this, masked repetition and semantic primes were presented at an estimated detection threshold using a prime-mask SOA equal to 70% of the observed semantic threshold. The key finding was that repetition priming yielded significant facilitation, while semantic priming yielded inhibition that was significantly less than the facilitation observed in the first experiment. This pattern was consistent with the predictions of center-surround theory.

The operation of the proposed center-surround mechanisms also has been examined in studies using an artificial semantic memory paradigm (Carr et al., 1994). In these studies, subjects made speeded classification judgments for novel visual stimuli that were arbitrarily assigned to the categories "fleps" and "gleps." Subjects initially classified five fleps and five gleps in 10 blocks of 100 trials in one session, followed by 10 more blocks of 100 trials on a subsequent day. By the end of the second session, subjects were quite adept at this classification task. In the third session, primes were added to the procedure using the familiar fleps and gleps. The initial priming session used a short prime-target SOA (150 ms) and high probability of prime-target relatedness (fleps priming fleps, and gleps priming gleps). Significant priming effects were obtained with

related primes yielding faster response times and unrelated primes yielding slower response times compared to a neutral condition. After four more prime sessions that varied the prime-target SOA and proportion of related trials, new fleps and gleps were introduced into the experiment with a brief study period. These then became primes for the more familiar flep and glep targets using a 2 second prime-target SOA. Following the primed classification task, the new items were themselves classified, and analysis of the primed task was based on a median split of the response times to the new stimuli. The rationale was that those items classified quickly were ones that were likely to have been correctly identified as a flep or glep in the primed classification task, while those items classified more slowly were ones where retrieval failure of the category information was likely to have occurred. The key finding was that the effect of relatedness between the new prime and the well-learned target varied as a function of that classification: Relatedness produced significant facilitation for primes that were classified quickly, and significant inhibition for primes that were classified slowly.

Other findings consistent with the predictions of center-surround theory have been reported in a study designed to determine whether the observed semantic inhibition might be due to response interference (Barnhardt, Glisky, Polster, & Elam, 1996). A subject unable to recall the prime's definition when it appeared might be reminded of it by the target, and hence the slower processing of the target might reflect processing the prime's definition. To address this possibility, the vocabulary word acquisition paradigm was modified so that some of the new words were learned with synonyms, while others were learned with associatively related words. Response interference would predict no difference as a function of these conditions, while center-surround theory predicts facilitation for the synonym and inhibition for the associate. Significant facilitation in a lexical decision experiment was observed for targets associatively related to rare word primes whose definitions were recalled, and significant inhibition was observed for targets associatively related to rare word primes whose definitions were not recalled. When the primes were a synonym of the target, significant facilitation was observed regardless of whether or not the primes were recalled.

In the previous studies, inhibition for related information occurred when retrieval of semantic information about the prime was made difficult by presenting it under perceptually impoverished conditions (masked), or by virtue of a low level of learning (the vocabulary acquisition studies and visual shape classification studies. A similar pattern has been reported in the reading of brain-damaged patients, where retrieval of information is presumably rendered difficult because of the damage to the processing mechanisms (Bushell, 1996).

The Neural Correlates of Inhibition

Behavioral studies infer inhibition based on slower or less accurate responding to stimuli. In some cases, a good case can be made for inhibition on this basis, but converging neural evidence would certainly buttress such claims. However, the evidence from functional neuroimaging studies is mixed with respect to the role of inhibition in memory. In part, this may stem from uncertainty

as to what should be seen in a neuroimaging study of inhibition: If there is some form of inhibitory module for a given task, then one might expect to find increased activation of that area when the need for inhibition is increased, and possibly a corresponding deactivation elsewhere, but it's less clear that current functional neuroimaging methods would be able to detect the consequences of inhibition in terms of deactivation. Similarly, it seems that deactivations of the type that lateral inhibition would create might be difficult to observe with functional neuro-imaging since both activation and deactivation might be occurring simultaneously in the same region.

Results that might be viewed as consistent with an inhibitory module have been reported in some functional neuroimaging studies of verbal working memory (Jonides, Smith, Marshuetz, Koeppe, & Reuter-Lorenz, 1998; Jonides et al., 2000). In one, subjects received target sets of letters to hold in memory for 3 seconds, followed by a probe that matched a member of the memory set half of the time. Memory sets were constructed to demand varying degrees of inhibition – in a high recency condition, half of the probes were members of the previous set, while in a low recency condition, none of the probes were members of the memory set on either of the preceding two trials. The basic assumption was that the high recency condition would recruit inhibitory processes because of the potential interference. The behavioral data indicated that responses to recent negative probes in the high recency condition were slower and less accurate than responses to nonrecent negative probes in the same condition and nonrecent probes in the low recency condition, consistent with a need to recruit inhibitory processing in the high recency condition.

The neural correlates of this effect were obtained by subtracting the low recency from the high recency activations, yielding a significant activation was obtained for left lateral prefrontal cortex (Brodmann's area 45). The greater activation in this area was apparently not simply due to a greater recruitment of working memory processes because a similar activation was not observed when a control condition that required storing a single letter for 200 ms was subtracted from the low recency condition.

A similar study compared younger and older adults using the memory interference paradigm (Jonides et al., 2000). Older adults were more susceptible to interference, as demonstrated by greater slowing in responding to the recent negative probes in the high recency condition compared to responding to nonrecent negative probes in the same condition. Younger adults showed a significant activation in Brodmann's Area 45, whereas older adults did not ($p. = .07$). More importantly, the activation observed in that region was significantly greater for the younger adults compared to the older adults. This pattern is consistent with Area 45 serving an inhibitory function, although an alternative interpretation in which it is involved in temporal coding cannot be ruled out completely on the basis of the data.

However, at least one other recent study using a similar paradigm has failed to find evidence consistent with a specialized inhibitory module (Bunge, Ochsner, Desmond, Glover, & Gabrielli, 2001), concluding instead that the same prefrontal regions that produce the activation of goal-relevant information for working memory are responsible for suppression of goal-irrelevant information. In this study, the key finding was that the same brain regions activated by

the interference manipulation were also activated by increases in memory load – bilateral middle frontal gyrus, left inferior frontal gyrus, bilateral anterior insula, caudal anterior cingulate gyrus, bilateral parietal cortex, and anterior cerebellum. Individual differences in brain activation were found that correlated with susceptibility to interference: Those subjects who showed the least effects of inhibition showed greater interference related activation in the right middle frontal gyrus, but this same region was also activated by a comparison of working memory load effects. The left inferior frontal gyrus (BA 45) activation associated with interference resolution in previous studies (Jonides, Smith, Marshuetz, Koeppe, & Reuter-Lorenz, 1998; Jonides et al., 2000) was not significant in this study, although activation was correlated with the ability to resolve interference.

These latter findings are consistent with a view in which the function of prefrontal cortex is to bias the processing of information elsewhere rather than to specifically accomplish inhibition (Miller & Cohen, 2001) . This view is related to an earlier account of visual selective attention in which visual cortical neurons associated with processing different aspects of a display compete for access to higher level processing and response mechanisms (Desimone & Duncan, 1995). These neurons affect each other via mutual inhibitory processes, but also are under the control of excitatory top-down modulation which may come from the prefrontal cortex. The role of the prefrontal cortex in producing behavioral inhibition then becomes intrinsically related to selective attention. Attention biases processing in favor of task-relevant information, and produces inhibition for task-irrelevant information as a consequence. The inhibition is created by local competition between conflicting information rather than by a central process governed by the prefrontal cortex. This account further assumes that different regions of the prefrontal cortex emphasize different types of information, with stronger biasing required to resolve competition in regions that emphasize information that is likely to elicit reflexive responding. Thus, an apparent role of orbital prefrontal cortex in inhibition would be explained in terms of its biasing task-relevant information against strong competition.

This type of account recasts behavioral inhibition as a consequence of biased processing generated by excitatory connections. Accomplishing behavioral inhibition is critical, as earlier accounts suggested, but the mechanism by which it is achieved is quite different than a simple suppression model. It should be noted, however, that there are relatively few studies bearing directly on this issue, and the existing data do not permit a definite resolution. Inhibition of the suppression form might occur in the form of local competition, but data on this question in studies of memory are lacking.

Conclusion

The intensive research of the past decade suggests that behavioral inhibition may often be accomplished by processing mechanisms somewhat different from those initially, and often implicitly, proposed. Behavioral inhibition is clearly an important component of performance in many domains, but evidence for some form of inhibitory module that sustains inhibition across

those domains is somewhat wanting, although it may be premature to rule it out altogether. If, as now seems possible, behavioral inhibition is accomplished in other ways, such as excitatory processes in prefrontal cortex working in conjunction with local competition in other cortical regions that may involve inhibitory connections, then inhibition in the suppression sense may ultimately be found at the local level in those other areas. This form of inhibition would seem more akin to lateral inhibition, and many of the behavioral demonstrations of inhibition reviewed above, such as backward inhibition in working memory and inhibition in semantic memory when retrieving weakly activated codes, also may reflect a form of lateral inhibition at work. Full explication of this aspect of inhibition may await further studies using different methods such as single cell recordings.

13

Towards Principles of Executive Control: How Mental Sets are Selected

Ulrich Mayr

Mental sets are hypothetical, representational devices that enable coherence of action over time in the face of interfering stimuli as well as flexibility of action when internal or external demands change. But: How are mental sets represented? And how are mental sets established, maintained, and changed? A significant advancement of our understanding of these issues can be expected from the rediscovery and refinement of the so-called task-switching paradigm which allows the examination of selection processes that mediate between competing mental sets. A diverse variety of task-switching phenomena has been obtained with this paradigm. However, so far, a coherent framework that accounts for these phenomena and at the same time positions set-selection processes within the broader neuro-cognitive literature is missing. The goal of this paper is twofold. In the first part, central task-switching phenomenon and issues are reviewed. In the second part a theoretical framework is sketched out that promises a unified account for the diverse set of results.

Towards Principles of Executive Control: How Mental Sets are Selected

A situation experimental psychologists have studied extensively throughout the century is the selection of simple actions, such as pressing one of two possible keys according to the value of a stimulus dimension or the presence or absence of a particular object in the visual field. One

important inference from this research tradition is that selection in such simple choice reaction-time situations can occur in a highly efficient, even automatic manner. Most telling in this respect are recent reports that strong response tendencies can be elicited even by stimuli of which participants are completely unaware (e.g., Klotz & Neumann, 1999; Leuthold & Kopp, 1998). Interestingly, such results fare well with early observations by Woodworth (1938) who described behavior in reaction time situations as a "prepared reflex". Responding conditional on a stimulus is supposed to be "reflexlike" if the relevant response rule is held in a prepared state. To this prepared state he refers to as a mental set (see also Hommel, 1998). More recently, Logan (1978), with explicit reference to Woodworth, stated: "... the most interesting things (...) might go on before the (stimulus) array is presented". And with the "most interesting things" he also explicitly refers to the notion of a mental set as something that is established before arrival of the stimulus information and that makes automatic selection of action possible.

What is a mental set? In functional terms, its role is to constrain the space of potential actions (i.e., the corresponding stimulus and response codes) to that subspace of "allowed actions" that fits the current behavioral goal. But what are the selection processes that determine which of the many possible mental sets are currently active? And what (if any) is the critical difference between selection on the level of sets on the one hand, and selection within mental sets (i.e., the state of the prepared reflex) on the other? Obviously, answers to these questions are fundamental to an understanding of the problem of executive control of thought and action, the general theme of this chapter. However, until recently there was very little work that directly addressed Logan's challenge of understanding the "most interesting things": the nature of mental sets and how they are selected.

Since a few years this situation is changing. Critical in this respect is the rediscovery of the so-called task-switching paradigm. This paradigm had been used occasionally throughout the century (e. g., Jersild, 1927; Pinard, 1932; Spector & Biederman, 1976), but was brought back into the literature more or less independently by a number of researchers (e.g., Allport, Styles, & Hsieh, 1994; Fagot, 1994; Meiran, 1996; Rogers & Monsell, 1995). The main feature of this paradigm is that relative to the standard choice RT situation an additional level of selection, namely that between mental sets or task sets is added. Performance in situations in which a mental set needs to be switched is typically worse than when the same set can be maintained across trials. This switch versus no-switch contrast yields so-called switch costs. Switch costs supposedly reflect in some way processing associated with the selection of mental sets. Core aspects and variants of the task-switching paradigm are listed in Table 1.

In this chapter I will highlight recent advances in this field and I will point out how these may bring us closer towards a general model of executive control. In the first part, important phenomena that have been obtained in the context of the task-switching paradigm will be presented. In the second and third part, the findings from the task-switching paradigm will be related to two theoretical concepts that may prove crucial for a better understanding of executive control: Long-term memory (LTM) retrieval and representational coherence.

Table 1. Variants of the Task-Switching Paradigm

The Task-Space: Often, task-switching studies use tasks requiring different perceptual or semantic judgements that can be applied to the same set of stimuli (e.g., judging an object's color and judging an object's form). Arguably, endogenous control of sets is necessary only with ambiguous stimuli (i.e, stimuli that fit to all possible tasks) because otherwise the stimulus alone could cue the response in a bottom-up manner. Accordingly, large set-selection costs are obtained only for ambiguous stimuli. Also, in many studies, the same two (or more) response choices have been used for the various tasks, although this is not a necessity and the consequences of this particular procedural choice are only beginning to be explored (Mayr, 2001; Meiran, 2000).

Alternating versus Pure Blocks: The original task-switching paradigm implied the comparison of performance in a block of trials in which participants had to alternate between tasks on a trial-by-trial basis with performance in pure-task blocks (e.g., Allport, Styles, & Hsieh, 1994; Jersild, 1927). A drawback of this version of the paradigm is that other factors than the switching demand may vary between the experimental and the control condition (e.g., overall task load, motivation, arousal).

Alternate-Runs Paradigm: Switch and no-switch trials are integrated here within a block of trials (Rogers & Monsell, 1995). Participants alternate between runs of two or more trials with the same task. To reduce sequencing demands, a sequential cue is provided that informs participants about their current position in the sequence. An important finding obtained with this paradigm is that switch costs are typically limited to position 1 on of a run of same-task trials.

Cueing Paradigm: Here, the relevant task is cued randomly on a trial-by-trial basis (Meiran, 1996), for example by a verbal task label (Goschke, 2000; Mayr & Kliegl, 2000). An advantage of this paradigm is the tight control over the time for passive decay of a task set and the time for active preparation by independently manipulating the response-cue-interval and the cue-stimulus interval (Meiran, 1996). In many instances, similar results are obtained with the alternate-runs and the cueing paradigm. However, one critical difference is that in the cueing paradigm, response times are reduced gradually across a number of same-task trials rather than abruptly at the first trial after a switch (see section Retrieval View of Task Switching).

The Task-Switching Paradigm: Basic Issues and Findings

Selection of Simple Actions versus Selection of Sets

Even simple choice-response-time tasks require some sort of selection. This raises the question whether there is any reason to believe that selection within a mental set (i.e., between stimulus or response codes) is a different type of process than selection between mental sets? Clearly, this question needs an answer before deeper explorations of selection of sets via the task-switching paradigm can be justified.

One way to look at this issue is by examining the degree to which switch costs as an indicator of between-task selection are sensitive to selection difficulty on the level of the primary tasks among which switches occur. If switch costs are independent of primary-task difficulty,

independence of selection levels can be assumed (e.g., Allport, Styles, & Hsieh, 1994). Several studies have taken this approach and generally found switch costs to be independent of primary-task difficulty (e.g., Allport, Styles, & Hsieh, 1994; Mayr & Kliegl, 2000; Mecklinger, von Cramon, Springer, & Matthes-von Cramon, 1999; Rogers & Monsell, 1995; Rubinstein, Meyer, & Evans, 2001). Gopher, Armory, & Greenshpan (2000) recently listed eight different primary-task difficulty manipulations that seem to be independent of switch costs. Given this general result of additivity between switch costs and within-set selection difficulty the few documented exceptions to this rule are theoretically of particular interest (Mayr & Kliegl, 2000; Rubinstein, Meyer, & Evans, 2001) and we will return to them in the course of this chapter.

Another way of looking at the independence issue is via psychometric methods. The question here is whether or not set-selection costs reflect unique interindividual variability that is not represented in primary-task performance. Several papers have looked at this issue and typically found a surprising degree of dissociation between measures reflecting set-selection demands and indicators of primary-task performance and also other cognitive abilities. For example, using a relatively wide sample of different tasks and a large number of participants both Kray & Lindenberger (2000) and Salthouse, Fristoe, Lineweaver, & Coon (1998) provided strong positive evidence for the critical dissociation with about 50 to 60% of the variance being unique to switch-related processes.

Evidence from patient and neuro-imaging studies allows making a similar point. Patients who exhibit task-switching deficits (often patients with left-frontal damage) usually do not exhibit deficits in indicators of response selection efficiency (e.g., Mayr, Diedrichsen, Ivry, & Keele, submitted; Rogers et al., 1998). A striking dissociation in this respect has recently been reported by MacDonald III, Cohen, Stenger, & Carter (2000). They had subjects switch on a trial-by-trial basis between the color-naming and the word-reading version of a Stroop task. Activation related to establishing a task set based on a cue was located in left dorso-lateral-prefrontal cortex whereas activation related to Stroop conflict (i.e., an indicator of response selection) was found in anterior cingulate cortex.

The general conclusion from the findings reviewed to this point is that whatever is reflected in switch costs, it is dissociable from indicators of "simple" response selection (as studied in traditional RT tasks). We can thus, feel justified to look at selection of mental sets as a unique domain of processing.

Preparation of Mental Set and Residual Switch Costs

A straightforward interpretation of switch costs is that they directly reflect the duration of a set-switching operation. Consequently, when the time to prepare for a set switch exceeds the duration of this set-switching operation switch costs should be eliminated. It is probably the fact that this simple model is clearly inadequate what stirred much of the initial interest in the task-switching paradigm. In particular Allport, Styles, & Hsieh (1994) reported strong evidence suggesting that giving subjects time for preparation does not eliminate switch costs (see Figure 1). It seems that even when participants know exactly what the next task is going to be they are still slowed

compared to a situation in which they had already worked with the same task on the preceding trial. An additional interesting result concerning residual switch costs is the so-called switch-cost asymmetry. Residual switch costs are larger when switching from a non-dominant task (e.g., Stroop color naming) to a dominant task (e.g., word naming) than the other way round (but see Mayr & Kliegl, 2000).
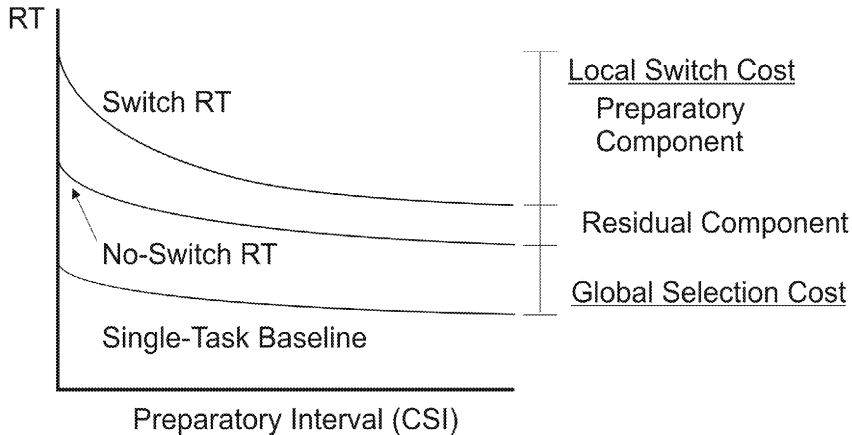
Fgure 1. Idealized presentation of important empirical components of set-selection costs (CSI = cue-stimulus interval).

What is behind these residual switch costs and the switch-cost asymmetry? (Allport, Styles, & Hsieh, 1994; see also Allport & Wylie, 1994) suggested that the critical determinant of switch costs is not so much a time-limited switch operation but rather positive priming from the preceding task set (that would help in case of a set repetition and would interfere in case of a set change) as well as negative priming resulting from a suppression of the preceding irrelevant, but after a set-switch, relevant task. The additional assumption that suppression of the dominant set should be particularly strong while working on the non-dominant set provides a straight-forward explanation for the switch-cost asymmetry. Switching from the non-dominant to the dominant task implies reactivation of a strongly suppressed set and should therefore take particularly long.

This interpretation of switch costs downplays the possibility that switch costs reflect some kind of a high-level control operation. Instead it highlights the role of automatic carry-over effects. However, it is important to acknowledge that even though residual costs often remain after long preparatory intervals, opportunity for preparation does lead to a substantial reduction of these costs (e.g., Mayr & Kliegl, 2000; Meiran, 1996, 2000; Rogers & Monsell, 1995, see Figure 1). The important question of course is what it is that people do to "configure themselves" intentionally, an issue that will be taken up again in the section Mental Sets, Working Memory

and Long-Term Memory. On a general level, several authors have argued that the two empirical switch-cost components (i.e., one sensitive to preparation, the other not) point to two distinct classes of processing or levels of representation involved in task switching (e.g., Meiran, 2000; Rogers & Monsell, 1995; Rubinstein, Meyer, & Evans, 2001). The one is supposedly under intentional control, the other is either non-penetrable or at least much more difficult to control.

A very different view of the residual-switch-cost phenomenon has been proposed by De Jong (2000). In short, he suggests that switch costs in the case of long preparatory intervals reflect a mixture of trials on which participants are either fully prepared or fully unprepared. Analyses of RT distributions (i.e., looking for a mixture between a fully prepared distribution and a fully unprepared distribution) yielded evidence that seemed compatible with this simple idea. Thus, it is possible that residual switch costs reflect two things: on the one hand, the principle possibility of complete preparation and on the other hand failures of preparation on a certain subset of trials which may be due to motivational constraints (but see Nieuwenhuis & Monsell, in press) or to failures of retrieving the adequate task rules (Mayr & Kliegl, 2000). Even though there are some reasons to doubt that the mixture approach explains residual-switch costs in their entirety (e.g., Allport & Wylie, 2000; Meiran, 2000; Nieuwenhuis & Monsell, in press) it most certainly is one piece to the puzzle.

Switch Costs versus Global Selection Costs

In task-switching situations there is not only a "local" cost at switch points. Also no-switch trials typically show substantially increased RTs when compared to performance in single-task blocks (e.g., Allport & Wylie, 2000; Fagot, 1994; Keele & Rafal, 2000; Kray & Lindenberger, 2000; Mayr, 2001). One possible interpretation of these global selection costs (sometimes also referred to as mixing costs or dual-task costs) is that they reflect the overall load associated with the need to represent two different tasks in working memory. Interestingly, however, results by Rogers & Monsell (1995; Experiments 3 vs. Experiments 4) as well as recent systematic investigations by Mayr (2001) suggest that these costs are much reduced in task-switching blocks with non-ambiguous stimuli even though they also require the maintenance of two different tasks. Thus, global costs arise directly from the need to select between competing mental sets.

One possibility is that global costs reflect constraints on differentiating competing, internal control settings. To the degree to which internal differentiation is difficult, either for situational or system-specific reasons, time-consuming updating processes should become relevant which in turn produces global costs. Interestingly, subject groups who arguable have more noisy representation of internal context such as old adults and some frontal patients also exhibit increased global selection costs. In fact, global costs often seem to be more sensitive to the effects of normal aging (e.g., Kray & Lindenberger, 2000; Mayr, 2001; Mayr & Liebscher, 2001) and frontal lesions (Keele & Rafal, 2000; Mayr, Diedrichsen, Ivry, & Keele, submitted) than local switch costs.

The issue regarding local versus global costs is further complicated through recent findings that raise the question whether there are any specific executive processes associated with

local switch costs. For example, according to Dreisbach, Heider, & Kluwe (in press) subjects operating in a task-switching block need to prepare for both no-switch and switch transitions alike and switch costs reflect nothing more than task-specific (non-executive) carry-over effects. Accordingly, they show that the probability of an upcoming task as signaled by "probability cues" (i.e., cues indicating that a particular task will occur with 0%, 25%, 50%, 75%, or 100% certainty) are additive with regard to switch costs (Sohn & Carlson, 2000; but also Sohn & Anderson, 2001). Dreisbach's et al. conclusions cannot be easily applied to the entire range of task-switching results. For example, switch costs in the alternate-runs paradigm where subjects can be certain when a switch needs to occur and when not, do show signatures of specificity for preparation effects (e.g., they are particularly sensitive to preparation and they are associated with unique interindividual variability). In contrast in a cueing paradigm (in particular one with relatively difficult "probability cues") processing the cue may itself becomes a "task" over which the last-relevant primary-task setting may be lost (i.e., so that no-switch trials are actually switch trials in disguise). At the very least, however, Dreisbach's et al. results suggest that very often, in particular in task cueing paradigms, no-switch RTs may reflect much of the same processes traditionally attributed to switch RTs. In line with this conjecture, recent neuro-imaging results using a task-cueing paradigm have found that patterns of activation for no-switch and switch differ only in quantitative terms (i.e., more activation in switch than in no-switch trials), but not in any marked, qualitative manner (e.g., Dove, Schubert, Wiggins, & von Cramon, 2000; Kimberg, Aguirre, & D'Esposito, 2000). Brain-imaging results using an alternate-runs procedure are missing so far.

Response Conflict

A theoretically interesting phenomenon that occurs when stimuli are ambiguous and stimulus values from the different tasks are mapped onto the same response alternatives is a particular type of response-congruency effect. Response times are larger when the value on the irrelevant task dimension specifies a different response than the value of the relevant task dimension and they are smaller when both stimulus aspects specify the same response (e.g., Rogers & Monsell, 1995). This result is important because it demonstrates that information regarding the currently irrelevant task is processed to some degree up to the response-selection stage. One interpretation of this finding could be that it is occurs because alternative sets are being held in a partially selected state in working memory. Alternatively, response-congruency costs could suggest that irrelevant stimulus values elicit automatic response tendencies irrespective and in opposition to higher-level settings. The broader issue to be returned to below is whether it is possible to hold more than one mental set active at the same time (Meiran, 2000) or whether mental sets are selected in an all-or-none manner (Mayr & Kliegl, 2000).

Verbal Processing and Selection of Sets

There is accumulating evidence that internal speech may be a critical factor in the endogenous selection of task sets. For example, Goschke (2000) compared two different task-switching

situations. In the first, subjects were asked to verbalize the label of the upcoming task during the cue-stimulus interval (e.g., say "color" for a color discrimination task). In the second condition, subjects were asked to verbalize task-irrelevant labels ("Monday" for the color task). Interestingly only for subjects working in the first condition switch costs were reduced as a function of the cue-stimulus interval whereas task-set preparation seemed to be blocked through the irrelevant verbalization.

Baddeley, Chincotta, & Adlam (2001) looked at the effects of articulatory suppression on switch costs (e.g., repeating the word "the" throughout a block of trials) and found a substantial negative effect that was specific to switch costs. Other secondary tasks that did not tap the articulatory system left switch costs unaffected. Baddeley et al. used a comparison between alternating lists and pure-task lists which leaves several possible sources of interference (e.g., task load or sequencing demands). However, if these results hold up with more refined experimental designs they would be highly suggestive of the articulatory system (originally conceived as a "slave system") being critically involved in executive control.

Again, patient data seem to point into similar directions. Several studies have found that patients with left-frontal deficits exhibit either local or global switching deficits (e.g., Keele & Rafal, 2000; Mayr, Diedrichsen, Ivry, & Keele, submitted; Rogers et al., 1998; Rubinstein, Evans, & Meyer, 1994). Even though not always reported explicitly, left-frontal patients often have language problems. For example, in the study by Mayr et al. left-frontal patients had a substantially reduced digit span (which presumably relies heavily on the articulatory system). Moreover, Mecklinger, von Cramon, Springer, & Matthes-von Cramon (1999) looked at patients with diffuse left or right-hemispheric damage. Interestingly, only left-hemispheric patients and of those only that subset which scored high on an aphasia test (no matter whether the damage was frontal or not) showed increased local switch cost.

It is not an entirely new idea that language is critical in organizing thought and action (e.g., Luria, 1966). The task-switching paradigm should allow a systematic examination of the precise role of language. Specific suggestions in this respect will be offered in the final parts of this chapter.

The Role of Task-Set Inhibition

The main role of mental sets is to provide stability and coherence of action across time in the face of a fluctuating and ambiguous environment. This requires fully activated set representations. However, full activation may get in the way of flexible changes of sets when task demands change. A possible solution to this stability-flexibility dilemma is an inhibitory process that turns down activation of the last relevant set. Mayr & Keele (2000) (see also Arbuthnott & Frank, 2000; Mayr, 2001, 2002) provided an empirical test of such an inhibitory process (see also Goschke, 2000). Specifically they showed that a switch to a mental set that had been abandoned two trials earlier took longer than a switch to a set that was abandoned less recently. This effect which has at least superficial similarity to the well-known inhibition-of-return phenomenon in the context of spatial attention appears to be a rather low-level process because it occurs even

when participants have complete foreknowledge of the sequence of mental sets to come. On the other hand it seems to be tied to top-down controlled selection of sets and does not occur when different task-relevant dimensions are activated in a bottom-up manner only.

Set inhibition provides another answer to the question what is behind residual switch costs. Residual switch costs were typically found in situations in which participants switched between two different tasks so that every switch to a task was one to the task most recently abandoned. As Mayr & Keele (2000) showed, at least part of these residual switch costs disappear when the switch occurs to a task that was abandoned less recently.

Summary. A number of important questions are raised by the list of findings gathered with the task-switching paradigm. For example, what is it people can do to prepare for a new set and why is the preparation often incomplete as suggested by the finding of residual switch costs? Can actually more than one mental set be active at a time as may be inferred from response-congruency effects? And what is behind the global cost effect? An attempt to make progress on at least some of these questions is presented in the remainder of this paper. The view presented in the next section is characterized by an attempt to work from very simple assumptions that are compatible with data outside the task-switching field, as well as with more general models of cognitive control.

Mental Sets, Working Memory and Long-Term Memory

An important function often ascribed to working memory is to keep information ready to use while other processes need to be intersected (e.g., Baddeley, 1996). Thus, a straightforward assumption may be that a mental set that is currently not relevant is held in working memory until it becomes relevant again. For example, according to (Meiran, 2000) alternative mental sets are all held partially active and switching implies a continuous process of activating one task set more than the other (i.e., by changing the attentional weighting of task-relevant dimensions). One task-switching result that seems in line with such a view is the occurrence of cross-task response-congruency effects. Irrelevant response tendencies may be activated simply because the currently irrelevant task set is still active in working memory. A potential problem with this view is that it is not entirely clear how incomaptible mental sets could be represented at all within the same representational space. Arguable, this should be just as impossible as representing alternative views of an ambiguous figure simultaneously (e.g., Chambers & Reisberg, 1985). Also, the idea that several mental sets could be active within working memory runs against realistic estimates of the capacity of the working memory focus (e.g., McElree & Dosher, 1989).

Working Memory as the Selection Device

A simple alternative view is that working memory itself serves as the critical selection device. In other words, only that mental set is allowed access to working memory in an all-or-none manner that is currently relevant. All other competing sets need to leave (Mayr & Kliegl, 2000;

Rubinstein, Meyer, & Evans, 2001), possibly with the help of task-set inhibition (Mayr & Keele, 2000).

One empirical result that seems difficult to reconcile with the notion that only a single mental set is active within working memory simultaneously, is the finding of response congruency effects across alternative tasks. These effects seem to suggest that selection occurs for both tasks, but that larger weight is given to the currently relevant task. However, an alternative vies is that response tendencies can be elicited through stimuli fitting to the alternate task via direct access to codes in long-term memory. This view is supported by the observation that a small, but reliable response congruency effect can be found even when the competing task is irrelevant for the entire block so that there is no reason to assume that it is contained in working memory (e.g., Mayr, unpublished data). Thus, a clear separation is made here between all-or-none selection into the working-memory focus and parallel activation of various codes in LTM.

The Role of Long-Term-Memory Retrieval

Direct tests of the number of sets that can be active within the working memory focus are difficult to conduct. However, there is a consequence from the all-or-none selection view that can be examined empirically. Specifically, if only one set can be present in working memory at a time then switching to a set necessarily implies retrieving it from long-term memory. Importantly, this should be the case even when that set was last abandoned only a few seconds earlier. Further, it seems reasonable to assume that active retrieval of the task-set (i.e., the task rules) is exactly what participants can do intentionally to prepare for an upcoming task.

In a recent series of experiments Mayr & Kliegl (2000) made an attempt to test this idea. Specifically, they predicted the so-called retrieval-demand effect on switch costs: larger switch costs when the switch occurs to a task that itself requires large rather than small retrieval demands. The reasoning was that retrieval of the task set during switching and retrieval of task-specific information within the task should interfere with each other, thus, producing increased switch costs. Switch costs were actually found to be larger when switching to a task that required retrieval of pre-experimentally learned information about stimulus words (e.g., whether it was shown in blue or green font on the computer monitor) than when switching to a task that only required retrieval of semantic information about the words (e.g., a living/nonliving judgement). Note, that as discussed earlier (see Selection of Simple Actions versus Selection of Set), difficulty of the primary task usually has no effect on switch costs. Thus, the effect of retrieval demands on switch costs is an important exception to this rule. It suggests that the retrieval-demand effect can actually be attributed to the retrieval component rather than to a general variation in primary-task difficulty (for explicit tests of the general-difficulty hypothesis, see Mayr & Kliegl, 2000, Experiment 2).

Mayr & Kliegl (2000) also tested the idea that task-set retrieval is the critical process behind task-set preparation by manipulating within the same experiment the cue-stimulus interval and the retrieval-demand of the switched-to-task (Experiment 3). As predicted, the retrieval-demand effect was found only for short preparation intervals but disappeared when participants

had sufficient time for preparation (i.e., to retrieve the relevant information before the stimulus comes on). Importantly, the retrieval demand effect did not disappear when the time between successive tasks was increased without also increasing the preparatory interval. Thus, the effect is specific to the time that can be used for preparation rather than to the general inter-trial interval.

Another important result is that the retrieval-demand effect was substantial for arbitrary task cues (i.e., cues that have no semantic relationship with the tasks). However, switch costs were reduced and the retrieval-demand effect on switch costs disappeared when task cues were used which directly specified the relevant task rules. For example, when the task was to press the left key for living and the right key for nonliving objects then the cue would be "living-nonliving" where the left-right position of each of the two words specifies the relative position of the relevant response keys. Apparently, such direct cues eliminate the need for active retrieval because they directly place them into working memory. Further, it is interesting to note that when using such direct cues the effect of manipulating the preparation interval was completely eliminated. This latter result suggests that loading task rules into working memory is not only necessary for preparation, it is also sufficient to explain the effect of task-set preparation.

The retrieval-view of task-set preparation is also in line with other reports in the literature that highlight the role of task cues. Rubinstein, Meyer, & Evans (2001) found dramatically reduced switch costs for explicit task cues. Moreover, left-frontal patients have recently been reported to exhibit increased switch costs, but only when arbitrary task cues were used (Rogers et al., 1998). There are also a number of reports which suggest a left-frontal involvement in difficult retrieval situations (Ranagath, Johnson, & D'Esposito, 2000; Raye, Johnson, Mitchell, Nolde, & D'Esposito, 2000). Thus, a left-frontal retrieval problem may be at the heart of the switching deficit. Another piece to the puzzle is added by Baddeley, Chincotta, & Adlam's (2001) finding that the above-mentioned effect of articulatory suppression on switch costs is reduced when direct task cues are presented (i.e., a "+" sign when subjects need to do an addition task). This findings links internal speech to the need for controlled retrieval and thus, supports the idea that articulation may be used for self-cueing purposes.

The Retrieval-Structure View of Task-Set Selection

The idea that long-term memory retrieval plays an important role during switching between mental sets can be extended towards a more comprehensive framework of cognitive control in multi-task environments. From this perspective, operating in such situations implies positioning a limited working-memory focus within a larger long-term-memory retrieval structure (see Figure 2). This notion is borrowed from the long-term working memory model by Ericsson & Kintsch (1995) who argue that working-memory limitations in complex real-world tasks (e.g., text comprehension) are circumvented by using well-established retrieval structures for bringing relevant information into working memory quickly, thereby making it unnecessary to hold this information online within a specialized storage device. This general view not only allows a comprehensive account of many of the task-switching results reviewed in the first section of this chapter (see Table 2). It also fares well with detailed assessments of processing dynamics in

typical short-term memory tasks, as for example in the Sternberg paradigm (McElree & Dosher, 1989).

Consistent with the proposal that memory retrieval can be either controlled or automatic in nature (e.g., Jacoby, 1991), traversals along retrieval paths can occur either via automatic, stimulus-driven control or via intentional control. The first can be held responsible for "negative" task-switching phenomena such as residual switch costs (where an irrelevant stimulus aspect may serve as a cue for the irrelevant task), but also of "positive" phenomena such as the reduction of switch costs with direct task cues. In contrast, intentional retrieval is responsible for the reduction of switch costs when preparation is possible.
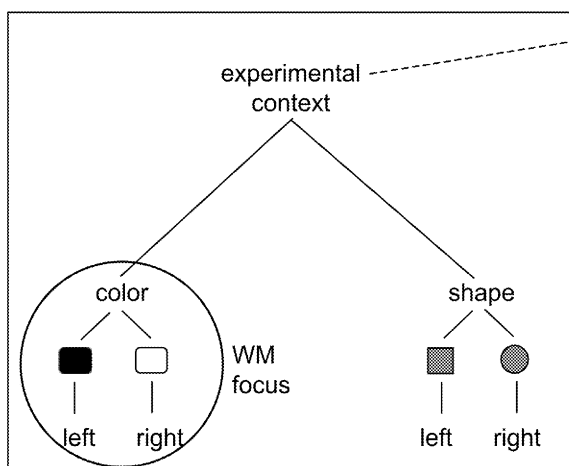
Figure 2. Sketch of the retrieval-structure view of task-switching situations. Task selection occurs by bringing the limited working-memory focus onto the LTM-representation of the currently relevant task rules. Traversals of the working-memory focus along the lines can occur either through intentional or automatic retrieval.

The retrieval-structure view also highlights the fact that subjects operating in a task-switching situation have considerable degrees of freedom as to how to deal with the control problem (see also De Jong, 2000). For example, after finishing a task, participants have the option of either maintaining their working memory focus on the current task, thus maximizing preparation for a no-shift situation. Such a strategy could be expected for no-shift trials in an alternate-runs paradigm (see Table 1) where participants can be certain that the task stays the same. In contrast, when tasks are cued randomly on a trial-by-trial basis it seems much more appropriate to "switch away" from the current task even on no-switch trials to a position where the next cue can be interpreted best. Interestingly, when comparing switch cost patterns between the alternate-runs paradigm and the cueing-paradigm an important difference can be noted (see Table 1). For the first, there is a large switch cost for the initial trial of a run whereas RTs for successive trials typically stay invariant (e.g., Mayr & Kliegl, 2000; Rogers & Monsell, 1995). This is what would be expected when participants stay with their focus on the current task after each trial. In contrast, in the cueing paradigm a "micropractice pattern" is found where RTs are reduced continuously within a run of same-task trials. This has been interpreted as a gradual

adaptation of a mental set to task demands (Meiran, 1996), an interpretation that cannot explain the lack of such an effect for the alternate-runs paradigm. The alternative interpretation based on the retrieval-structure view is that repetitions of a cue-task association as occur in the cueing paradigm lead to short-term strengthening of that association. In contrast, in the alternate-runs paradigm where retrieval (i.e., a cue-task association) plays no role in no-switch trials, such strengthening does not occur.

Table 2. Important Task-Switch Phenomena and their Accounts within the Retrieval-Structure Framework

Phenomenon	Retrieval-Structure Account
switch-cost reduction as a function of preparation	endogenous retrieval of relevant task rules from LTM into the working memory focus
residual switch costs	retrieval failures and/or residual inhibition associated with the switched-to set
global set-selection costs	result of a „set-selection mode" (see section Coherence and Retrieval)
response congruency effects	exogenous activation of response codes in LTM
articulary-suppression effects switch costs	interruption of verbal self-cueing in the course of LTM on retrieval
backward-inhibition effect	aftereffect of clearing of working memory focus from the no-longer relevant set and/or of keeping irrelevant sets out of working memory focus
left-frontal task-switching deficit	involvement of left-frontal brain areas in situations of „difficult" retrieval requiring verbal self-cueing
unique aspect of „prepared-reflex" state	either the complete absence of endogenous LTM retrieval during response selection or the giving up of control to direct activation of response codes in LTM

As simple as the retrieval-structure view may be, it does generate a number of additional interesting questions. One leads back to the basic issue of the nature of task switch costs. When operating within a retrieval structure as shown in Figure 2 it is likely that between trials, people position their working-memory focus such that the distance to all possible tasks is minimal (i.e., the "experimental-context" node in Figure 2). If this is true, then trial-to-trial transitions with task repetitions imply that not only the task is repeated, but also the cue-to-task retrieval path. In contrast, for switch transitions both the task and the cue-to-task retrieval path are switched. The question then is: What actually is the source of switch costs, the switch in retrieval path or the switch in task? Using a paradigm in which two different cues were used for each task Mayr and Kliegl (in preparation) used a paradigm with a 4:2 mapping between cues and tasks to get at this

issue. With such a mapping three different trial-to-trial transitions can be implemented: (1) the traditional no-switch transition where both cue and task are repeated, (2) traditional task-switch case where both cue and task change and (3) a cue-switch condition in which the cue changes whereas the task remains the same. The most important finding was that a large proportion (50-75%) of the total switch cost could be attributed to the switch of the retrieval path even when the task stayed the same. Furthermore, this component of the total switch cost was also the one that was reduced or even eliminated when preparation time was increased. These results underscore the utility of the retrieval-structure view of task switching according to which switch costs largely represent the time it takes to "navigate" the working memory focus within task-relevant long-term memory structures.

A second interesting question that can be re-phrased now is: What exactly is the defining characteristic of the state of the prepared reflex? There are two theoretical options. One possibility is that selection becomes "reflex-like" when a mental set is active within working memory. The critical feature of the "prepared-reflect state" would then be that further intentional retrieval from long-term memory becomes unnecessary. A second possibility is that the state of the prepared reflex is not dependent on the establishment of a mental set at all, but rather implies "giving up control" to those automatic response tendencies that operate directly through activating codes in long-term memory (and which according to the present view are responsible for response-congruency effects between relevant and irrelevant tasks). Even though probably difficult, an empirical decision between these two theoretical options would be of fundamental importance for models of executive control.

Selection of Sets and Representational Coherence

So far, this chapter has dealt with data from a single (though complex) situation, the task-switching paradigm. In light of the flurry of research on the task-switching paradigm as a new tool to look executive control it is important to keep in mind that the human control system has not evolved to deal with task-switching per se. Ideally, executive control is supposed to support selection and implementation of optimal action paths in real-world problem-solving or decision-making situations. The task-switching paradigm allows addressing one particular component of this problem: How are action rules changed and implemented given unambiguous information (i.e., provided through a task cue) about what the currently relevant rules are? In such a situation, there is never any doubt (at least not from the perspective of the ideal observer) which information to select and which information to select against. It is with this implicit assumption that we readily interpret certain effects such as residual switch costs or congruency effects as an interesting deviation from the behavior of an ideal control system. However, in complex, real-world problem situations more often than not there is no 100% valid task cue that tells us what the current rules of action are. Rather, various conflicting cues are usually present. To evaluate the best move in ambiguous situations, potentially relevant cues from all possible sources need to be taken into regard. The question is how this demand of integrating all potentially relevant codes can be resolved with the ultimate demand of selecting the actually relevant and not the

irrelevant codes. A concept that at least in principle holds a solution for this integration-selection dilemma is that of representational coherence.

Representational Coherence

The core idea here is that mental representations have an inherent tendency to strive towards coherence. This notion can be traced back to Fritz Heider's Balance theory (Heider, 1958) which in turn is heavily influenced by Gestalt Psychology. Coherent representations according to Heider were characterized by patterns of interconnectivity between representational units which yield mutually positive subgroups (e.g., if A and B are positively linked and B and C are positively linked then A and C should also be positively linked). What has been added to this view through modern cognitive theorizing is a mechanistic account of how representational coherence can be achieved, namely through a constraint-satisfaction process as embodied in connectionist networks. Via repeated updating of all links constraint satisfaction guarantees convergence towards a coherent (albeit sometimes only locally coherent) representation.

Representational systems striving for coherence via constraint satisfaction have proven very powerful in a number of domains. Among many other domains, Holyoak & Thagard (1998) have used such models to account for human problem solving behavior (e.g., analogies; e.g., Holyoak & Thagard, 1998) or complex decision making (Holyoak & Simon, 1999). Importantly, such systems naturally accomplish the opposing problems of integration and selection: All potentially relevant codes are considered, those "fitting together" form a coherent representation, the remaining codes are eliminated (through lateral inhibition). Thus, consistent with the single-set constraint proposed for representations of mental sets, the end-product of a coherence-seeking constraint-satisfaction process is a single, coherent interpretation of the world (or the current task situation) including the behavioral goals and the means to achieve them.

Neurocognitive Implementation of Representational Coherence

It is interesting to turn to the neurocognitive characteristics required of a system that supports construction of coherent representations. For example, given that such representations need to incorporate all possible goal-relevant aspects it needs to be situated such that it has access to information from all possibly relevant processing sites. Prefrontal cortex is bi-directionally connected with basically all other brain areas. Further, single-cell recording work on primates suggests that prefrontal cortex contain neurons which can code basically all tasks-relevant aspects (e.g., stimuli, responses, or expected rewards). Recent estimates from Miller's group suggest that in any task, about 80% of all neurons assayed are involved in some way in task-relevant processing (e.g., Asaad, Rainer, & Miller, 1998).

An equally important system requirement is that the information coded needs to include not only the basic-level task parameters, but also abstract task rules. Again, research by Miller revealed prefrontal neurons which show a highly contextualized firing pattern. For example, they would respond to a certain stimulus in the context of task A, but not in the context of task B

(Asaad, Rainer, & Miller, 1998). Obviously, this is what one would expect from a system that supports the integration of rule-level information.

Finally, coherent representations need to control behavior across time and in the presence of interfering stimuli. Whereas many brain areas allow maintenance of neurnal activity across time, only neurons in prefrontal cortex seem to allow neuronal activity that is resistant against interference (Miller, Erickson, & Desimone, 1996). Taken together, prefrontal cortex seems to provide all features necessary for a computational space that allows to establish and maintain coherent representations.

Recent, neurally plausible models of prefrontal functioning make use of the idea of a coherence-seeking constraint-satisfaction process. For example, Durstewitz, Kelc, & Güntürkün (1999) provide a detailed account of how dopamin, an important neurotransmitter in prefrontal cortex, may be involved in protecting coherent representations from distraction. Dehaene, Kerszberg, & Changeux, (1999) (see also Miller & Cohen, 2001) described a brain-level model that attributes to prefrontal cortex (and associated cortical areas) the role of a computational space that integrates information from all modular systems ("global workspace") and finds a single, coherent representation. Once established this representation modulates processing in specialized modules in a top-down manner. The authors show that this model is able to learn via trial-and-error to perform in the Stroop task. The behavioral dynamics of this model (e.g., distribution of errors over time) is qualitatively very similar to that of humans performing the Stroop task.

To summarize, a core purpose of the frontal-executive system may be the establishment of coherent representations. These representations link goals and all potentially goal-relevant stimulus or response aspects together and thus have the critical properties we like to ascribe to mental sets. Moreover, the idea of coherent representations allows to integrate work on various levels: from single-cell recordings and the role of dopamin in stabilizing representations to complex problem solving and decision making in realistic situations. Functionally, this general idea solves the problem how integration of potentially relevant information and selection of the adequate information can be embodied within the same system and without requiring an omniscient supervisor.

Representational Coherence and the Retrieval-View of Task Switching

A question that remains at this point is how the coherence idea fits to the notion of retrieval from LTM as a critical executive set-selection process. At least certain accounts of retrieval are in strong theoretical tension to the idea of a parallel constraint-satisfaction process leading to coherent representations. For example, based on evidence from the psychological refractory paradigm, Pashler (1994) has suggested that selection for action in general, and memory retrieval specifically, is a serial, centrally limited process. Obviously, a strictly serial translation of inactive LTM codes to active working-memory codes is incompatible with the idea of a coherence-construction process that involves all potentially relevant codes.

More recently however, evidence is accumulating which suggests that different codes from long-term memory can become active in parallel (e.g., Hommel, 1998; Logan & Schulkind,

2000). In fact, the cross-task congruency effect observed in task-switching experiments can be interpreted as one manifestation of parallel retrieval of response tendencies.

The possibility of parallel retrieval of potentially relevant codes from LTM into an active state allows for an interesting solution to the integration-selection dilemma. By this solution, selection of sets could be described as a two-phase process. First, all potentially relevant codes are retrieved from long-term memory into an active state along with the relations between these codes. Second, a coherent representation is constructed from this raw material via parallel constraint-satisfaction. In the course of this process, the irrelevant codes are eliminated from the active workspace via lateral inhibition. The such established representation is then maintained to exert top-down effects on lower-level processors (e.g., Dehaene, Kerszberg, & Changeux, 1998) until the next updating situation, again involving parallel retrieval of potentially relevant codes.

Interestingly, there is precedence for such a model from the text comprehension and the language production domain. Kintsch's (1988) construction-integration model assumes that the interpretation of the surface structure of a text proceeds in two phases. First, all possible interpretations are retrieved, forming an incoherent set of codes. Then a successive constraint-satisfaction process results in one coherent representation (and deactivation of irrelevant codes).

In the context of serial order control of speech Dell, Burger, & Svec (1997) argued that at least well-practiced speakers retrieve both present and future speech codes in parallel. Theoretically, they derive this proposal from what they call the "throw-away" principle by which it is easier to get rid of an activated code than find in the lexicon a missing, inactive code. Of course, this holds only for systems that possess a "throw-away mechanism" such as lateral inhibition of irrelevant codes.

In the context of the retrieval-view of task switching, the above considerations can be incorporated relatively easily. All we need to do is posit that retrieval of all potentially relevant codes can occur in parallel and that exclusion of irrelevant codes occurs thereafter. The increasing evidence suggesting that inhibition of irrelevant codes does take place during selection of sets (e.g., Arbuthnott & Frank, 2000; Goschke, 2000; Mayr & Keele, 2000) is compatible with this view. Given that in typical task-switching situations unambiguous task cues are provided, task-relevant information will dominate the constraint-satisfaction process and will allow control to occur in a seemingly serial manner. However, the general tendency of the system to consider all potentially relevant codes will make it susceptible to influences from irrelevant codes. At least in principle, phenomena like residual switch costs or congruency effects could be accounted for in this manner. From this perspective, such effects are not the result of a system imperfection, but rather a consequence of the very process that determines which representation is allowed to control action.

The virtue of this view is that it promises a unified account of how our cognitive systems deals with control problems in different domains and across different levels of observation. However, there are a number of important questions that remain open. For example, the precise way in which the various task-switching phenomena can be accounted for by this view needs to be worked out. An interesting question in this respect is to what degree a coherence-seeking

constraint-satisfaction process can occur before the stimulus appears (e.g., during the preparatory phase) or whether it requires also (or is at least much facilitated by) codes activated through the stimulus presentation.

Another interesting question is how a system that allows only one coherent representation at a time establishes sequential control of action in cases in which no successive task cues are provided. For example, when the rule given to subjects is to switch tasks every two trials without external cueing (e.g., Kray & Lindenberger, 2000), how is the information about the upcoming, alternative task B maintained while working on task A? In such cases, guidance through internal speech may become particularly important (e.g., Baddeley, Chincotta, & Adlam, 2001). Internal speech is not only well suited to represent sequences of events. Given that it is based on a phonemic/articulatory code, it may also allow representing alternative tasks on a "superficial" level that does not interfere with representations of the currently relevant task. In other words, speech codes could serve as pointers to potentially possible, but mutually conflicting task rules.

Conclusion

In the first part of this chapter I reviewed a diverse set of findings from the recent task-switching phenomena. These findings need to be accounted for by any theory of executive control. In the following parts I presented two simple ideas which together could form the cornerstones of such a theory. By the retrieval-view of task switching each change in task requires retrieving the now relevant task from long-term memory into working memory where only one task-set can be maintained simultaneously. This view not only makes a number of specific predictions that stand up against empirical testing (e.g., Mayr & Kliegl, 2000; Mayr & Kliegl, in prep.), it also gives simple accounts for many of the observed task-switching effects (see Table 2). Finally, the second idea discussed in this chapter is that selection of sets needs to be viewed as a process that seeks representational coherence across potentially relevant codes. This idea has important precedence in theories of language comprehension (Kintsch, 1988) and production (Dell, Burger, & Svec, 1997), problem solving and decision making (Holyoak & Simon, 1999), but also in biologically plausible models of executive control (e.g., Dehaene, Kerszberg, & Changeux, 1998). The coherence idea and the retrieval view are principally compatible with each other (if one allows for parallel retrieval from LTM). Most important, the coherence view is a big step towards a model of control that does not require an omniscient agent who determines what is to be selected and what not.

Section E

ADAPTIVE SPECIALIZATION OF MEMORIES

14

The Principle of Species Independent Learning Phenomena

Onur Güntürkün and Daniel Durstewitz

Learning theory provides an exceptionally successful framework to predict the behavior of humans and other animals in learning situations. Unfortunately research has concentrated mostly on the small number of conditions in which learning theory fails without devoting similar efforts to explain why predictions are successful in the vast majority of the remaining cases. Here, we will outline that the success of learning research is possibly related to the fact that learning implies modifications of synapses contingent on the temporal order of spikes. Spiking-time-dependent synaptic modifications reflect the temporal asymmetry of the physical world, a fundamental constraint common to all living beings which might have shaped the molecular architecture from very early on. Resource limitations might have led to additional constraints, producing deviations from general learning theory. As one example, we will discuss the apparent inability of pigeons to associate tones with visual cues. This case illustrates nicely that the specific constraints in pigeons are very likely related to an absence of a common synaptic territory of the auditory and the visual system in higher association areas. Hence, additional constraints might involve local architectural specializations of neural systems without corroborating the general framework of learning theory.

Animals come in a bewildering variety of sizes and shapes. Some have pentachromatic color vision, others are blind. Some hop on two feet, others have several dozen appendages, while again others attach to the substrate for their entire life. But regardless of their different appearances and life styles, all animals are able to learn. Obviously, the ability to extract some lessons from the past has such a tremendous evolutionary advantage that we would expect

learning to be a central feature no behaving creature should miss. What we should not easily expect, however, is the fact that the principles of learning seem to be remarkably similar for all living beings. Thus, the variety of forms contrasts with the uniformity of learning principles. During the 40s to 60s, the heydays of Behaviorism, this uniformity was envisaged as a result of a general process learning theory. This theory was seen as covering all aspects of experience dependent behavioral changes, regardless of species, sensory system, or genetic background. The degree of self-confidence of the Behaviorist approach is best appreciated when reading the famous quote of Teitelbaum (Teitelbaum, 1966, pp. 566-567):

> "We arbitrarily choose almost any act from the animal's repertoire and reinforce it with food, or whatever else the animal will work to obtain. Although typically we teach a rat to press a bar or a pigeon to peck a key to obtain a pellet of food, we readily train either to dance around the cage if we choose. We usually use a light to signal the delivery of a pellet but we can use a tone or a buzzer or any other stimulus the animal can detect…. In effect, in any operant situation, the stimulus, the response, and the reinforcement are completely arbitrary and interchangeable. No one of them bears any biologically built-in fixed connection to the other."

It does not take a great prophet to foresee that this extreme position could not go on without serious challenges. And indeed, this belief was called into question during the 70s (Seligman, 1970; Shettleworth, 1972). Criticism of the traditional approach was stimulated by observations of learning phenomena that were contrary to widely espoused general principles of association learning and that appeared to illustrate biological constraints (Domjan, 1983). Discussion of the issue suggested that a revolution in the study of learning was in the making that could concentrate on specialized mechanisms which had evolved to facilitate learning in biologically important situations. In particular, these new studies challenged the assumption that learning occurs the same way regardless of the cues, responses, and reinforcers involved in a learning situation. This equipotentiality principle was viewed as a fundamental assumption of general learning process theory, and the inadequacy of the principle was considered good reason to dramatically alter traditional learning research approaches (Domjan, 1983). However, despite revolutionary proclamations, the ensuing years merely saw the equipotentiality principle to falter without major changes to general learning theory (Shettleworth, 1998).

Rereading the papers with clashes between learning psychologists and ethologists, a glaring omission is obvious: There is a complete neglect of the neural substrate that produces learning (but see Macphail (1993), for a scholarly exception). Ultimately, answers to the question why general learning theory often succeeds but sometimes fails have to be found there. This approach will be the theme of our endeavor. We will first focus on the ubiquity of cases where classic learning theory accurately predicts detailed results of learning experiments. We will argue that the tremendous importance of a high temporal contiguity, which is so characteristic for virtually all learning studies, might go hand in hand with common basic membrane mechanisms of the nervous tissue. Discussing the constraints literature with their emphasis on the inadequacy of the equipotentiality principle, we will discuss the possibility that a lack of common synaptic space between two sensory systems might cause difficulties to associate stimuli perceived by these sensory pathways.

The Power of General Process Learning Theory

Thorndike (1911) was the first to formulate the general process learning theory. Studying cats, dogs, chickens, monkeys, and a fish species he observed only quantitative learning differences. According to his view, the behavior of the animals could be understood as the result of a common set of mechanisms governed by the Laws of Exercise and Effect. In the following account we will follow his distinction between the variable rate of learning on the one hand, and the more invariant laws of learning on the other.

Habituation learning, defined as a decreased response to repeated stimulation, is a good point in case. Although it is a simple non-associative form of learning, it is characterized by nine invariants that typically occur in all preparations and which were first listed by Geer, O'Donohue, & Schorman, (1986) and Thompson & Spencer (1966). Groves & Thompson (1970) formalized this overview further by assuming that all invariants could result from the interaction of two hypothetical processes. One is a decremental (habituation) and one an incremental (sensitization) process that develop independently in the brain. The details of the interaction can, e. g., account for an initial hump in the habituation curve, which, according to Groves & Thompson (1970) can be observed in animals as diverse as newborn humans, spinalized cats, rats, mudpuppies, and quails. Scrutinizing the literature further, this list can easily be expanded to include protozoa (Wood, 1973), anemones (Logan, 1975), leeches (Burrell & Sahley, 1998), and slugs (Burrell & Sahley, 2001). A detailed review of the synaptic mechanisms involved in learning in Aplysia as well as Hermissenda shows that indeed the predictions made by the dual process theory hold up to astonishing detail for the habituation process, while some discrepancies are visible for sensitization (Macphail, 1993). Thus, habituation learning seems to involve very similar mechanisms in all animals studied so far.

The general picture for associative learning is comparable. For example the growth of associative strength during classical conditioning is mostly described using the notation of Rescorla & Wagner (1972). This equation turns out not only to predict accurately the progress of learning in all vertebrates but also in insects like bees (Menzel & Giurfa, 2001). Similar cases of identical mechanisms in vertebrates and bees are seen for second-order conditioning, within-compound association, blocking, and conditional discrimination (for review see Bitterman, (2000). Why are so many aspects of learning theory valid for so many different conditions and species? The answer might be that most learning phenomena depend on basic physical constraints, information-theoretic constraints like maximization of information content, as well as on a small set of physiological key mechanisms reflecting these basic constraints. One of these key aspects could be temporal contiguity (Abrams & Kandel, 1988).

The conventional wisdom of learning studies has been that conditioning requires the associated stimuli to occur immediately after each other and in the correct temporal order. This is shown in a study by Dickinson, Wat, & Griffiths (1992) who examined the effects of delayed reinforcement on learning to press a key. Each time a rat pressed a lever, a food pellet was delivered after a certain delay. Delaying reinforcement for only a few seconds dropped off responding dramatically. Further increasing the delays reduced performance even more until no learning was observable at delays of 64 seconds. Since delayed feedbacks drastically reduce learning efficiency, animal trainers often use immediate secondary reinforcers like verbal

prompts ("very good", "excellent") to bridge the delay until primary reinforcers are provided. Given this importance of high temporal contiguity, we will scrutinize in more detail the cellular properties behind this phenomenon to discuss the possibility that it may represent an invariant of nervous systems.

Cellular Basis of Association Learning

In most of the above mentioned situations the learning process is temporally asymmetric. This makes a lot of sense from a functional point of view: If some stimulus S1 temporally precedes another stimulus S2, S1 might be taken as a predictor of S2 but not vice versa. Interestingly, a temporal asymmetry in the cellular mechanisms underlying learning was postulated already by the Canadian psychologist Hebb (1949) in his famous statement (p. 62):

> "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. The most obvious and I believe much the most probable suggestion concerning the way in which one cell could become more capable of firing another is that synaptic knobs develop and increase the area of contact between the afferent axon and efferent soma."

Thus, it is assumed that a change in synaptic strengths between neurons underlies information storage and altered behavior, a view widely adopted by neural network theories which revealed the staggering computational power of such a simple principle (Hertz, Krogh, & Palmer, 1991). However, in many learning theories within cognitive neuroscience and by neural network formal learning rules, Hebb's statement was taken to indicate that coincident pre- and postsynaptic activity would lead to a strengthening of the synaptic weights between neurons (leading to the slogan "Neurons that fire together, wire together"). That is, the temporal asymmetry pointed out by Hebb was largely neglected (Sejnowski, 1999). We will return to the importance of temporal asymmetry on the behavioral level in another example at the end of this chapter.

Since the initial findings by Bliss & Lomo (1973) that post-synaptic potentials can be enduringly increased by high-frequency, tetanic afferent stimulation, physiologists have assumed that long-lasting synaptic changes like long-term-potentiation (LTP) and long-term-depression (LTD) might in fact constitute the cellular correlates of learning as postulated by Hebb (see Dudai, 1989, Chap. 6, for an overview). There are also a number of studies that tried to establish a link between the cellular phenomenon of LTP/LTD and behavioral learning (most recently using gene knockout techniques and transgenic mice) (see Dudai, 1989, Chap. 6, and Squire & Kandel, 1999, Chap. 6, for an overview). Most convincingly this endeavor succeeded in simple organisms like the sea-slug Aplysia where the physiological and molecular cascades underlying habituation and sensitization have been worked out in impressing detail (Kandel, 2001; Squire & Kandel, 1999).

Here we will focus on a number of recent findings that studied the expression of LTP and LTD based on the precise relationship between pre- and postsynaptic spike times. These findings

might shed some light on the cellular bases of temporal contiguity. According to Hebb's original statement the synaptic weight from a cell A to a cell B should be strengthened if A tends to fire B - that is the synaptic weight change is supposed to capture a causal relationship between the firing of two cells (not just their mere broad temporal correlation), and hence the precise temporal relationship between spiking times should be relevant. This has indeed been confirmed in various species and various systems like the frog Xenopus retinotectal system (Zhang, Tao, Holt, Harris, & Poo, 1998), the electrosensory lobe of electric fish (Bell, Han, Sugawara, & Grant, 1997), the mammalian hippocampus (Bi & Poo, 1998; Debanne, Gähwiler, & Thompson, 1994, 1998; Levy, Brassel, & Moore, 1983; Magee & Johnston, 1997) and neocortex (Feldman, 2000; Markram, Lübke, Frotscher, & Sakmann, 1997). The strengthening (LTP) or weakening (LTD) of synaptic weights of excitatory synapses onto Xenopus tectum neurons, and onto mammalian hippocampal and neocortical pyramidal cells, in fact obeys Hebb's law as illustrated in Fig. 1a,b: If the presynaptic spike precedes the postsynaptic spike, i.e. if the presynaptic cell could have been involved in firing the postsynaptic neuron, synaptic strength is increased. If, however, the postsynaptic cell fires first, before a presynaptic spike reaches the cell, LTD occurs. Thus, remarkably, a switch of the temporal order of pre- and postsynaptic spiking by just a few milliseconds could lead from strong LTP to strong LTD.
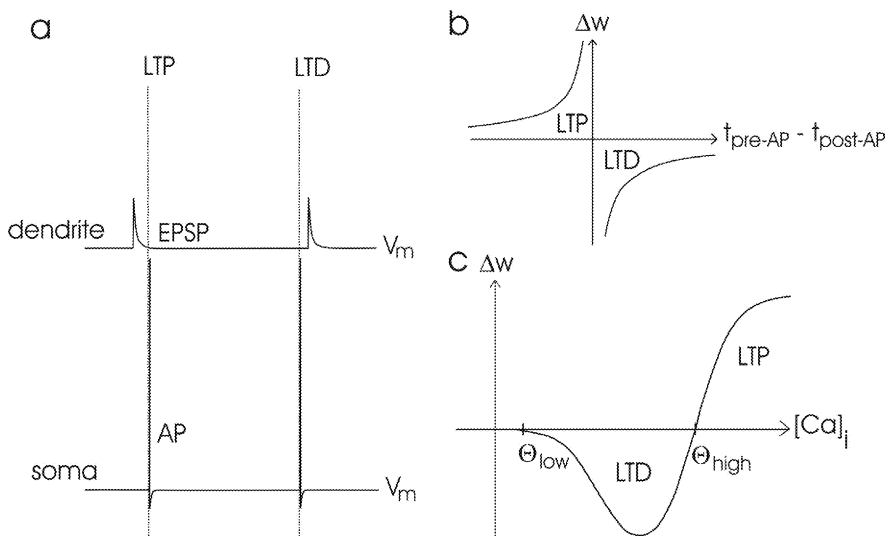
Figure 1. Dependence of the sign of the change in synaptic efficacy on spike-timing and intracellular Ca^{2+}-concentration. (**a**) If an EPSP precedes the postsynaptic spike the synapse is strengthened, i.e. LTP is induced, while the synapse is weakened (LTD) if the order is reversed. (**b**) Dependence of amplitude and sign of synaptic weight change (Dw) on the temporal difference of pre- and postsynaptic spiking (illustration based on results as in Bi & Poo (1998). (**c**) Dependence of amplitude and sign of synaptic weight change (Dw) on intracellular Ca^{2+} concentration with a lower threshold (Q_{low}) for LTD and a higher threshold (Q_{high}) for LTP (illustration based on results as in Artola & Singer, 1993).

Typically the time window for the induction of LTP and LTD is about +/-40 msec wide, but in general the extent of the temporal windows for LTP and LTD as well as their integrals (determining the relative balance between LTP and LTD) can differ (see (Abbott & Nelson, 2000). There are interesting exceptions from the temporally asymmetric rule as depicted in Fig. 1a: For example, in the electrosensory lobe of electric fish the temporal order of LTP and LTD is reversed (Bell, Han, Sugawara, & Grant, 1997). In neocortical pyramidal cells, if GABAergic inputs were elicited while the postsynaptic cell was spiking, LTD of the inhibitory connection was induced, whereas LTP was induced when the GABAergic input occurred more than 100 msec after the last spike in the pyramidal cell (Holmgren & Zilberter, 2001). In the former case, however, the targeted neuron is inhibitory (unlike cortical pyramidal cells), while in the latter case the synaptic input to the postsynaptic neuron is inhibitory rather than excitatory and thus should prevent the cell from firing. Hence, rather than being true exceptions, these kind of mirror-imaged learning rules might reflect different causal relationships in the activity of the two connected neurons.

How is the temporal relation between pre- and postsynaptic spikes detected by the postsynaptic cell and translated into differential regulation of synaptic weights? There may be two important ingredients, back-propagating spikes and local Ca^{2+} influx into the spine-head through NMDA synaptic and voltage-gated Ca^{2+} channels (in addition, Ca^{2+}-release from internal stores is likely to play a role). Ca^{2+} influx triggers the intracellular events that eventually lead the expression of LTD or LTP, with a lower Ca^{2+} threshold for LTD and a higher threshold for LTP, giving rise to a biphasic Ca^{2+}-dependence of the synaptic weight change (Fig. 1c; Artola & Singer, 1993; Lisman, 1994). Ca^{2+} might enter the cell mainly through glutamate-activated NMDA synaptic channels and high-voltage-gated Ca^{2+} channels, and, in addition, is released from internal stores through various synaptically induced or Ca^{2+}-triggered intracellular processes (Mainen, Malinow, & Svoboda, 1999; Nishiyama, Hong, Mikoshiba, Poo, & Kato, 2000; Sabatini & Svoboda, 2000; Schiller, Schiller, & Clapham, 1998; Yuste, Majewska, Cash, & Denk, 1999). As both NMDA channels and voltage-gated Ca^{2+} channels are voltage-dependent, this is where back-propagating action potentials come into play.

In hippocampal and neocortical cells, spikes elicited in the axonal output region propagate back into the dendrites, invading spine heads on their way (Johnston, Hoffman, Colbert, & Magee, 1999; Spruston, Jonas, & Sakmann, 1995; Stuart & Sakmann, 1994). Now, whether LTP or LTD will be induced, apparently depends on whether this feedback signal coincidences with a local EPSP in the spine head (Fig. 2c; Magee & Johnston, 1997; Nishiyama, Hong, Mikoshiba, Poo, & Kato, 2000). In fact, it has been shown that a back-propagating action potential riding on top of a local EPSP leads to supralinear Ca^{2+}-influx which can surpass the sum of the Ca-influxes caused by an EPSP or a back-propagating spike alone (Magee & Johnston, 1997; Schiller, Schiller, & Clapham, 1998; Yuste & Denk, 1995; Yuste, Majewska, Cash, & Denk, 1999). In particular, an EPSP followed by a postsynaptic action potential evokes a larger Ca^{2+} influx than with reversed temporal order (Koester & Sakmann, 1998). This is probably due to the fact that NMDA-receptors activated by the presynaptic release of glutamate exhibit a nonlinear voltage-dependence: They are blocked by Mg^{2+} at low voltages, while at higher postsynaptic membrane potentials the Mg^{2+} block increasingly removes, such that coincident presynaptic transmitter release plus postsynaptic depolarization lead to the most effective opening of this channel, letting
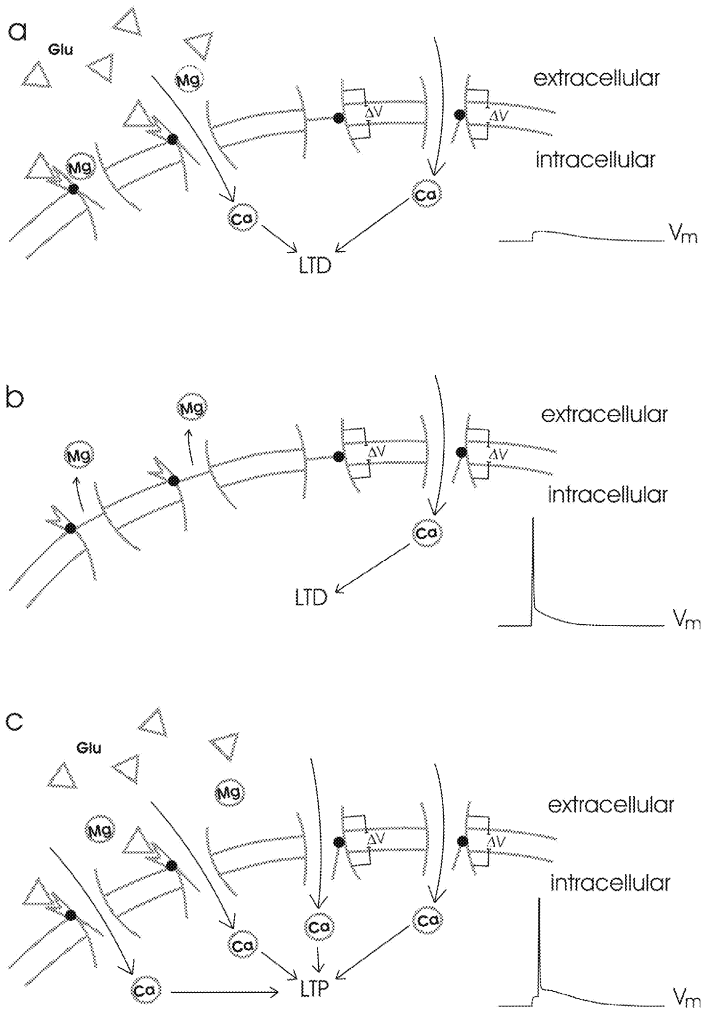
Figure 2. Ca $^{2+}$ -influx into the cell through NMDA synaptic and voltage-gated Ca^{2+} channels depends on nearly coincident timing of presynaptic glutamate release (triangles) and the back-propagating spike (see voltage-traces in lower right corners). (**a**) Glutamate release alone induces an EPSP not sufficient to open all NMDA channels but letting enough Ca^{2+} into the cell to promote LTD. (**b**) A back-propagating spike alone opens only a few Ca^{2+} channels, sufficient to induce LTD but not LTP. (**c**) If a back-propagating spike occurs briefly after glutamate release, the Mg^{2+} block of NMDA channels will be efficiently removed while the receptors are still activated, plus a number of Ca^{2+} channels will open such that large amounts of Ca^{2+} flow into the cell causing LTP.

Ca^{2+} rush into the cell (Schiller, Schiller, & Clapham, 1998; Yuste, Majewska, Cash, & Denk, 1999). Back-propagating spikes propel out the Mg^{2+} block of the channel and will be most effective if slightly preceded by presynaptic glutamate release (Koester & Sakmann, 1998; Paulsen & Sejnowski, 2000), conjointly causing a large Ca^{2+} influx through the NMDA channels that is sufficient to pass the LTP-threshold (Fig. 2c). High-voltage-activated Ca^{2+} channels activated by back-propagating spikes might also contribute to the strong rise in Ca^{2+} (Markram, Helm, & Sakmann, 1995; Sabatini & Svoboda, 2000; Schiller, Schiller, Stuart, & Sakmann, 1997). In summary, if glutamate release activating NMDA receptors for tens of milliseconds and causing local depolarization's lasting for a couple of milliseconds at least precedes a back-propagating spike, large amounts of Ca^{2+} will be shoveled into the cell. On the other hand, if the brief action potential precedes the EPSP by only a few milliseconds, the membrane will probably be completely repolarized by the time the synaptic transmitter ships in (Häusser, Major, & Stuart, 2001; Paulsen & Sejnowski, 2000). Hence, it is important that the EPSP precedes the spike. The amount of Ca^{2+} influx due to an EPSP or back-propagating spike in isolation might be sufficient to trigger LTD while failing to cross the LTP-threshold (Fig. 2a,b; Christie, Schexnayder, & Johnston, 1997).

To conclude, on a cellular level temporally asymmetric synaptic learning rules seem to reflect the temporal asymmetry and predictive structure of the world (Rao & Sejnowski, 2001). The spike-timing dependence outlined above seems to describe a general rule, possibly shared by most, if not all animals. And so is the requirement of temporal contiguity on the behavioral level, which is one of the backbones of general process learning theory. Thus, the universality of the laws of learning might derive from universal physiological mechanisms common to all living beings, which, in turn, might be based on fundamental constraints of our physical world.

The Evolutionary Diversity of Learning

Breland & Breland (1961) planned to use a number of rather unconventional laboratory species like pigs and racoons to perform funny, human-like behaviors that could be demonstrated in the public. Given the power of general process learning theory they did not envisage any problems. Unfortunately, nature came in their way. Some of the animals were supposed to deposit coins into a piggy bank to subsequently obtain food reinforcement. However, as soon as their racoon got hold of a coin it started rubbing and fondling it and was highly reluctant to drop it into the slot. This behavior was increased with two coins since the animal now started some 'washing procedure', constantly rubbing the coins against each other. Needless to say, this sequence greatly increased the delay to reward. The hungrier the animals were, the more they showed a tendency to display such apparently counterproductive behavior. The Brelands did suggest a framework within which an animal's behavior in learning situations could be related to its overall behavioral organization, but unfortunately learning theorists largely ignored their work, perhaps because their accounts were mostly anecdotal.

The door to analyze constraints on learning was finally pushed open wide by the work of Garcia and colleagues on flavor aversion learning. This phenomenon is probably known to the

reader by unpleasant personal experience: If after eating a new kind of food nausea develops, we avoid this food for very long time (sometimes for our entire life), although on some accounts we know that sickness was not related to our meal. In a landmark paper, Garcia & Koelling (1966) had rats drink from a tube of flavored solution and also exposed them to a noise and a flash each time they licked at the fluid dispenser. Half of the rats were made ill some time after drinking, while the other half was shocked through the feet while they licked at the dispenser. When later tested with 'flavored-only'- or 'noise & flash-only'-water, poisoned rats avoided the flavor, while shocked animals stood away from the noisy bright water. Two major deviations from classic knowledge were shown here in a nutshell. First of all the delay between the flavor (conditioned stimulus, CS) and nausea (unconditioned stimulus, US) could be 12 h or even more and still learning occurred. Second, this learning was stimulus-specific and thus was the first major blow (as it turned out, a deadly one) to the equipotentiality principle.

Soon after Garcia had published his papers on flavor avoidance learning, a whole flood of studies related to possible constraints on learning appeared. For example, field biologists were long aware that some animals have to attend to certain cues while they can ignore other, equally discernible ones due to the specific needs of their living conditions. Herring gulls, for example, have excellent color and form vision, yet are completely ignorant to the coloration, size and form of their own eggs, and therefore happily incubate artificial eggs placed into their nest (Tinbergen, 1953). Different from herring gulls, which drive away other individuals that try to nest in their direct vicinity, guillermots do not build nests but lay in close groups. Consequently, these birds discriminate their eggs from others (Tschanz, 1959). Similarly, noddy terns which nest where exchange of chicks is unlikely, do not recognize their own young, while sooty terns which nest in dense colonies, do recognize their own chicks and attack strangers (from Shettleworth (1972). More systematic analyses of learning procedures by Shettleworth (1975) showed that responses like face washing in golden hamsters that are difficult to reinforce with food were also decreased by food deprivation, while responses like digging that are readily increased by food reward were also increased by food deprivation. Thus, learning does not de novo wire a *tabula rasa*. The table is already wired by evolution and therefore prepared for the world the animal is living in.

These few examples do not imply that general process learning theory has to be abandoned. Contrary to early indications, even conditioned flavor aversion learning was found to show blocking, overshadowing, latent inhibition, and sensitivity to context (Shettleworth, 1993). It is therefore not so remote from other principles of learning but only shows a few, albeit important deviations which can be understood in terms of behavioral evolution. However, the problem with evolutionary interpretations is the ease with which we can find post-hoc explanations of all sorts of phenomena that do not readily fit into a general learning framework. This is due to evolutionary research being an empirical but not necessarily an experimental science. However, in some rare cases post hoc interpretations can be experimentally tested and even neurobiologically analyzed. These examples than offer insights into the neural basis of learning constraints.

Constraints on Learning in Pigeons

If pigeons are trained to depress a treadle in the presence of a compound auditory-visual stimulus either to avoid electric shock or to obtain food reward, the animals easily learn the procedure. If, however, the individual elements of the compound stimulus, red light and pure tone, are presented separately to assess their control of treadle pressing, something strange happens: in the test, the tone turns out to control responding in the shock avoidance condition, while the red light controls performance in the appetitive food reinforcement condition. Thus, the tone dominates aversion learning, while the color stimulus dominates food reward learning (Foree & LoLordo, 1973; LoLordo, Jacobs, & Foree, 1982). Based on these observations, Delius & Emmerton (1978) conducted a meanwhile classic experiment on which we will dwell in some detail.

They used pigeons to run two parallel experiments. In the one involving classical conditioning they implanted shock electrodes and placed the bird onto a foam rubber cradle in the center of a conditioning chamber (Fig. 3). In front of it was a light panel that could be illuminated with red or white light. A loudspeaker suspended from the ceiling provided either a 1 kHz or a 2 kHz tone. During conditioning with auditory stimuli, for half of the animals the high, for the other half the low pitch served as CS- or CS+, respectively. CS+ was followed by a mild electric shock (US). The heart rate change subsequent to CS+ application was the conditioned response (CR). During conditioning with visual stimuli, red and white lights were deemed to be CS+ or CS- in a balanced order. Thus, depending on the experimental group they had been allocated, the pigeons had to associate one of the auditory or one of the visual stimuli with shock.

In the experiment using instrumental conditioning the animals were confined to another conditioning chamber with two pecking keys and a food delivery device (Fig. 3). During visual discrimination the two keys could be illuminated with red or white light. For half of the animals pecking on red (irrespective if presented on the upper or the lower key), for the other half pecking on white was reinforced with access to food. During auditory discrimination both keys were illuminated with green light. If the high pitched tone was delivered, the upper key had to be pecked, while the lower key was correct during low pitch presentation. Note that in this last condition, different from the three other conditioning situations, not only a sensory signal had to be associated with a specific behavioral or physiological response, but also have the different tones to be linked to different visually perceived spatial locations. Taken together, the animals had to associate colors and tones to either shock or to food reward contingent on pecking. Depending on their group, a specific color or a specific tone signaled that either shock had to be expected or a certain key had to be pecked. Since the same colors and tones were used in both paradigms, different procedural outcomes could not be based on perceptual differences.

The results showed that the colors came to control the key pecking in the appetitive instrumental paradigm but not the heart rate in the aversive classical procedure. At the same time tones controlled cardioacceleration in the aversive classical but not key pecking in the appetitive instrumental procedure (Fig. 3). The authors interpreted this set of data as a learning constraint shaped by the specific evolutionary needs of a granivorous animal which lives under the selection pressure created by various animals of prey. In the normal environment of pigeons, sounds are unlikely predictors of food, since grains are silent companions. However, in order to discriminate

grains against a scattered background, pigeons need excellent vision including color processing. Therefore, the inability to discriminate tones and the ease to discriminate colors for food reinforcement is understandable. On the other hand, aversive heart-rate conditioning is likely to be related to natural avoidance behavior, and indeed the shocked pigeons not only displayed cardioacceleration but also struggling. In the wild, avoidance behavior is mainly a response to predators. Sound is an excellent predictor of stealthy predators, while under many circumstances like during the night or in a bushy environment, color is not. Therefore, the double dissociation between aversive and appetitive conditioning with tones and colors might be understood as a compromise of an animal with just two milliliters of brain. Pigeons might be too short of neuronal space to be able to relate and store all the possible associations between the multitude of events they can perceive. They might be forced to select for associations with a higher probability of occurrence.

Up to now all this sounds like one of these post-hoc 'just so' story that have plagued evolutionary interpretations. But it is not. Specific testable extrapolations derive from this approach. First of all, bird species that feed on noisy prey should differ from pigeons. Indeed, barn owls easily associate auditory and visual cues for food reward (Wagner, 1993). Additionally, there is an extrapolation that is related to pigeons. As shown by Delius (1985), grains may be silent by themselves, but generate a good deal of noise when they are pecked at. Any peck that reaches its target yields massive acoustic feedback, partly mediated by bone-conducted
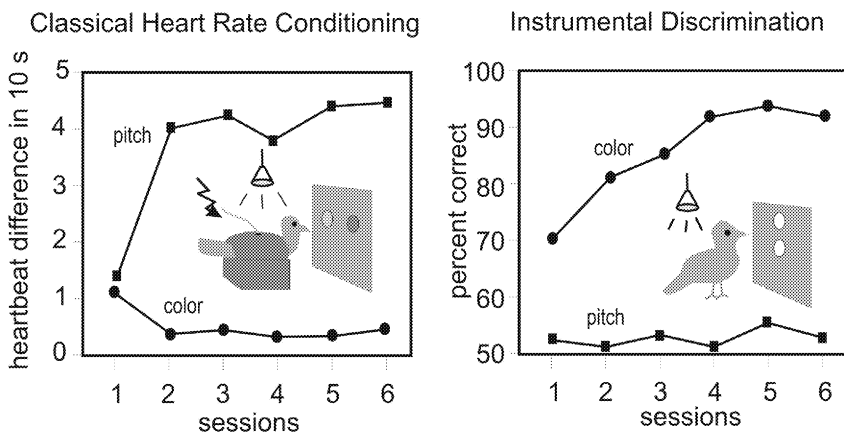
Figure 3. Schematic depiction of the experimental setup and main results of Delius & Emmerton (1978). In the upper panel the classical heart rate conditioning is shown. In the auditory test, the animal has to associate one of two tones delivered by a loudspeaker suspended above the birds with shock (lighting arrow). In the visual test, one of two color cues in front of the animal are to be associated with shock. Heartbeat differences after S+ delivery are the depending variable. As shown, pigeons are able to learn a pitch but not a color discrimination in this context. In the lower panel the instrumental discrimination is shown. In the auditory test, animals have to learn to peck a certain key after hearing a certain tone. In the visual test, they have to choose the key with the correct color to obtain food reward. As shown, under these conditions pigeons learn the color and not the pitch discrimination.

sound. The avian skull is especially suited for such bone-transmission as the jaw bones link up with the middle-ear bones that support the eardrum. It is likely that the pecking related auditory feedback is exploited as a cue for the properties of the grain the animal is pecking at. However, this auditory feedback has a highly specific temporal order: the auditory feedback is generated subsequent to the visually guided peck ('first see the target then hear the sound') and never the other way round. But in the experiment of Delius & Emmerton (1978) the tone was given first and the pigeons then had to peck one of the keys ('first hear the sound then see the target'). Thus, it is conceivable that pigeons can learn auditory discriminations during appetitive conditions only if the tones are delivered after their pecks. Delius (1985) tested this hypothesis. In this experiment, the pigeons had to discriminate between two tones of different lengths (10 and 90 ms). In a two key Skinner-box, within a trial, each pecking response on a given key immediately yielded an S+ tone, while pecks on the other key always triggered S- tones. 16 consecutive pecks on the S+ key yielded reinforcement. Responses on the S- key were never rewarded. After a reinforcement the allocation of S+ and S- to the two keys was determined according to a quasi-random sequence. Pigeons learned this procedure very well (Fig. 4). This means that simply reversing the sequence of events to the natural order (first visually guided peck, then emitted tone) enables learning, while during the procedure used by Delius & Emmerton (1978) (first delivered tone, then visually guided peck) the animals were unable to learn the association. During a control procedure, the discriminative tones triggered by the key pecks were delayed by 600 ms. Immediately learning broke down. Thus, not only the temporal order of the events was critical, but also their direct immediacy. For pigeons, auditory discrimination learning under appetitive conditions seems therefore only to be possible under highly circumscribed conditions – conditions that exactly mimic the natural feeding situation.
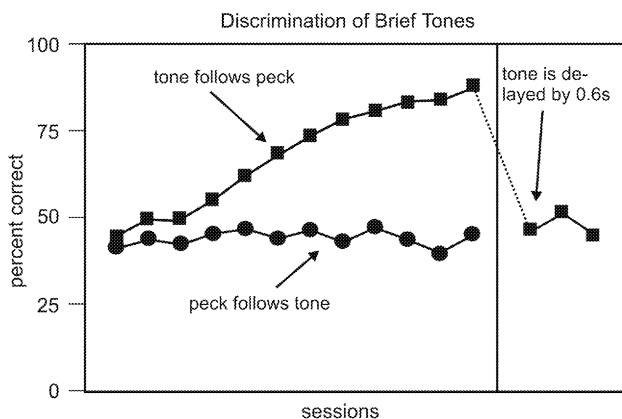
Figure 4. Auditiory discrimination learning by pigeons under two different conditions. Under one condition ('peck follows tone') the animals had to choose a pecking key after hearing a certain tone. As shown, pigeons were unable to learn this association. Under the other conditon ('tone follows peck') the animals had first to peck a key to evoke a given pitch. Depending on the pitch they had to go on pecking or had to switch to another key. Pigeons learn this quite well. If the tone is delayed by 0.6 s, they fail. Data based on (Gebauer, 1980) and referred by Delius (1985).

The Neural Basis of Learning Constraints

What could be the neural basis of these constraints? The critical aspect here might be that the animals in the condition they could not accomplish had to associate two different tones with pecking responses to two different visually perceived spatial positions, i.e. had to integrate auditory and visual information for guidance of the spatially directed pecking response. Obviously, this association requires the visual and auditory modality to come together somewhere in the brain to be synaptically associated. Up to now only a single forebrain area in birds could be shown to provide extensive room for multimodal associations. This is the neostriatum caudolaterale (NCL).

The NCL is a semilunar area in the caudal forebrain of birds that has reciprocal connections to all sensory systems (Kröner & Güntürkün, 1999). The inputs are relayed via secondary sensory areas of the different modality-specific systems. Cells in the NCL respond to various modalities and seem to code mainly for the relevance of stimuli and not for their sensory features (Diekamp, Kalt, & Güntürkün, 2002; Kalt, Diekamp, & Güntürkün, 1999). NCL-lesions cause deficits in cognitive domains related to the holding of information for subsequent action sequencing and the establishment of higher-order associations (Diekamp, Kalt, Ruhm, Koch, & Güntürkün, 2000; Güntürkün, 1997).

The pattern of sensory afferents within NCL might provide clues to the functional architecture of the pigeon's nervous system. In ventral NCL visual inputs from the tectofugal visual pathway and trigeminal afferents from the n. basalis overlap virtually completely (Fig. 5d). The large common territory of the visual and the trigeminal system might be related to the specialization of the tectofugal visual pathway to the lower frontal visual field which overlaps within the egocentric space with trigeminal inputs from the beak (Güntürkün & Hahmann, 1999; Hellmann & Güntürkün, 1999). Thus, a common sensory focus of both systems seems to have created a need for common coding which is accomplished by extensive areas of overlap in the associative NCL. A second visual pathway, the thalamofugal system (not shown in Fig. 5), represents the lateral visual field and terminates in the dorsal NCL, mainly outside the domain of the trigeminal and the tectofugal visual system (Kröner & Güntürkün, 1999).

The modalities which show no or little overlap within NCL are those from the auditory and the tectofugal-visual/trigeminal systems (Fig. 5b). This absence of a common synaptic territory might be the reason for the constraints described by Foree & LoLordo (1973) and Delius & Emmerton (1978). Since auditory input and visual information from the frontal area have no common targets in a higher order area, pigeons might have difficulties to associate sounds with visual cues at which they have to peck. Indeed, many experiments have shown pigeons to have difficulties to associate visual and auditory cues (Delius, 1985).

However, the trigeminal pathway from the n. basalis also transmits auditory information, since the n. basalis not only receives trigeminal projections but also some auditory afferents from the lemniscal nuclei (Schall, Güntürkün, & Delius, 1986; Wild & Farabaugh, 1996). Hence, pigeons have two auditory systems with terminals within NCL, the main auditory pathway terminating in dorsal NCL and the small auditory system terminating together with trigeminal information in ventral NCL. The auditory neurons within n. basalis are very likely activated by the auditory feedback during pecking. This means that most acoustic input into NCL is

transmitted by the main auditory system delivering input into dorsal NCL (outside the tectofugal visual domain). Only during pecking a second auditory system is switched on providing acoustic information into ventral NCL (right into the tectofugal visual representation). Therefore, associations between tectofugal visual information and auditory stimuli are only easily accomplished during pecking bouts. Thus this pattern of wiring reflects specifics of the causal structure of the pigeon's sensory world: "first you see a target to peck at – then you feel and hear the impact of your own peck". From these conditions, Schall & Delius (1991) formulated the prediction that the critical association between frontally presented visual targets and different tones which are elicited by the pecks of the animal are formed via the basalis-system. To test their hypothesis, they conditioned pigeons to discriminate between two acoustic signals generated by the animals own pecks. Then they lesioned the basalis. Indeed, the discrimination of the two sounds delivered after pecking was lost, although the animals main auditory pathway was still intact.
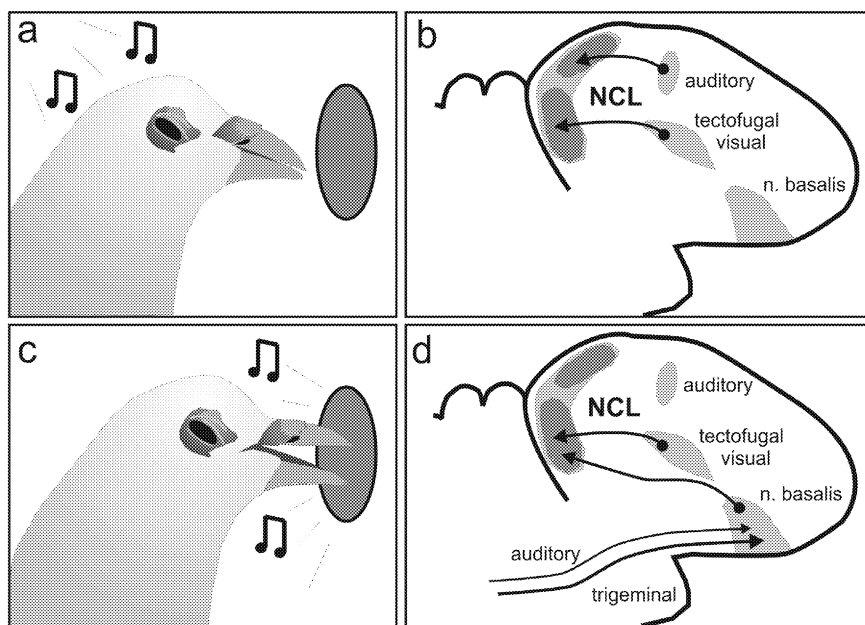
Figure 5. Schematic diagram showing the possible neural basis of learning constraints in the example outlined in the chapter. If pigeons (**a**) have to associate a tone with a visual cue (here a pecking key), (**b**) the projections of the auditory and the tectofugal visual system (were the frontal visual field is represented) have no common area of terminals in the higher-order associative forebrain structure NCL (neostriatum caudolaterale). Consequently, no learning occurs. If however, (**c**) pigeons elicit a certain tone with their own peck, (**d**) auditory processes to the nucleus basalis are evoked which overlap in NCL with the projections of the tectofugal visual system. This association is learned.

Taken together, these findings suggest that the constraints on learning in this case might be related to the absence of a common synaptic territory between the main auditory and the visual system, preventing pigeons from coupling visual cues to temporally preceding acoustic signals not processed by the basalis pathway. As long as the tones are delivered without the animal pecking a key, pigeons have a hard time to learn that they have to choose a certain key after hearing a specific tone (Figs. 5a and b). If however, the tone is elicited by the peck of the animal, auditory input is relayed via the basalis-system into ventral NCL. There it finds extensive common synaptic space with visual information coding for one or the other key (Figs. 5c and d).

Of course, our interpretation of the neural basis of learning constraints in this model rests on the implicit assumption that diverse terminal fields within NCL curtail synaptic associations. In principle, it is conceivable that indirect synaptic links exist between the visual and auditory modalities. It is also possible that sensory representations converge in structures further downstream. Our knowledge on the avian brain is presently too limited to exclude these possibilities. However, learning constraints are very likely related to local neural architectural adaptations of a given species as outlined in this example. They confine the set of all possible temporal associations to those most likely in the sensory environment of a given species, implementing a priori probabilities, without necessarily violating – in this sense – general learning theory. Such restrictions could save anatomical and energetic resources, and possibly also enable faster responding or buildup of most relevant associations.

The tremendous power of general learning theory, on the other hand, probably is a direct result of fundamental physical constraints of the world in which all species live. Neural systems had to incorporate these invariances to achieve predictability. Any animal that consistently failed to reliably predict the near future lost the game of evolution. Those who could cope well were probably those that inherited a neural system with learning principles that matched the physical reality.

15

The Principle of Adaptive Specialization as It Applies to Learning and Memory

C. R. Gallistel

Biological mechanisms are adapted to the exigencies of the functions they serve. The function of memory is to carry information forward in time. The function of learning is to extract from experience properties of the environment likely to be useful in the determination of future behavior. These different functions lead to different manifestations of the biological principle of adaptive specialization.

Adaptive Specialization in the Memory Mechanism

We do not know what the neurobiological mechanism of memory is, so we cannot say how it is adapted to its function. We can, however, look at other mechanisms that serve the same function to see what adaptations they suggest we may find in a mechanism with this function. One such mechanism is computer memory; another is DNA, the molecular mechanism for carrying hereditary information from one generation to the next. Both of these "memory" mechanisms suggest two exigencies and two principles: The exigencies are thermodynamic stability and high density. The principles are that information is information and that information conveyance requires a code.

Thermodynamic Stability

A memory mechanism requires a physical change that endures for as long as the information it encodes is to be preserved. Volatile changes decay in a fraction of the interval over which the information is to be preserved. An example, of such volatile memory in some computers is capacitative memory, where the information is encoded by the charge pattern on a bank of capacitors. Capacitative memory banks are volatile because the charge on a capacitor decays rapidly; when the charge pattern is no longer readable, the information has been lost. A volatile memory makes sense when it is a buffer where information is ordinarily overwritten by new information within an interval shorter than the decay time. When the same information must be held for longer than the decay time, a volatile memory must be continually refreshed, which uses energy and generates heat. For this reason, computer memories whose function is to preserve large amounts of information for long periods of time are non-volatile: they rely on thermodynamically stable physical changes.

Volatility is a consideration in assessing the plausibility of a memory mechanism often employed in connectionist or neural net modeling. A conventional computer has one or more memory mechanisms, components specifically devoted to carrying information forward in time. A neural net has no component devoted by design to this function. This lack reflects the absence of an established memory mechanism in our current understanding of neurobiology and the bottom-up commitment in neural net modeling, the attempt to build computational models on a neurobiological foundation.

Whether neural net modeling is wise to embrace a constraint that may someday be seen as having arisen from simple ignorance remains to be seen, because dispensing with a memory mechanism poses computational challenges. On the rare occasions when the environment provides all the information needed to perform a computation (or determine an output) at one time - in one input vector - the absence of a memory poses no problem. In many situations (arguably in almost all), however, the information is given piecemeal, at unpredictable intervals. Then, the absence of a memory poses a problem. A common solution is to have the activity engendered by the information that arrives first circulate in reverberating loops until the rest of the information required to determine the output arrives. A reverberating loop is a highly volatile mechanism; in the absence of the energy required to maintain continuous signal transmission, the signal dissipates in a matter of milliseconds. Reverberating loops have a long history in neurobiological speculation about memory (Hebb, 1949), but their energetic cost is seldom considered. That cost weighs against the hypothesis that large amounts of information are carried forward over long intervals by this mechanism.

Turning our attention to DNA, the only currently known mechanism for carrying large amounts of information forward in time within biological systems, we find again that the mechanism is not volatile. Absent assaults by active agents of degradation like bacteria, the information in organismic DNA is preserved for hundreds or even thousands of years after the death of the organism, which is to say, after the cessation of energy input. The thermodynamic stability of this mechanism is the more remarkable in that so many other aspects of cellular activity and function are highly dynamic. Living is a highly dynamic and energetically costly

business, but the mechanism for carrying forward the information necessary to build a living system is neither. That is the key to its successful functioning.

In sum, the known mechanisms for carrying large amounts of information forward through long intervals of time in both artificial and biological systems suggest that thermodynamic stability is a strong exigency for such mechanisms. Once the information is registered, its continued preservation should require little or no metabolic expenditure.

High Density

The spectacular and continuing increase in the density of information storage has been a salient aspect of the technological history of the last five decades. The powerful, small modern computer is made possible by it. There is reason to expect that this increase will continue for another several decades, because the information density in the best modern chips and on the best modern drives is still many orders of magnitude lower than the density of storage achieved in DNA. DNA stores information at the sub-molecular level. At each base-pair position in the helix, there are four possible base pairs, so each position carries 2 bits of information, and the 10 base-pairs in a 34 angstrom long turn of a helix with a 10 angstrom radius carry 20 bits, which works out to about 2 bits per cubic nanometer (2×10^{18} bits per cubic millimeter). This is within two or three orders of magnitude of what is thought to be the limit on information density that is theoretically possible at ordinary temperatures and pressures (Frank, 2002)[1]. and about 10 orders of magnitude greater than the density achieved in the highest density contemporary computer memories.

Because of the enduring influence of associative theories of mind on neurobiological theorizing, it is widely hypothesized that the mechanism of memory in neural tissue is a change in synaptic conductance (Kandel, Schwartz, & Jessell, 2000). How much information can be stored in a conductance change at a single synapse depends somewhat on the coding scheme, but it does not appear that it could be more than a few bits. Synaptic densities in neocortical tissue can be on the order of one billion (10^9) synapses per cubic millimeter(Braitenberg & Schüz, 1991). Thus, if every synapse in a cubic millimeter of cortex were devoted to memory storage, the density of information storage would be 8 or 9 orders of magnitude less than is achieved in DNA.

This is an extremely conservative calculation. By which I mean that it is highly biased so as not to make the hypothesis of synaptic storage look too bad. It is widely supposed in contemporary associative theorizing that different states of the world are represented by different stable activity patterns (called attractors) in networks composed of large numbers of interconnected neurons. Information about the world is stored in the patterns of synaptic weights that cause such a network to settle into the activity pattern appropriate to a given input, when it is given that input. A single pattern of weights can support more than one stable state, because the stable state into which the network settles is a function of its connectivity (synaptic weights) and the input

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[1] Current estimates of the density achievable at ordinary temperatures and pressures are about 1 bit per cubic angstrom (Frank, 2000). Densities currently achieved are many orders of magnitude less than this.

pattern it is given. However, there is a calculable limit on the number of different stable states that can be sustained in a network of a given size. The limiting number is a function, primarily, of the number of elements (neurons) in the network and secondarily of the richness of their connectivity. Rolls and Treves (1998) calculate that the number of different possible attractor states in the rat hippocampus is about 12,000. This means that the rat hippocampus, which occupies a volume of many cubic millimeter, can store less than 16 bits of information, less than can be put into a single turn of the double helix.

A single 32 bit word address in a contemporary computer can represent $2^{32} =$ more than 4 billion different states of the world; whereas, according to calculations of Rolls and Treves, a neural attractor network the size of the rat hippocampus can represent only 12,000. If information in the brain is carried forward by the patterns of connectivity in neural networks like those envisioned by Rolls and Treves and many others, then one would like to understand why the brain uses a mechanism for this critical function that has such spectacularly bad density characteristics.

In sum, a second exigency in the design of memory mechanisms is the maximization of information density. This gives reason to wonder whether the currently widespread assumption that the memory mechanism must involve a change in synaptic conductance is well founded. If so, then it would seem that the level of information density achieved is many, many orders of magnitude less than what is known to be possible in biological tissue and is currently achieved in manmade devices like, for example, the flash memory in a digital camera.

Information is Information

An important principle in modern computing and communication is that different kinds of information are equivalent and interchangeable when it comes to storage and conveyance; a mechanism suited to store or convey one kind of information is equally well suited to store or convey any other kind. Distinctions between kinds of information are crucial when it comes to mechanisms for encoding and decoding and when it comes to algorithms (computation). For example, in a digital video camera, there is a microphone for encoding the sound stream, whereas there is a 2-dimensional array of light sensitive diodes behind a focusing lens for encoding the luminous flux. And, there are different algorithms for compressing the first-order signals before placing the resulting bit patterns in memory, because the statistics of sound streams and images are different. There are corresponding differences on the decoding side, where the bits stored in memory—and perhaps transmitted over the internet--are converted back into image and sound. But at the level of storage and transmission, a bit is a bit. For the mechanisms that operate at this level, the origin and fate of the information they carry is irrelevant.

One manifestation of this principle in a computer is that the same memory mechanisms are used to store both program code (information specifying the algorithm) and data code (information on which the algorithm operates).

The same is true for biological storage and signaling mechanisms. Very different kinds of information about organismic, cellular and molecular structures and how to build them are carried from generation to generation by the sequence of base pairs in DNA molecules. Some

sequences specify protein structure, but many others (the control elements) specify when and where a given protein is to be made.

The function of the action potential is to convey information rapidly over long distances. Here again, only one such mechanism is required. The mechanism that carries information about the sound stream the length of the auditory nerve is the same mechanism that carries information about the visual image the length of the optic tract, and information about mechanical deformation of the skin of the big toe, the length of the body.

Even intracellular and intercellular chemical signaling pathways, where one might expect chemical necessity to operate, are so constructed that in fact none does. The ubiquitous G-protein coupling mechanisms that operate where extracellular chemical signals are converted to intracellular chemical signals remove all chemical connection between the external and internal signals. As a result, within the same basic framework, any extracellular signal can be made to affect any intracellular cascade. The same principle applies within the intracellular cascades. It has been argued that this principle is a key to understanding how complex organic structures have been able to evolve (Carroll, Grenier, & Weatherbee, 2001).

The principle that information is information gives reason to think that the mechanism for carrying information forward in time within the nervous system may be universal, just as is the mechanism for carrying information rapidly from one place to another. For those interested in the physical basis of memory in brains, the question whether the molecular mechanism is or is not universal is of the first importance. For the sake of scientific progress, one hopes that it is. The information-is-information principle gives some grounds for such a hope.

Coding

The transmission and storage of information are basic elements of information processing. Wherever we have to do with information processing, we have to do with codes. Central to a full understanding of an information storage or conveyance mechanism is an understanding of the code it uses. This was immediately appreciated by leading molecular biologists after the discovery of the structure of DNA. Given the structure of the molecule and the knowledge that it carried the information specifying many different protein sequences, it seemed beyond reasonable doubt that the information about how to make a protein was carried by the sequence of base pairs. But what was the code? How long a sequence of base pairs was needed to specify one amino acid (the building block of a protein)? And what was it about such a sequence that determined which amino acid it specified? And how did the decoding mechanism determine where a coding sequence began and ended? Answering these questions about the code became central to the progress of molecular biology (Judson, 1980).

In neurobiology, the situation is different. Du Bois-Reymond discovered the physical mechanism by which information is carried along nerves in 1848 (Du Bois-Reymond, 1848). It was understood at the cellular level by the 1950s (Hodgkin & Huxley, 1952a, b, c, d; Hodgkin, Huxley, & Katz, 1952), and the crucial components of the mechanism, the voltage sensitive ion gates, are now well on their way to being understood at the molecular level (Jiang et al., 2002a, 2002b). However, 150 years after the discovery of the transmission mechanism, we have only

recently begun to make progress in understanding the code, what it is about a sequence of action potentials that carries the information (Rieke, Warland, de Ruyter van Steveninck, & Bialek, 1997). Although the nervous system is clearly an information processing system, we have hardly taken the first steps toward understanding how it realizes elementary information processing functions. We do not know the mechanism by which it stores information and, although we have known for 150 years the principal mechanism by which it transmits information over long distances, we are only now beginning to understand the code involved.

The coding principle is important to keep in mind when considering suggested memory mechanisms. One might reasonably ask that they suggest a means by which information may be encoded, since the essential function of a memory mechanism is the conveyance of information. It is widely suggested that Hebbian synapses are the (or an important) mechanism of memory (e.g., Kandel, Schwartz, & Jessell, 2000). An objection to this proposal is that Hebbian synapses, as traditionally conceived, lack a fundamental property of any code, intelligibility. A code must code for something. Hebbian synapses, as traditionally conceived, do not and cannot code for anything, because they are the physiological embodiments of associative bonds.

Historically, the strength of an associative bond does not and cannot code for an objectively specifiable property of experience, because it is a one-dimensional consequence of many different experiential factors. It is generally taken to be determined by—at a mini-mum—the number of trials on which two signals have been temporally paired, how closely paired they were, and how strong the signals were. Mathematically speaking, the function that maps from elementary experience to the strength of an associative bond (or Hebbian synapse) is a many-to-one function. This means that for any one value of the function (any one state of the synapse), there are an infinite number of different combinations of values for the input (numbers of trials, temporal separations, and signal strengths) that could have produced that state. Thus, the state itself, the synaptic conductance, is unintelligible; it cannot tell us anything about the experiences that produced it.

The unintelligibility of the associative bond—the fact that it cannot represent something about the animal's experience—is why associative theories of learning have traditionally been anti-representational (Hull, 1930; Skinner, 1950; Smolensky, 1986), that is, non-symbolic theories. The general idea in an associative theory is that experience rewires the nervous system so as to make it generate better adapted behavior but not so as to encode what it is about the experienced world that makes that behavior adaptive.

This is not to say that changes in synaptic conductance could not be the basis of memory. They could. But to make this possible, the causal conditions for the production of the changes would have to be such as to make the resulting changes correspond poorly to the traditional conception of an associative bond. It was that conception for which Hebb (1949) hypothesized the existence of what have come to be called Hebbian synapses. Thus, the situation here is different from the situation regarding the coding scheme in nerve transmission. There, the difficulty is not in specifying how information might be encoded by the stream of action potentials; the difficulty is in determining how in fact it is encoded. With Hebbian synapses, the difficulty is in specifying how information could in principle be encoded by such a mechanism.

What constraints must there be on the encoding process? And how would such a code constrain possible decoding mechanisms?

Adaptive Specialization in Learning Processes

Learning processes are those by which brains acquire knowledge of the animal's environment. They are computational processes because useful knowledge is not directly expressed in low level sensory signals; it must be extracted from those signals by computational processes. Different kinds of knowledge require different kinds of computations. The structure of these computations reflects the structure of the problem to be solved, just as the structure of a sensory organ reflects the structure of the physical problem that is to be solved (sound gathering, light focusing, and so on).

The associative approach to learning has little use for a concept of adaptive specialization, because it assumes that a single learning process—association formation—mediates all or most learning (Creutzfeldt & Houchin, 1974; Domjan, 1998; Hawkins & Kandel, 1984; Miller & Escobar, 2002). For that to be the case, there would have to be core structural features that constitute the essence of all knowledge acquisition problems. No one, however, has ventured to describe the computational principles common to diverse knowledge acquisition processes because, from an associative perspective, learning is not a matter of knowledge acquisition; it is a matter of a plastic nervous system molded by experience to generate more adaptive behavior-- but without coding the properties of the world to which the behavior it generates is adapted.

There is now, however, little question that learning does involve knowledge acquisition—the extraction of information from experience. Animals do learn distances and directions in their environment, the times of day at which events happen, the durations of intervals, the numbers of events, and the rates of events (Gallistel, 1990; Gallistel & Gibbon, 2000). Thus, it is no longer possible to ignore the issue of adaptive specialization, because it does not appear to be reasonable to assume that there can be a general purpose knowledge-extraction algorithm, equally suited to extract any kind of information from any kind of input. The following examples illustrate the general principle that it takes different computations to extract different kinds of information from different data. It is these computational principles that act via natural selection over evolutionary time to produce adaptively specialized learning mechanisms.

Learning Current Location

Figure 1 shows a tracing made by Harkness & Maroudas (1985) of the track of a foraging ant of the species Cataglyphis bicolor found in the hot and featureless Tunisian desert. This species does not lay odor trails. The tortuous solid line represents the outward journey when the forager was searching hither and yon for carrion; the straight dashed line represents the journey back to the nest after it found something at the location marked with an X. The directness of the return track implies that the ant knew where it was during its wanderings; there was information in its brain specifying the direction back to its nest. This information about its direction from its nest

is contingent on the details of its twists and turns on this particular outing, so it cannot have been inherited. It must have been acquired from sensory and efference-copy signals generated as the ant wandered, neural signals that indicated from moment to moment the direction and speed of its progress.
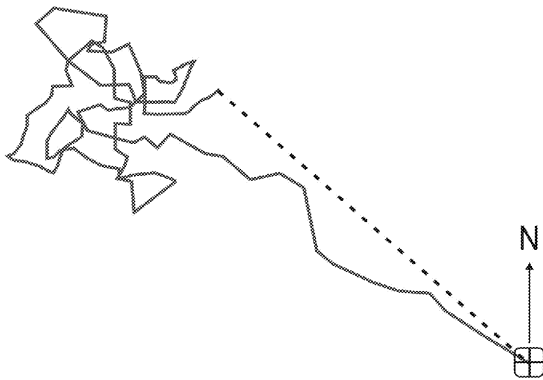
Figure 1. Tracing of a foraging journey by an ant of the species *Catagly-phis biolcolor*. Solid portion = outward journey (search); dashed portion = return to nest after finding food at point X. (Reproduced from Harkness & Maroudas, 1985, by permission of the authors and publisher).

Experiments in which foragers of this species were displaced into unfamiliar territory at the start of their homeward journey show that these foragers will run the correct compass course for approximately the correct distance even when they are traversing territory they have never seen (Wehner & Srinivasan, 1981). This implies that the ant's moment-to-moment knowledge of its ever-changing location derives from a process called path integration or dead reckoning. The essence of dead reckoning is the integration of velocity with respect to time. Equivalently, it is the keeping of a running sum of successive small displacements. These displacements are vector quantities, so each displacement must be resolved into components (for example, latitudinal, or north-south, change and longitudinal, or east-west, change). The vector sum at any moment, which is itself a vector, is the animal's net displacement, that is, its change in position, the difference between (for example) its latitude and longitude when it started and its current latitude and longitude.

The circuitry for performing this computation, whatever it may be, is an example of a problem-specific knowledge acquisition mechanism. The nervous system extracts a particular kind of information about the animal's relation to its environment—its location within that environment—by a computation that directly reflects principles that govern the world the animal lives in. Position is the integral of velocity with respect to time, quite independent of any computation that the animal may make. This enduring environmental fact no doubt explains the emergence of mechanisms within the brains of animals for integrating velocity signals to obtain position signals, in the same sense as the refractive properties of light explain the evolutionary development of the lenses found in eyes. The path-integration computation (partially) solves this problem and only this problem. No one would suggest, for example, that it is in any way suited to obtain information about the grammar of a locally spoken human language.

Dead reckoning to obtain knowledge of position also illustrates the fundamental role that memory plays in learning. The essence of the computation is the keeping of a running sum. A running sum requires a memory to carry forward in time the previous value of the sum, so that the latest displacement may be added to it.

Learning the Solar Ephemeris

Dead reckoning requires knowledge of the compass direction of one's movement (direction in a framework defined by the earth). There is no point in adding the latest displacement to the sum of previous displacements unless all the displacements have been measured in a frame of reference with a fixed orientation with respect to the earth. Maintaining a fixed frame of reference for estimating one's displacement with respect to the earth is not simple, because, in most environments, where only nearby landmarks can be perceived, their compass direction changes as the animal moves--the principle of motion parallax. Thus, any one feature of the terrain cannot be used as a point of directional reference. The farther away a landmark is, the smaller the parallax change in its direction for a given displacement. Thus, it is highly desirable to use as a point of directional reference something that is a very long ways away, something like the sun or the stars. And, in fact, it has been known for nearly a century that a variety of diurnal animals, including ants and bees, use the sun as the point of directional reference when navigating.

The sun is effectively a point at infinity; hence, it has no parallax motion. Unfortunately, however, it does not have a fixed compass direction. Its compass direction changes as the earth rotates. It can change by more than 40 degrees in a single hour. Moreover, the compass direction of the sun at any one time depends in a complicated way on the subject's latitude and on the season of the year. Thus, to use the sun as a point of directional reference, the navigator must know the local solar ephemeris, the sun's compass direction at that location on the earth's surface as a function of the time of day at that season of the year. And, of course, the navigator must also know the time of day.

Knowledge of the time of day is provided by an inborn clock with a period of about 24 hours (Turek, 1998). The clock has a learning mechanism, called the entrainment mechanism, which uses the transitions in overall level of illumination at dawn and dusk to synchronize its oscillations with the day-night cycle. Note that the genes specify the fact about the world that is everywhere and always the same, namely, the period of the day-night cycle, while the experience provides the information that is contingent on one's location, namely the phase of the cycle. To function properly the circadian oscillation in the nervous system must be in phase with the local day-night cycle, and so there is a mechanism that extracts that information from the experience of changes in ambient illumination. This entrainment mechanism is not a general purpose learning mechanism. It extracts this particular kind of information from this particular sensory input and passes it to this particular component of the nervous system (the clock component). Because the local solar ephemeris, like the local phase of the day-night cycle, depends on where the observer is (and on the season), it is unlikely to be genetically given. However, it has one component that is everywhere and always true, namely, that the sun is somewhere in the east all morning long and somewhere in the west all afternoon. It turns out that this knowledge, like the

period of the day-night cycle, is genetically specified. It can be made behaviorally manifest in the absence of the relevant experience (experience indicating the different directions of the sun at different times of day). These experimental findings suggest that the mechanism for learning the solar ephemeris is a parameter-estimation mechanism; the bees learn from observing the sun's direction relative to the local terrain the appropriate parameters for a genetically specified universal ephemeris function (Dyer & Dickinson, 1996). When the values of its parameters have been correctly set by local observations of the sun's direction at a few widely differing times of day, the function correctly predicts the local direction of the sun as a function of the time of day. But in the absence of observations sufficient to correctly establish the values of its parameters, the built in function, using default parameter values, extrapolates directions for the sun at all times of day, given information about its direction at one time of day.

Dyer & Dickinson (1994) raised bees in an incubator, so they never saw the sun. Then, they allowed them to forage in the latter part of the afternoon, when the sun is more or less due west. They foraged from a feeding station due west of the hive, which means that they flew toward the sun on the way from the hive to the station and away from it on the way back to the hive. In the hive, they danced so as to indicate to other foragers the solar bearing of the food source (its direction relative to the sun). The sun is not visible within the hive, but the gravitational vertical takes the place of the sun in the symbolism of the bees' dance. The dance has the form of a figure 8 The angle relative to the vertical of the middle portion of the dance, where the two loops of the 8 are joined, specifies the solar bearing of the food site. Thus, on these afternoons, the bees ran straight up (symbolically, straight toward the sun) during the critical middle portion of the 8.

The bees were allowed to forage only in the late afternoon, until a day dawned with heavy overcast, which blocked their view of the sun, and which promised to last all day. Now, the bees were allowed to forage for the first time in the morning. The experimenters observed their dance when they returned to the hive from the feeding station. Because the experimenter's knew the compass direction of the feeding station (due west), and because the dance indicates its solar bearing, its direction relative to what the bee takes to be the direction of the sun, the experimenters could infer from the direction of the dance within the hive the direction of the sun specified by the solar ephemeris function in the brain of the dancing bee. In the early morning, when they first began to forage, the bees ran straight down (symbolically straight away from the sun) indicating, more or less correctly, that in order to get to the feedings site it was necessary to fly straight away from the sun.

These bees had never seen the sun in the east and could not see it there on the morning in question. They had never reached the feeding station by flying <u>away</u> from the sun; yet that is what they were in effect telling the other bees to do. That the sun was in the specified direction relative to the local terrain (in the east) was a genetically based inference drawn from the information extracted from their previous afternoon foraging experiences, during which the sun was in the west. Thus, the direction of the sun at 7:00 in the morning was not information that had been provided by their prior experience of the sun in the afternoon, although it depended critically on that prior experience. Without having seen the direction of the sun (relative to the terrain around the hive) at a known time, and without having visited the feeding site, the bees could have known neither the compass orientation of the local terrain (how it was oriented with

respect to the axis of the earth's rotation, which, together with the period of rotation, determines the local solar ephemeris) nor the direction of the feeding site from the hive. On the other hand, without prior knowledge of the universal characteristics of the solar ephemeris, the bees' experience of the sun in the afternoon did not specify how to fly relative to the sun in the morning. In particular, it did not specify that it was necessary to fly away from the sun in the morning even though one flew into the sun in the afternoon. Thus, the bees' estimate of the direction of the sun at 7:00 in the morning depended jointly on information extracted from experience and on an inference (or extrapolation) based on information about the universal properties of the solar ephemeris built into the mechanism that learns the solar ephemeris. It also depended on their inborn clock, which provided the information about the time of day.

As the morning wore on, the bees continued to indicate in their dance that the solar bearing of the feeding station was 180° away from the sun, although in fact, of course, the sun was moving into the south. (The experiments were conducted in the northern hemisphere.) Had they been able to see the sun, that is, had they more accurate knowledge of the local solar ephemeris, they would have danced more and more horizontally, as was known from observation of bees that had seen the sun throughout the day. Somewhat before noon, the directions of the dances became widely dispersed. Some danced as if the sun were in the south, as it would be if they were in the northern hemisphere; while others danced as if it were in the north, as it would be if they were in the southern hemisphere. This period of (justifiable) confusion persisted less than an hour before all the bees had reversed the direction of their dancing. Now, they danced as if the sun were due west, in the direction of the station). In fact, of course, it was only somewhat west of south. They should have danced as if one had to fly with the sun on the left, which is how bees with full experience of the solar ephemeris at that locale in fact danced, but, because they relied on a (now incorrect) inference, based on limited experience, they danced as if one had to fly straight into the sun.

In summary, the mechanism by which bees learn the solar ephemeris has built into it what is universally and enduringly true about what has to be learned. It seems likely that this knowledge is built in by means of a genetically specified function relating the sun's direction to the time of day. The function takes as its input (argument) the time of day signal from the circadian clock, and it gives as its output a cyclically varying signal that specifies the compass direction of the sun at that time of day. The function is such that no matter what the values of its parameters, the sun is predicted to be somewhere in the east in the morning and somewhere in the west in the afternoon. Just as the entrainment mechanism extracts from experience the information necessary to set a parameter of the circadian clock (its phase), a learning mechanism extracts from experience the information necessary to set the parameters of the ephemeris function so that it correctly predicts the local direction of the sun at any time of day. Again, this is also not a general purpose learning mechanism. It is structured to extract a particular kind of information from a particular kind of input.

Learning a Language

The just rendered account of how bees learn the solar ephemeris is strikingly similar to a widely (though by no means universally) accepted theory of how humans learn a language (Baker, 2001;

Chomsky, 1975, 1981; Lightfoot, 1999). According to this theory, humans are the only species that can learn a human language because they have a unique genetic endowment, which specifies a universal grammar. The universal grammar specifies the things that are universally true about human languages. The universal grammar, like the universal solar ephemeris function, has parameters. Different values for these parameters yield different languages. Learning the local language is a matter of extracting from what one hears people say the values of the parameters.

Because the vast majority of sentences we both hear and produce are unique (heard or produced only once in a lifetime), we are constantly in the position of the bees in the just recounted experiment. Our previous experience does not—in the absence of extrapolation—give sufficient information to specify an interpretation for what we hear and say, that is, a mapping between the prelinguistic representation of what was to be communicated and the utterance itself. It is the universal grammar together with the parameter values derived from local experience that provides the mapping. In the absence of the universal grammar, most utterances would not mean anything to most hearers, because none of the utterances they had heard in the past would be the same as the utterance just heard. Similarly, in the absence of a universal grammar, speakers would not be able to convert their prelinguistic thoughts into the unique utterances by which they generally communicate their thoughts, because they would never before have experienced the requisite meaning-utterance pairing. This is closely analogous to the case of the bee, which, in the absence of a universal solar ephemeris function, would have no way to estimate from its experience of the sun's direction at other times of day what its direction might be at the current time of day.

In summary, there is reason to think that both the learning of the solar ephemeris in bees and the learning of language in humans is a matter of extracting from experience the information necessary to specify the parameters of built in functions. Although the two mechanisms are similar at this level of abstraction, they are otherwise dissimilar. No one would suppose that the mechanism that enables a bee to learn the solar ephemeris would enable it to learn a human language. And only the most extreme proponent of the Whorfian view that all human knowledge depends on language would argue that the mechanism that enables us to learn a language enables us to learn where to look for the sun when we emerge from our house in the morning.

Conditioning

Conditioning refers to the learning that occurs in experimental paradigms designed to study the laws of association formation. In these paradigms, the experimenter programs the animal's experience in such a way that an outcome that it either wants or wants to avoid (typically, food, in the first case, and shocks to the feet in the second case) is contingent on either a neutral stimulus (typically, the sounding of a noise or tone or the appearance of a luminous pattern) or on a response of the animal. When the outcome, which is called the reinforcer or unconditioned stimulus (US for short), is contingent only on the occurrence of a motivationally neutral stimulus (called the conditioned stimulus or CS for short), then the process is called Pavlovian conditioning. When the outcome is contingent on something the animal does, it is called instrumental or operant conditioning.

In associative approaches to learning, conditioning and learning are synonymous, because conditioning paradigms are those by which psychologists determine the laws of learning (Miller & Escobar, 2002). In the light of the examples just discussed, one might wonder whether it makes sense to speak of the laws of learning. If problem-specific computational principles are needed to understand everything from ants learning their location, bees learning the solar ephemeris, and humans learning language, should we expect that there exists a form of learning that does not make use of problem specific computational principles? Clearly, if it does exist, the place to look for it is in the results from conditioning experiments. Moreover, most contemporary work on the neurobiology of learning is predicated on the assumption that the learning that occurs in conditioning experiments is the foundation of most if not all learning (e.g. Fanselow, 1993; Hawkins & Kandel, 1984; Mayford, Abel, & Kandel, 1995; Miller & Escobar, 2002; Usherwood, 1993).

Because associative theories of learning do not specify how an animal extracts information from its experience, descriptions of conditioned behavior commonly do not discuss the timing of conditioned responses. In those paradigms in which the time of reinforcement occurs at a fixed interval following an earlier event, like the onset of the CS, or the delivery of the preceding reinforcement, conditioned responses are timed so as to approximately coincide with the predicted reinforcement (Figure 2). The timing of their response is evidence that subjects in conditioning experiments extract from the flow of events the durations of the intervals between events. Like the direction of the ant's homeward track, this response timing is a direct manifestation in subsequent behavior of information that has been extracted from previous experience and carried forward in memory. It suggests that the learning that occurs in conditioning experiments might be profitably subject to the kind of problem-specific computational analysis that was applied to the preceding examples. Conditioned behavior might also be the result of problem-specific computations that extract relevant information from the subject's experience.

Although conditioning paradigms were not developed within a conceptual framework that emphasizes the problem-specific nature of the learning principles, they do in fact pose a specific kind of computational problem; they present the subjects with problems in multivariate, non-stationary time series analysis. In a conditioning paradigm, the next occurrence of the reinforcer is probabilistically dependent on the earlier occurrence of another event or events (a CS, a response, or both), so, from a computational perspective, the problem the subject must solve belongs to the domain of time series analysis. The problems posed are generally multivariate because the subjects must generally compute which of several experienced CSs predicts the US (Kamin, 1969; Wagner, Logan, Haberlandt, & Price, 1968). Finally, they require what is called a non-stationary time series analysis, because the predictive relation between the CS and the reinforcer or between the response and the reinforcer often changes in the course of the experiment (for example, in experiments that have a conditioning phase, during which the CS is paired with the US, followed by an extinction phase, when it is not).

These considerations suggest that conditioned behavior might be profitably analyzed from the same computationally oriented, information-processing perspective that seems relevant to understanding the already discussed examples of problem-specific learning mechanisms. Gallistel

& Gibbon (2000) have reviewed the conditioning literature from this perspective, showing that this kind of analysis resolves several seemingly intractable paradoxes.
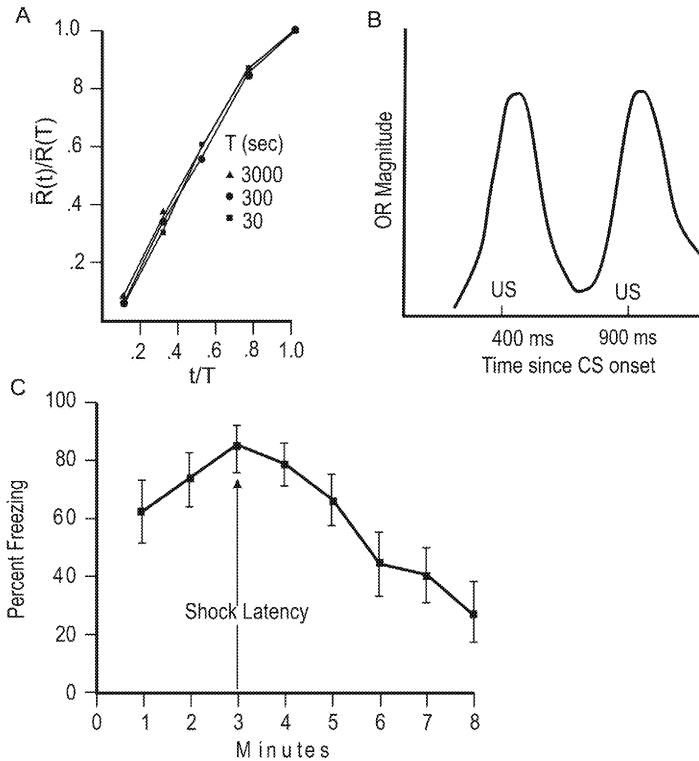
Figure 2. The conditioned response peaks at approximately the time that reinforcement is expected. A. The normalized rate of pecking (essentially, the probability that the pigeon has begun to peck) as a function of the proportion of the fixed interval that the schedule imposes between successive rewards for pigeons pecking to obtain food on fixed interval schedules of 30, 300 or 3000 seconds. (Data from Dews, 1970); (plot from Gibbon, 1977, by permission of the publisher.). B. The motions of the nictitating membrane (eyelid) in a rabbit in a paradigm where a shock to the skin around the eye occurred either at 400 ms or 900 ms after the onset of a warning tone. The sequence of latencies (400 or 900 ms) was randomized, so the subject could not know which latency would be in effect on any given trial. These data are from a probe trial, when there was no shock. (From Kehoe, Graham-Clarke, & Schreurs, 1989, by permission of the authors and publisher.) C. The percent freezing in rats given one-trial contextual fear conditioning. They experienced brief footshock 3 minutes after being placed in a novel chamber. These data come from the next day, when subjects were returned to the chamber and their freezing behavior was measured (freezing is a behavior indicative of the anticipation of shock). (From Fanselow & Stote, 1995, by permission of the authors).

In their analysis, the multivariate problem is solved by means of a matrix computation that rests on the principle that independent random rates are additive. A random rate process is the simplest kind of process that generates recurring events. A random rate (or Poisson) process is the default assumption in time series analysis in the same way that a normal distribution is the default assumption in many other kinds of statistical analyses. If you know nothing about a US (reinforcing event) other than that n events have been observed in t amount of time, then you assume that it is a random rate process, because a random rate process is entirely characterized by a rate parameter, the number of events per unit of time. A random rate process is simpler from a statistical point of view than a process that generates a normal distribution, because to specify the latter you need two parameters, a mean and a standard deviation. A random rate process is also the simplest from an information processing point of view, because it has the property that the event is equally likely at any moment in time. The rate parameter determines what that likelihood is, but the likelihood is everywhere the same. Moreover, the process has no memory for its past: the expected time to the next occurrence of the event is the same no matter how long it has been since the last event. Knowledge of a rate parameter in a random rate process is the minimum knowledge it is possible to have about the time at which the next event will occur. The only thing less than this is no knowledge at all.

The above statements are true of random rate processes whether or not they are incorporated in the mechanism of conditioning, just as the laws of optics are true whether or not they are incorporated in biological lenses. However, in the model of the conditioning process proposed by Gallistel & Gibbon (2000), the mechanism that solves the multivariate aspect of the problem incorporates these principles just as faithfully as the vertebrate lens incorporates the laws of optics. Because random rate processes are additive, computing the true rates of US occurrence predicted by each of arbitrarily many assumed-to-be-independent CSs reduces to solving a system of simultaneous linear equations, in other words, to an exercise in matrix algebra. The formula, first given by Gallistel (1990), is:

$$\vec{\lambda}_t = T^{-1}\vec{\lambda}_r$$

where $\vec{\lambda}_t$ is the vector (the ordered list) of the (true) rates of US occurrence predicted by each CS acting in isolation, $\vec{\lambda}_r$ is the raw or uncorrected rate vector,

$$\vec{\lambda}_r = \begin{vmatrix} \dfrac{N_1}{T_1} \\ \dfrac{N_2}{T_2} \\ \vdots \\ \dfrac{N_m}{T_m} \end{vmatrix}$$

and $\mathbf{T}^{-1}$ is the inverse of the temporal coefficient matrix:

$$
\mathbf{T} = \begin{vmatrix}
1 & \dfrac{T_{1,2}}{T_1} & \cdots & \dfrac{T_{1,m}}{T_1} \\
\dfrac{T_{2,1}}{T_2} & 1 & \cdots & \dfrac{T_{2,m}}{T_2} \\
\vdots & \vdots & \ddots & \vdots \\
\dfrac{T_{m,1}}{T_m} & \dfrac{T_{m,2}}{T_m} & \cdots & 1
\end{vmatrix}
$$

with N_i is the cumulative number of USs in the presence of the ith CS, T_i is the cumulative amount of time that the ith CS has been present, and $T_{i,j}$ is the cumulative amount of time that ith and jth CS have been jointly present. Gallistel & Gibbon (2000) propose that subjects extract from their experience by means of counters and timers the requisite running total counts and durations (the N_i 's, T_i 's, and $T_{i,j}$'s) and make this computation in order to determine the rates of US occurrence predicted by each CS, and thence, on the assumption of independent causation (rate additivity), the rates of US occurrence to be expected from any combination of the CSs.

For present purposes, the only thing one needs to appreciate about this computation is that it is built directly on the objective (or analytic) properties of random rates. For that very reason, it is as problem specific as the computation with which we began, the integration of velocity with respect to time to obtain position with respect to time. No one would suggest that this matrix computation explains either how an ant learns where it is or how a human learns a language. This computation solves this problem and only this problem It is but one example of the many problem-specific computations proposed by Gallistel & Gibbon (2000) to explain various experimentally determined properties of conditioning. If their analysis is any where near the mark, then the mechanisms that operate in conditioning are as problem specific as the ones already reviewed in other domains.

One may well ask, however, why one should take the Gallistel & Gibbon (2000) proposals seriously. Are there not explanations of conditioning results in terms of a general process associative theory, a theory (or theoretical framework) that incorporates no problem-specific principles? And are not these theories in some sense simpler and more parsimonious?

Gallistel and Gibbon's answer is that problem-specific models explain quantitative results that are deeply difficult for associative theories to explain, results that call into the question the basic assumptions of the associative framework. Many of these results come under the heading of the time scale invariance of conditioning. This empirical principle asserts that the time scale of a conditioning protocol does not matter; within broad limits, the results will be the same even if all the intervals in the protocol are changed by some multiplicative factor. Insofar as this principle holds, it implies that it is not the absolute durations of the intervals in the protocol that

matters, it is the proportions among those durations. Scaling the protocol up or down does not change those proportions.

Take for example, the two proportions that exist in every classical conditioning protocol, the proportion between the ISI and the ITI. The ISI is the interstimulus interval, the interval between the onset of the CS and the onset of the US (the interval between the predictor event and the predicted event). The ITI is the intertrial interval, the interval between the offset of the US, which marks the end of one trial, and the next onset of the next CS, which marks the start of the next trial. The longer the intertrial interval is in relation to the interstimulus interval, the more precisely (relatively speaking) the CS predicts the occurrence of the US. By the principle of time-scale invariance, the results of a conditioning experiment should not change—other things being equal-- as long as the proportion between these two intervals does not change. In other words, what matters is the relative precision with which the CS predicts the US, how much it reduces the subject's uncertainty about when the US will occur (Gallistel, 2002, in press).

This principle appears to hold in the only conditioning paradigm in which it has been strongly tested (Figure 3). Increasing the ISI has no effect on the number of reinforcements that must be given before the conditioned response appears, provided the ITI is increased in proportion. So long as the relative precision with which the CS predicts the US is constant, the number of reinforcements that must be given to produce a conditioned response is constant.
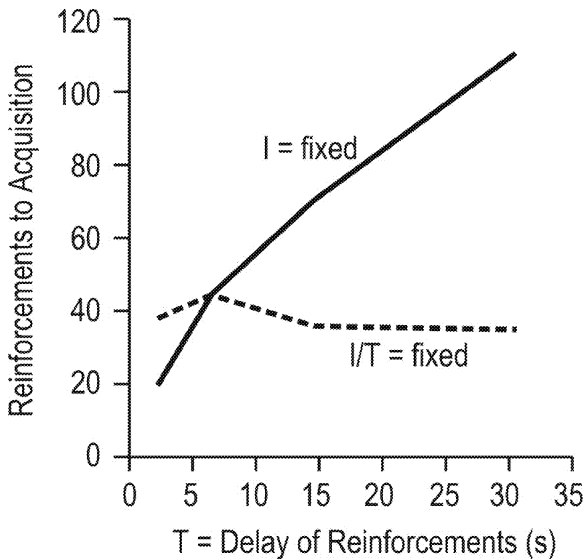
Figure 3. Reinforcements to acquisition as a function of T, which is the CS-US interval (the delay of reinforcement), when the interval, I, between trials is fixed (solid line) and when it is increased in proportion to the increase in T (dashed line). (From Gallistel & Gibbon, 2000, by permission of the publisher).

The result in Figure 3 is difficult for associative theories to deal with because they assume that the temporal pairing of the CS and US is critical to conditioning. Temporal pairing seems like a simple notion, but what exactly does it mean? In associative theories it has meant that both the CS onset and the US onset must occur within a critical temporal window, or "trial." If they both fall within that window (if, for example, they both occur on the same trial), then the two events are temporally paired; if they do not, then they are not. If this is true, then conditioning cannot be time-scale invariant in the way just specified, because, as one scales down the temporal intervals in the protocol, there must come a point at which the ISI is longer down than the critical window. Beyond that point, the conditioning process will no longer treat the CS and US as temporally paired, and conditioning will not occur. Put another way, the notion of temporal pairing in associative theorizing has always assumed that whether or not the associative process treats two events as paired depends on processes that have an intrinsic time scale of their own—temporal windows, trials, trace decay rates, state decay times, and so on (see, for example, Gluck & Thompson, 1987; Hawkins & Kandel, 1984; Rescorla & Wagner, 1972; Sutton & Barto, 1990; Tang et al., 1999; Usherwood, 1993; Wagner, 1981). The associative process is sensitive to the absolute durations of the intervals in a conditioning protocol, whereas the principle of time-scale invariance implies that it is only relative duration that matters.

A second example of the principle of time-scale invariance is seen in the lack of effect of partial reinforcement on the rate at which a conditioned response is acquired (Figure 4). It has been known since Pavlov (1928) that it is not necessary to deliver reinforcement every time the CS is presented. Even if one delivers the reinforcement on a randomly chosen fraction of the occasions on which it is presented, subjects nonetheless develop a conditioned response to the CS. In at least one commonly used conditioning paradigm, pigeon autoshaping, on average only one out of ten presentations of the CS may be reinforced, and still the subjects acquire. In fact, the number of reinforcements required to induce them to respond to the CS is no larger under these circumstances than it is when every CS presentation is reinforced (Figure 4). This result appears to directly contradict a basic assumption in associative theories, which is that reinforcement and non-reinforcement have opposing effects. Reinforcing the CS when it is presented strengthens the association; failing to reinforce it, either weakens the association, or, strengthens competing inhibitory associations. In either case, the behavioral effects of non-reinforcement oppose the behavioral effects of reinforcement. Therefore, intermixing an average of 9 non-reinforced presentations of the CS for every reinforced presentation, should greatly increase the number of reinforcements required to induce conditioned responding, which is contrary to experimental fact (Figure 4).

That partial reinforcement should not affect the outcome of a conditioning experiment (the number of reinforcements required to acquisition) is another manifestation of time-scale invariance. Interpolating non-reinforced presentations of the CS increases the average amount of exposure to the CS per reinforcement. Put another way, it reduces the rate of reinforcement in the presence of the CS. The more non-reinforced trials there are on average, the greater the reduction in this rate; hence the longer the subject must expect to wait for a reinforcement when the CS is present. In the previous example, however, we saw that how long a subject has to wait for its reinforcement in the presence of the CS does not matter in and of itself. What mattered was how long that wait was relative to the expected wait in the absence of the CS (Figure 3). The

subject's estimate of the latter wait depends on how much unreinforced experience it has with the experimental chamber during the periods when the CS is not on, that is, during the intertrial intervals. The more unreinforced intertrial intervals it has experienced the lower its estimate of the background rate of reinforcement, the rate in the absence of the CS. When we interpolate unreinforced presentations of the CS, we also interpolate an equal number of unreinforced intertrial intervals. Thus, if we ask, after r number of reinforced presentations of the CS, what
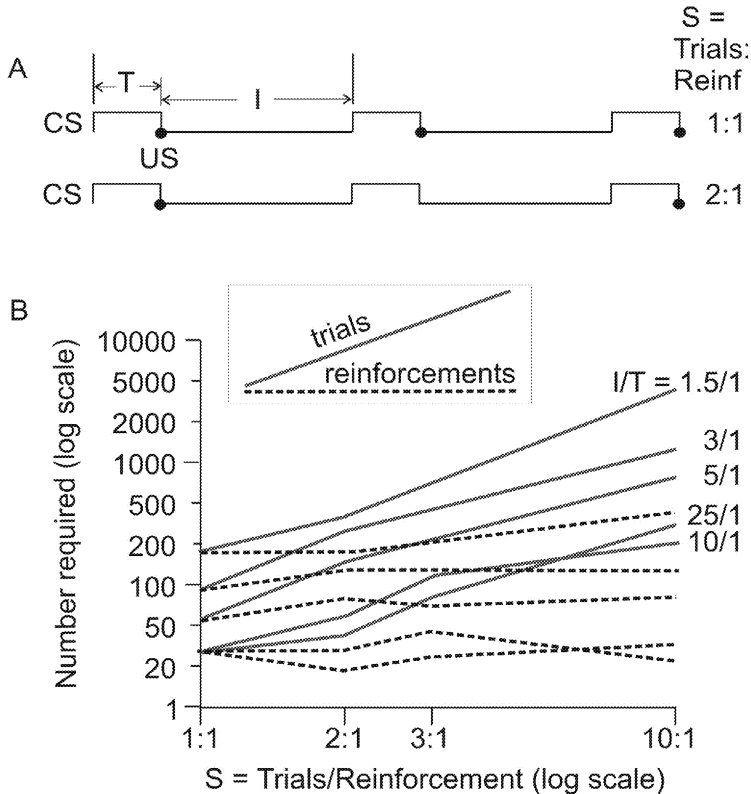
Figure 4. A. Time line showing a simple conditioning protocol. The elevations in the time line indicate the intervals during which a key on the wall of the pigeon's chamber was illuminated. The dots on the line at the end of CS presentations signify the delivery of food, which always came at the end of key illumination (whether or not the pigeon pecked the key). This Pavlovian procedure induces (classically conditions) key pecking. Reinforcement may be delivered every time the CS is presented (top line) or on some random fraction of the presentations (second line). B. Reinforcements to acquisition (dashed lines) and trials to acquisition (solid lines) as a function of the fraction of the CS presentations (trials) that terminate in reinforcement (food delivery). Each pair of solid and dashed lines is joined at the left, where the number of reinforcements equals the number of trials (a 1/1 schedule of reinforcement). The between curve variable is the ratio of the interval between trials to the trial duration; the greater this ratio, the smaller the proportion of total time the conditioned stimulus (the key light) is on.

is the ratio (proportion) between the expected wait when the CS is present and the expected wait when it is absent, the answer is unaffected by whether or not we have interpolated unreinforced presentations of the CS. The interpolation increases both waits by the same factor. Thus, the interpolation of unreinforced presentations should have no effect, as in fact it does not.

Whereas the time-scale invariance of the conditioning process directly challenges fundamental assumptions in associative theories of conditioning, it is a direct consequence of fundamental assumptions in a problem-specific approach. Problem-specific information-processing models assume that the learning mechanisms that extract relevant information from a given domain of experience are tuned to the deep principles governing that domain. From a problem-specific perspective, what the subject tries to extract from the temporal flow of events it experiences in a conditioning experiment is information that reduces its uncertainty about when the next event it cares about will happen (i.e., the next reinforcer). This is the kind of information that a time-series analysis tries to extract, which is why the mathematics of time-series analysis are assumed to be relevant to characterizing the underlying learning mechanism in conditioning. Time series analyses, like all statistical analyses, are scale invariant; they are unaffected by rescaling operations that increase or decrease all the inputs by some multiplicative factor. The following consideration shows that this must be true, without involving any actual mathematics: Computer programs that do statistical analyses, do not prompt the user for the units that go with the numbers in the data files. This implies that the units are irrelevant to the analysis, which implies that rescaling the numbers will have no effect, because changing the units from, for example, minutes to seconds, simply scales up all the numbers by a factor of 60. Thus, without going into mathematical details, it is possible to appreciate that a problem-specific, information-processing approach to understanding mechanisms of conditioning will be time-scale invariant. Hence, absent some overriding assumptions, it will predict the manifestations of time scale invariance in Figures 3 and 4.

Conclusion

The biological principle of adaptive specialization applies to learning and memory mechanisms just as much as it applies to other biological mechanisms. At the memory level, this suggests that we should look for the properties in the neurobiological mechanism of memory that we see in other good memory mechanisms. These properties are thermodynamic stability and high density.

We might also expect to find that the basic mechanism of memory, the mechanism that carries information forward in time, is domain independent, that is, it does not differ depending on the kind of information that is to be carried (visual information, auditory information, spatial information, temporal information, declarative information, episode information, biographical information, procedural information, etc.) Computer memories and DNA both have the function of carrying information forward in time, they both display the properties of thermodynamic stability and high density, and they both are domain independent. The action potential mechanism has the function of conveying information rapidly over long distances within the nervous system. It, too, is domain independent.

Finally, mechanisms that convey information are necessarily coding mechanisms. There must be principles that specify what it is about the state of the mechanism that conveys information about states of the world. Thus, another thing we can look for in the neurobiological mechanism of memory is the coding principle: how does the physical change that constitutes the memory represent information about the world?

In contrast to mechanisms of memory, there are reasons to think that learning mechanisms should be and are domain specific, just as are sensory organs. Learning involves extracting from raw sensory experience information about behaviorally important properties of the environment. Extracting this kind of information requires computations that are specific to the kind of information to be extracted and the sense data from which it is to be extracted. A very simple illustration of this principle is the dead reckoning mechanism, which enables subjects to learn their location from their experiences while getting to that location. The crucial sense data in this case are those that indicate the animal's velocity (its direction and speed of travel). The crucial computation is the integration of these velocity signals with respect to time to obtain signals that specify position.

This mechanism for extracting information from experience differs strikingly from the mechanism that learns the local solar ephemeris, which is the compass direction of the sun as a function of the time of day. At the heart of this mechanism is a genetically specified universal ephemeris function, with settable parameters. Learning the local ephemeris involves extracting from observations of the solar bearing at different times of day the requisite values of the parameters. When the parameters are correctly adjusted, this mechanism takes the time-of-day signal from the built-in circadian clock and generates a signal specifying the compass direction of the sun at that time.

The mechanism for learning the local solar ephemeris appears similar in broad outlines to the language learning mechanism envisaged by many linguists. At the heart of this mechanism is a genetically specified universal grammar, likewise with settable parameters. Learning to speak and understand the local language involves extracting from samples of that language the requisite values of grammatical parameters. When those parameters are correctly set, the subject speaks and understands the local language.

If problem-specific computational mechanisms are involved in everything from an ant's learning where it is, to a bee's learning where the sun is, and a human learning a language, one might reasonably suppose that learning is always mediated by one or more problem-specific mechanisms, whose structure suits them to solve one and only one class of problems. This supposition, however, conflicts with the long-standing tradition that an associative learning process mediates most learning. If all learning is mediated by problem- specific learning mechanisms, what is going on in Pavlovian and instrumental conditioning paradigms, which were created to study the laws of associative learning? It turns out that these paradigms all challenge subjects with a computationally coherent class of problems: multivariate, non-stationary time series analysis. Moreover, learning mechanisms specifically designed for this kind of problem deal successfully with quantitative property of conditioning—time scale invariance—that challenges the fundamental assumptions of associative theory.

If even Pavlovian conditioning is mediated by a problem-specific learning mechanism, then it is reasonable to conclude that learning processes are like other biological processes in that their structure is adapted to their function. There is a multiplicity of learning processes, each suited to solving a different kind of information-extraction problem.

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