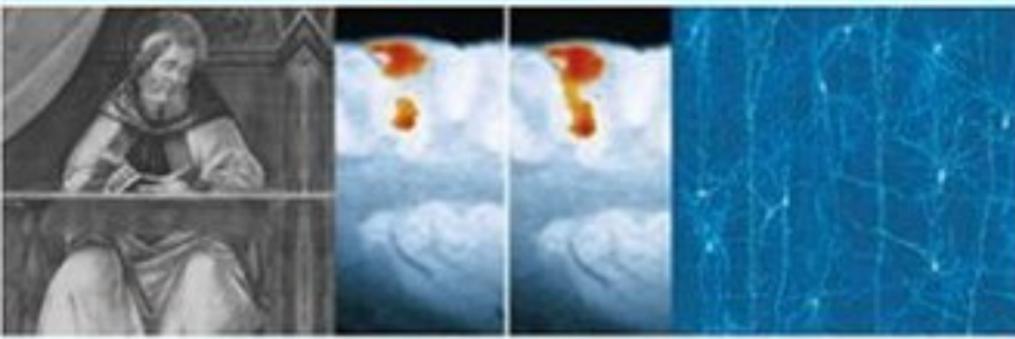


YADIN DUDAI



Memory from A to Z

keywords, concepts and beyond

OXFORD

Memory

From A to Z

Keywords, Concepts, and Beyond

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Dar es Salaam Delhi Hong Kong Istanbul Karachi Kolkata
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Published in the United States
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First published 2002

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British Library Cataloguing in Publication Data

Data available

Library of Congress Cataloging in Publication Data

10 9 8 7 6 5 4 3 2 1

Typeset by Cepha Imaging Pvt. Ltd., Bangalore, India

Printed in Great Britain

on acid-free paper by T.J. International, Padstow, Cornwall, UK

Preface

This book contains terms that I wish my students to Howard Eichenbaum, Mark Konishi, Serge Laroche, know. I hope that the book will also be of interest to Joseph LeDoux, Rafi Malach, Henry Markram, Randolph additional audiences. Over the years, the members of Menzel, Richard Morris, Karim Nader, Lars Nyberg, my research group have joined from a variety of Noa Ofen-Noy, Robert Rescorla, Nava Rubin, Dov Sagi, backgrounds, ranging from psychology via biology to Menahem Segal, Roni Seger, Alcino Silva, Burton Slot computer science. The common denominator was nick, Wendy Suzuki, and Misha Tsodyks. I am grateful always keen interest in the marvels of *meritoty. to them all for their wise advice, although, of course, facilitate the translation of this interest into science, they should be blamed for nothing.

the members of the team must master a language. This I am particularly grateful to my wife, Rina, for her is an attempt to present and explain selected elements¹ giving support, keen interest, and shrewd comments. in this language. The fact that the science of memory I also appreciate the reactions of many students is but one branch of science, combined with the who attended my lectures at the Weizmann Institute unavoidable idiosyncrasy in the selection, resulted inof Science, the University of Edinburgh, New York the inclusion in the book of some terms that are University, and the Gulbenkian Institute of Science, shared by other sectors of the scientific *culture Oeiras, Portugal. Major parts of this book were written as well.

at the Weizmann Institute, and others at the Center for

The entries can be read as is. They may also be used¹ Neuroscience, University of Edinburgh, and at the as a versatile tool kit: a source for definitions, informa- Center for Neural Science, New York University. I am tion, and further reading; a trigger for contemplation grateful to Joe LeDoux and Richard Morris for their and discussion; and an aid to study, teaching, and friendship and for being such patient and kind hosts. debates in classes and seminars. The entries are not¹ thanks go also to Tom Boyd from the Royal Society, replacement for comprehensive professional reviews¹ London, for the reference on the first use of the they could, however, incite interest in further delving *mouse in scientific experiments; to Francis Colpaert into the literature. In writing the entries, I tried to for advice on the *state-dependent learning literature follow the advice of Poe (1846) that the optimal length and for Collin¹ the moonston¹ (1868/1992); to Liba of an item should fit to be read in a single sitting. I do Cehnbrov and Anna Llionsky from the Wix Central realize that cultural respect for the exploitation of Library services at the Weizmann Institute, to Shoshi human *attention span has probably declined over the Hazvi from the Department of Neurobiology at the past 150 years, but still, I hope that I did not deviate Weizmann Institute, and to librarians at the University much from Poe¹s *criterion.

of Edinburgh and New York University, for assisting me

The definition(s) at the beginning of each entry, and in obtaining hard-to-get copies of enjoyable books and the ones scattered throughout the text introduce into articles. Reading these sources reinforced my conviction this book elements of a lexicon. The humble fate often that some important questions, ideas, and even lexicographers did not escape my notice: ÔÉthesé¹s answers are much older than we tend to pretend, a fact unhappy mortals¹ can only hope to escape reproach, of life that should be occasionally *recalled and re-*con- and even this negative recompense has been granted¹ solidated in our *collective memory. very few¹ (Johnson 1755). A number of colleagues have read versions of selected entries and provided the right combination of encouragement and reproach. Among them were Ehud Ahissar, Amos Arieli, Diego Berman, Aline Desmedt, Haim Garty, Patricia Goldman-Rakic,

¹ Throughout the text, terms preceded by an asterisk refer to entries in the book.

Acknowledgements

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Fig. 31, Elsevier ScienceFig. 32, American Psychological AssociationFig. 33, Academic Press;Fig. 34 Cambridge University PressFig. 35 Oxford University PressFig. 36, Cambridge University Press;Fig. 38Yale University LibraryFig. 40Elsevier Science; Fig. 44, Elsevier ScienceFig. 45, Elsevier Science; Fig. 47 Nature Publishing Group, LondonFig. 50 Oxford University PressFig. 51, University of Nebraska Press;Fig. 54 American Psychological AssociationFig. 56, Elsevier ScienceFig. 60, Taylor & Francis, UK Fig. 9, National Academy of Science, Washington, DC;and The Psychonomic Society, Austin, TXFig. 61 The Fig. 10, Kluwer Academic/Plenum Publishers and Guildford Press, NYFig. 64, Clarendon Press, Oxford; MIT Press;Fig. 11 Oxford University Press and The American Physiological SocietyFig. 18 Nature Publishing Group, LondonFig. 20, British Psychological Society and Cambridge University PressFig. 22 Elsevier ScienceFig. 23 Nature Publishing Group, London;Fig. 24Carl Donner, Scientific American Inc., NY and Oxford University PressFig. 26 Cambridge University PressFig. 27, Nature Publishing Group,

Cover: Insets (from left to right): Augustine, as depicted by Botticeli (Uffizi Gallery, Florence; *classic); Learning-dependent changes in the activity of human cortex, as detected by fMRI (*functional neuroimaging, *skill; courtesy of Avi Karni); Neurons in the *cerebral cortex (courtesy of Henry Markram).

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The conceptual framework

The premises that underlie the selection of entries, the adaptation and formulation of definitions, and the views expressed in this book.

I am a functionalist with a biologist's bias and with a conscious awareness of other disciplines. My approach (1954). Whenever possible, I tried to adhere to one of the following tenets: (a) the function of the brain is to create and retain internal representations of the world that could guide behaviour; (b) the function of learning is to permit the adaptation of internal representations to a changing world; (c) learning and memory require neural plasticity for their actualization; and (d) learning and memory are system properties, made possible by the concerted operation of multiple levels of the system. Each entry opens with a definition, or a set of definitions. What a definition is, is extremely difficult to define. A liberal list contains no less than 18 different species of definitions, and multiple candidate definitions are not mutually exclusive, and reflect, the following meanings of definition: (a) the minimal set of attributes that uniquely describes an item or a concept; and (b) the formulation of a thing in terms of a more elementary level of organization or theory. These meanings are not mutually exclusive, and reflect, an attempt to adhere to Ockham's razor, over time); (c) learning and memory require neural and the basic reductionistic approach, which has been plasticity for their actualization; and (d) learning and memory are occasionally used in more than one way, I provided multiple definitions when appropriate. The difficulties and uncertainties involved in defining entities at the cutting edge of knowledge could without addressing its input-output relationships. The view that attempts to define entities at the cutting edge of knowledge could (semantics) of internal representations emerges in the cause more harm than good: For when we define, we brain. Identification of the behavioural level is self-evident. Identification of the level that encodes internal bounds of our own notions (Burke 1757). There is, representations is not. It is currently believed that however, the opposite view, that the risk is well the level critical for encoding the semantics of internal representations in the brain is the circuit level, or the circuit level. More reduced levels implement plasticity, but in the absence of the circuit being aware of Burke's caveat, I am much in favour of context, do not suffice to endow the representation Meno's conviction.

with its semantics. It is essential, therefore, that research programmes on memory never lose sight of the circuit systems. Bodies of knowledge in general are associative and the behavioural levels. This is not easy. The circuit systems. I tried to reinforce this notion by proposing that the behaviour level is often excessively complex, the behaviour being selected associations. The reader is invited to form level amazingly tricky. Furthermore, the remarkable additional ones. Associations are not only aids to success of molecular neurobiology is enticing. I thus understand, they are also proven mnemonic devices: the richer the associative network, the higher the probability that the item will be stored (*metaphor) to memory research (Dudai 1992). I hope that this is reflected in the entries throughout this book. and *retrieved.

The conceptual framework

¹Functionalism in its broadest sense is any view that analyses something in terms of how it functions (Lacey 1996). There are several versions of functionalism, one of which is Ôfunctional analysisÕ (Cummins 1975). This is the research strategy that relies on the decomposition of a *system into its component parts while attempting to explain the working of the system in terms of the capacities of the parts and the way they are integrated with each other (Block 1980). Still, the structure of the parts and of the integrative system matters solely as much as it implements or shapes the function. Functional analysis is the sense of functionalism implied here.

A Priori

1. Independent of experience.

2. Beforehand.

A priori it could be assumed that students and aficiona-source of a priori knowledge in the individual brain: the dos of memory will benefit from contemplating the genetic material. Genes carry information about a variety of concepts of Ôa prioriÕ. Before defending the aforesaid of behavioural capabilities and capacities (*neuro-statement, however, a brief clarification of the different genetics). This information is hence ÔinnateÕ or as meanings and uses of Ôa prioriÕ is appropriate. the individual is concerned, this is a fide-a-priori

Prior to the eighteenth century, the pair of terms Ôknowledge. For the species it is not, because the knowledge prioriÕ/Ôa posterioriÕ (Latin for Ôfrom what is earlierÕ/Ôedge is supposed to have been acquired over time, a what comes afterÕ) was used to distinguish between posteriori, by natural selection in evolution. However, it modes of reasoning: ÔThe mind can discover and undeis also useful to consider as Ôa prioriÕ that knowledge stand the truthÉ by demonstration. When the mind that cannot be explained by the individualÕs experience reasons from causes to effects, the demonstration isience. Such knowledge is generated by *developmental called a priori; when from effects to causes, the demonprocesses, via the interaction of genes and environment stration is called a posterioriÕ (Arnauld 1662). Onlyin prenatal and early postnatal periods. It is also later were these nonidentical terminological-twins used produced throughout life by the endogenous activity of to refer to types of knowledge: knowledge independentthe brain, which depends on the processing of both of experience is Ôa prioriÕ, that which is grounded innate and acquired knowledge. Definition 2 is collo-experience is Ôa posterioriÕ (Kant 1781). Traditionallyual: according to it, ÔexperienceÕ is Ôexperience at th since then, the pair Ôa prioriÕ/Ôa posterioriÕ is associated with timeÕ, e.g. while on a learning task. Hence in the philosophical discourse with two other pairs of according to this liberal interpretation any experience opposites: ÔanalyticÕ vs. ÔsyntheticÕ, and ÔnecessaryÕ provides a priori knowledge for future experiences. ÔcontingentÕ (Moser 1987; Grayling 1997). A statementThis connotation of a priori gravitates toward the triv is ÔanalyticÕ if its truth value can be determined by, and will not be further discussed here.

understanding the concepts or terms contained in it, A priori knowledge of both innate and postnatal whereas it is ÔsyntheticÕ if in order to determine its truthorigin fulfils multiple roles in behaviour and behav value we must know how the concepts or termsioural *plasticity:

involved relate to other constituents of the world. 1. Innate knowledge underlies reflexes and predeterHence, adapting a commonly used illustration, Ôsingleminded behavioural routines such as used in feeding, are unmarriedÕ is analytic, because ÔsingleÕ is Ôunmating, fighting, and fleeing (Lorenz 1981; Dudai riedÕ, whereas Ôsingles are happyÕ is synthetic, because 1989). These behaviours vary in their dependency on is not evident from ÔsinglesÕ how their mood should postnatal experience. Some are essentially independent (the latter statement also demonstrates that some kinds of experience, although they still may be perfected or of truth are *context specific or in the eye of the modified by it, e.g. -type *classical conditioning. Other beholder, but this is another story). In formal terms, an behaviours require experience for maturation, fine analytic statement is thus a tautology, and its truth tuning, and optimal *performance. This experience value follows necessarily. The latter property leads us to have to be provided during a restricted Ôsensitive to the third related pair of opposites: ÔnecessaryÕ periodÕ in life, as in *imprinting (Lorenz 1981) and ÔcontingentÕ. ÔnecessaryÕ refers to statements that Ôtaste song (Nelson and Marler 1994). Another, more be either true or false due to what they state, whereas igeneral type of ÔpreparedÕ or Ôconstrained learningÕ, ÔcontingentÕ statements the truth value is contingentwhich the type of associations, but not their actual upon other occurrences or relationships in the world. content, is constrained a priori, is *conditioned taste Discussion of the ÔnecessaryÕ/ÔcontingentÕ pair is withension: we are inclined a priori to associate the taste the realm of metaphysics, the ÔanalyticÕ/ÔsyntheticÕ of foodstuff with subsequent visceral malaise but not deprives logicians of sound sleep, whereas Ôa prioriÕ with a painful blow to the skin (Garcia et al. 1968). Ôa posterioriÕ is within the domain of epistemologAdmittedly, most philosophers would not like the use of (the science of knowledge) (Moser 1987; Grayling 1997the term ÔknowledgeÕ in the context of such Ôsimple Bealer 1999).

It is the epistemological connotation of Ôa prioriÕ that interests us here. Furthermore, we focus on only a limited portion of the universe: the individual organism, its brain, behaviour, and memory. Construing ÔexperienceÕ in definition 1 as any behavioural or physiological experience of the individual, leaves only one

A Priori

tells him that young geese follow the farmer around (*level). Then there is the ongoing flux of the short-lived without previous conditioning or training. If Lorenz pre-representations themselves, which are unique to were to add that the young goose knows that it should each individual of the species, and could be regarded as follow the farmer, or that the farmer is a friend, flashes of subjective knowledge preceding *perception philosophical ears would be pricked (Cooper 1972) and the *acquisition of memories. In this case, the past However, first of all, ÔknowledgeÕ is here used in its literally chases the present, and Ôa prioriÕ may refer to a *reductive connotation, not necessarily involving time-scale of seconds only. Still, this is Ôa prioriÕ, because *conscious awareness (*internal representation); at least part of the information is not derived from ond, irrespective of the status of philosophical ears, the actual experience in the outside world.

question whether animals are Ôconsciously awareÕ or not. The ÔselectionistÕ hypothesis hence implies that we is not yet settled (*declarative memory).

continuously anticipate the world and generate approx-

2. Innate knowledge underlies capacities and operate models of it, and that both endogenous and tional rules of higher brain faculties such as language exogenous information combine to represent reality and mathematical abstraction in humans (Ôthe speaker e.g. Arieli et al 1996). This raises the question how of a language knows a great deal that he has not learned. faithful to reality are our internal representations Chomsky (1966); compare Socrates on geometry: ÔT₁ false memory, *real-life memory). We may assume to discover by recollection what you do not know, or that in the course of evolution, our ability to model the rather what you do not rememberÕ (Pitkänen 1986b).

world, learn about it, and interact with it has been

3. Perhaps most intriguing is the notion that a priori shaped to reach a reasonable correspondence of the knowledge that draws from a combination of innate internal models to reality. The fact that organisms suc- and acquired resources permits our brain to anticipateeed in negotiating with an ever changing milieu attests the world on a momentary basis (e.g. Anokhin 1974). to that. But not all our memory *systems (*taxonomy) This issue relates to one of the most profound problemshave been subjected to the same selective pressures, in the neurosciences and the philosophy of mind: the such as the pressure for improved precision and detail. relationships of internal representations to the outsideHence, whether a specific type of memory, such as world. Let us consider two basic possibilities. One is*declarative, is inherently faithful to reality or not, is that input from the world somehowinstructs the brain itself a priori influenced by evolutionary forces.

to generate specific internal representations of reality. Last, we should not *forget that in daily life we are all This type of process does not necessitate a priori knowlestrained by a priori assumptions that could *bias edge, although it may still benefit from it. The other our personal (or *cultural) attitude toward events, possibility is that the world somehowselectsrepresenta- facts, and disciplines. The attitude toward ÔmemoryÕ is tions among Ôpre-representationsÕ, which are generated expected to be an exception.

endogenously in the brain (Young 1979; Heidmann et al 1984; Dudai 1989; Edelman 1993; *stimulus). The Selected associations: Acquisition, Development, Palimpsest

ÔselectionistÕ view has a Darwinian flavour, and likens the ontogenesis of our mind to the phylogenesis of our

species. According to this view, the mammalian brain For *classic philosophical attitudes to innate knowledge in general is not a passive observer but rather an active agent that see Locke (1690) and Leibniz (1704).

anticipates the immediate future (*planning), and toward that end keeps itself busy by generating internal

*models of reality. The postulated rules that guide Ôthe

survival of the fittest internal modelsÕ may take into

account predictions based on both innate knowledge

and accumulated experience, and congruency with the

on-line demands of the real world as conveyed by the A *neurotransmitter at central *synapses and at

senses. Such capacity is hence expected to be subserve₁ the vertebrate neuromuscular junction.

in every individual of the species by two tiers of a priori

knowledge. First there are the species-specific innate Acetylcholine (ACh; the acetic acid ester of choline) components responsible for much of the rules and was among the first chemicals to be proposed as a the hardware, namely the computations, *algorithms neurotransmitter, and the first neurotransmitter to and neuronal devices that enable the brain to generate identified in and isolated from neural tissue (Dale and stabilize the aforementioned pre-representations 1914; Loewi 1921). It was also the first for which the

Acetylcholine

existence of a proteineous membrane *receptor had been suggested (Nachmansohn 1950) vivo ACh is synthesized from the amino alcohol choline and acetyl coenzyme A. The job is done by the enzyme cholinesterase (Kitamoto et al 1992). ACh is hydrolyzed by another enzyme, acetylcholinesterase, one of the fastest enzymes ever (Taylor and Radic 1994). Receptors for ACh are of two major types:

1. α -Nicotinic, so-called because they bind nicotine (the tobacco poison). Nicotinic receptors are ion-channel receptors, i.e. they contain a pore that mediates the flux of ions across the membrane and is gated by the neurotransmitter (Karlin and Akabas 1996).
2. α -Muscarinic, so-called because they bind muscarine (a mushroom poison that kills flies). Muscarinic receptors are α -metabotropic, i.e. they do not include a channel but rather exert their effect by modulation of intracellular signal transduction cascades (Wess 1993).

Each of these receptor types can be further classified into subtypes. The subtypes are commonly characterized by their affinity and specificity for activators (agonists) and inhibitors (antagonists); the identity of the deficits in dementia. The α -cholinergic hypothesis proposes that cholinergic dysfunction is not only a correlate, but also a cause of cognitive and behavioural dysfunctions. The hypothesis was highly successful at least on one front: it generated a surge of research on the potential role of cholinergic modulation in learning and memory, and served as an incentive for the development of cholinergic drugs to treat dementia (see below).

Cholinergic innervation of various brain areas such as the α -cerebral cortex could be described as either α -projectional or α -modulatory. Multiple processes and mechanisms have been suggested to underlie the postulated roles of ACh in

extrinsic, e.g. stemming from central cholinergic nuclei in the brain, or intrinsic (Johnston et al 1981; Mesulam 1983). The central cholinergic nuclei in the basal forebrain and the brainstem (Figure 1). The major ones are in the basal forebrain and they innervate the neocortex, the hippocampus, and parts of the α -amygdaloid complex. Those in the brainstem innervate among other the thalamus. The innervation by the central cholinergic nuclei is an example of a α -diffused neuromodulatory system, i.e. a neuromodulatory system that does not target specific synapses or neurons but rather a whole region or multiple regions (see also α -dopamine, α -noradrenaline).

The cholinergic basal forebrain system, itself a collection of nuclei, has been repeatedly implicated in cognition, including α -attention, learning, and memory.

A correlation was found in a number of studies between degeneration of basal forebrain nuclei, cholinergic dysfunction and cognitive deterioration in Alzheimer's disease (α -dementia) and in aged humans and rodents. This has led to the α -cholinergic hypothesis of memory

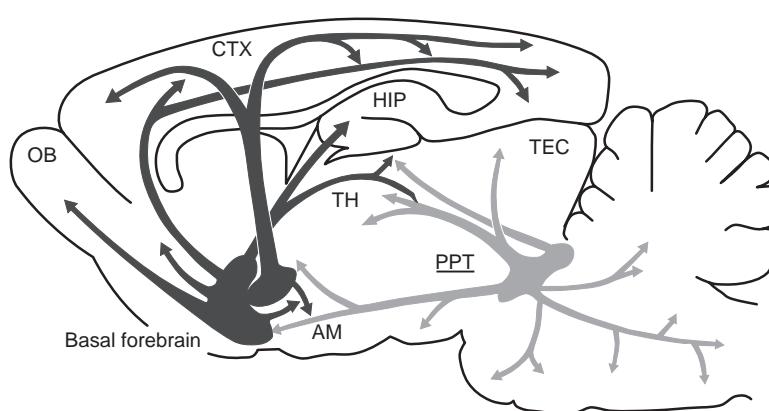


Fig. 1 A schematic diagram of the central cholinergic projections in the mammalian brain. There are two major projectional networks from the basal forebrain, innervating among others the α -cerebral cortex (CTX), α -hippocampus (HIP) and α -amygdala (AM), and laterodorsal tegmental nuclei (marked in the figure as PPT), innervating among others the thalamus (TH) and tectum (TEC). Local cholinergic circuits are not shown. (Adapted from [Kondo et al.](#))

Acetylcholine

learning and memory. As is the case with other neuro-and in certain cases an obligatory role of ACh, acting transmitters and neuromodulators, the physiological either via muscarinic or via nicotinic receptors, in a roles of ACh in brain should be judged not only by its variety of learning situations and of neuronal *plastic-independent activation of specific cellular receptors and mechanisms that *model attention and learning their downstream intracellular signal transduction cas- (Auerbach and Segal 1996; Geay 1996; Picciotto et cades, but also by its contribution to the activation anal. 1998; Berma et al 2000; Mansvelder and McGhee cross-talk of webs of signalling cascades induced by 2000; Nail-Boucheret et al 2000; Rasmusson 2000; coactive sets of neurotransmitters and neuromodulators Shulz et al 2000). For example, in many preparations, (*coincidence detector, *context). Similarly, at the cir- ACh enhances transmitter release, and in some it supports *level, the function of the cholinergic system must ports *long-term potentiation. Stimulation of the basal be assessed in the context of the concerted activity of forebrain cholinergic input was shown to enable the multiple neurotransmission and neuromodulatory path- reorganization (*plasticity) of cortical sensory *maps, ways on the target circuit (Decker and McGaugh 1991) and hence possibly *internal representations, in ACh was portrayed as a cellular code for saliency (*response to modality-specific input (Bjordahl et al 1998), *attention, *state dependency, and even as a direct 1998; Kilgard and Merzenich 1998); a caveat is, how Ôstorage signalÖ that instructs the appropriate circuits over, appropriate regarding such an approach, because, encode novel information as lasting *internal representations as noted above, the basal forebrain is also a source of tions (Mishkin and Murray 1994; Naor and Dudai 1996; noncholinergic innervation to the cortex. Another Everitt and Robbins 1997; Wenk 1997; Shtul et al 2000). report that made it to the headlines was that transplants of similar cellular and circuit mechanisms, with alleviates cognitive deficits in rats with a cholinergically the specific role of the cholinergic function in a given denervated cortex (Winkler et al 1995).

cognitive and behavioural situation being dependent upon the task, the context, and the identity of the brain system in cognition stems from human pharmacology. All the above functions could actually be different manifestations of the brain of cells engineered to release ACh into the target circuit (Barkai and Hasselmo 1997). Furthermore, to the understandable dismay of non-smokers, nicotine appears to be moderately beneficial to smokers, nicotine appears to be moderately beneficial to

In recent years, the function of ACh in the mammalian brain has been scrutinized by a variety of novel methodologies, techniques, and preparations. Not all appears that cholinergic drugs establish themselves as cognitive attention and memory (Di Carlo et al. 2000). It thus appears that cholinergic drugs establish themselves as cognitive attention and memory (Di Carlo et al. 2000). It thus that ACh is indeed obligatory for learning, certainly not specific roles of ACh in cognition and memory are fully in all types of learning, but the overall picture favours understood. This, of course, is not unique to the cholinergic idea that it does play an important part in many drugs; if understanding the mechanism of action was a learning situations. A somewhat surprising finding *criterion for the introduction of a drug, many of our was reported by several laboratories following the most efficient medications would not be in use.

introduction of a powerful experimental tool, the chimera-immunotoxin 192IgG-saporin. This toxin is a synthetic chimera between the toxin saporin, that kills cells, and an antibody to a subtype of a receptor, for nerve growth factor that resides on most types of cholinergic neurons in the basal forebrain. The compound guides itself to these cholinergic neurons and destroys them selectively, while leaving other neurons, the majority of which are noncholinergic, intact.

In disparity with the effect of less selective lesions of basal forebrain cholinergic nuclei, in several preparations, the guided toxin had only a small effect if at all on memory (e.g. Baxter et al 1995; but see, for example, Power et al. 2002). In contrast, a variety of other new experimental manipulations did support a correlative

Selected associations: Attention, Dementia, Neurotransmitter, Receptor, Synapse

For an early suggestion that there should be a receptor, long before ACh itself was discovered, see Langley (1878).

1. The initial *phase in the formation of a *memory trace.

2. The process by which new information is converted into a memory trace.

Acquisition

In disparity with the effect of less selective lesions of basal forebrain cholinergic nuclei, in several preparations, the guided toxin had only a small effect if at all on memory (e.g. Baxter et al 1995; but see, for example,

Power et al. 2002). In contrast, a variety of other new experimental manipulations did support a correlative

3. The change in *performance during training that is taken to represent the progression of *learning.

Memories are like people—*they are born, live, and from physiology and psychophysics, the decay time die*. Acquisition is their moment of birth. The other major phases in the life history of a memory are consolidation (if it is ever to become a long-term memory), storage, retrieval, and extinction mechanisms hence differentiate transitory from lasting (*experimental extinction, *forgetting). Depending on the context of discussion, *Acquisition* implies a temporal phase (definition 1, e.g. Stalling et al 1987); or a decay time.

This process that takes place during this phase (definition 2, e.g. Tulving 1983); or a change in *performance that depends on the learning *paradigm and protocol. reflects this process (definition 3, e.g. *behaviourism). It is convenient to distinguish *Instant* from increasing. This change in performance is quantified by an acquisition curve or *Learning curve*, in which refers to single-trial learning. This takes place performance is plotted against the amount of practice in certain situations of intense aversive conditioning (e.g. Skinner 1938; e.g. Figure 41, p. 144). Commonly, some types of *imprinting; in the formation of *flash- of the task if its performance has reached a preexisting memories; and probably in some other situations, *criterion, such as time to reach the goal in a *maze or in which acquisition curves have a step-function shape a certain probability of success on a discrimination (e.g. *insight). In contrast, incremental acquisition problem (e.g. *delay task). The process of acquisition refers to situations in which information accumulated was termed *Engraphy* by Semon (1904), meaning *to engrave* over multiple experiences to construct the engraving of an *engram, but *Engraphy* has never been used as a synonym (Pavlov 1927; Skinner 1938; Hebb 1949; Dudai 1989). Gradual acquisition of *habits and *skills is for *learning*, but the latter term has a broader meaning in usage. The repetitive practice is expected to involve gradual modification of internal representations.

Acquisition is composed of subprocesses. The first is *encoding*, which in general refers the conversion of message from one language, or code, to another. *Encoding* is frequently used in the learning literature to refer to situations over hours, days, even months. But does *Encoding* involve accumulative modifications that are restricted to the original representation? This is a synonym for *Acquisition*, but this is unsatisfactory. Internal representations are formed at the beginning of training? This might be naive. Internal representations because there is more to *Acquisition* than *Encoding*. Expected to form dynamic distributed networks in neuronal encoding, information is transformed into (*cell assembly). Therefore, a more realistic view is the neuronal codes used in computation and representation that recurrent discrete events of acquisition and consolidation, that stem from each accumulative experience. In the first case, the electromagnetic, mechanical, or chemical information is converted via the sense organs into new representations and link them to the old world. In the second case, the information is converted via the sense organs into neuronal activity. In the second case, the information is converted via the sense organs into neuronal activity.

information from the body itself is conveyed by specialized neuronal circuits, or via body fluids in the form of chemical messages (hormones) that evoke neuronal activity. No information can be handled by the central nervous system without being encoded into the appropriate neuronal code. Encoding is thus involved in brain activities that do not necessarily culminate in memory. Two influential factors in the acquisition of a memory, such as on-line processing concepts that reflect this notion will be mentioned here. of information (*attention, *percept), or control of ongoing physiological routines. For a memory to be stored in memory be *retrieved in due time. Two influential factors in the acquisition of a memory, such as on-line processing concepts that reflect this notion will be mentioned here. One is the *Encoding-specificity principle* (Tulving 1983). It states that memory performance is best when

born, an additional process, of initial *Registration* (*Recording*), is also needed. This permits the *internal representations of transient *stimuli, once formed, to become or induce an engram. From what we know

the cues present at retrieval match those present in during the training (Wagnleitner et al 1998b). It is not yet known, however, which of the activated areas is indispensable for acquisition. The other is termed "transfer-appropriate processing" (Morris et al 1977). It states that memory is more likely to be acquired if it is presented in a context that is similar to the one in which it was learned. This is because the context provides cues that help the brain to identify the memory and retrieve it.

Multiple approaches are used to investigate the mechanisms of acquisition. Cellular physiology, neuropharmacology, neurochemistry, and molecular biology are all applied to dissect the molecular and cellular mechanisms involved. Candidate cellular acquisition devices are ion channels and membrane receptors on synaptic terminals that receive the teaching input, itself encoded in ion currents and neurotransmitters (*Aplysia long-term potentiation). A substantial amount of information is also available on the processes downstream from the synaptic membrane, that involve activation of intracellular signal transduction cascades, and couple acquisition to consolidation.

We even seem to start to understand in molecular terms. "Begin at the beginning," said the King of Hearts, "and why is it that in many learning situations, distributed go on till you come to the end: then stop." He thus training with intercalated intervals between repetitive provided White Rabbit with an algorithm (Carroll 1865). The term "algorithm" is derived from Latinization, in which acquisition mechanisms are tion of the name of one of the most creative mathematicians in medieval Islam, Al-Kwarizmi (780-850).

Brain areas and neuronal circuits that subserve acquisition have been identified in *habituation, *sensitization, *classical, and *instrumental conditioning in a variety of *simple or less-simple *systems (Aplysia, Drosophila, *fear conditioning, *honeybee). In recent years, *functional neuroimaging has made a remarkable contribution to the identification of brain systems that subserve acquisition in the human brain (e.g. Nyberg et al 1996; Flett et al 1997; Tulving and Markowitz 1997; Buckner and Koutstaal 1998; Epstein et al 1999; Fernández et al 1999). The circuits that acquire information about a memory vary with the type of memory, but a few general conclusions emerge. It is sensible, therefore, not to from the studies so far: (a) acquisition of declarative memories engages widely distributed areas, which for solving a class of problems. It is hence close to include modality specific cortex, and in addition supramodal areas, particularly in the mediotemporal lobe (*hippocampus, *limbic system); (b) these areas may be vaguer. Furthermore, a rule may partially overlap brain areas that later retrieve the knowledge by the executing agent of the input learned information; and (c) in some studies it was relationship, algorithm does not. A system can execute possible to show a correlation between the activation of algorithms perfectly without having the faintest idea of an identified brain region during the training what it is doing, why it is all done, and what the outcome experience and the subsequent ability to remember this is likely to be. As there is no a priori reason to assume that biological learning at the synaptic or circuit level is governed by a knowledgeable supervisor activation in the left prefrontal and temporal cortex (*homunculus), it does not make a lot of sense to claim

that synapses or circuits follow "rules"; rather, they ~~exist~~ificial neural networks (ANN; Fausett 1994). These cute algorithms. Finally, an assumption (usually tacit) are artificial systems (i.e. either abstract *models or of the neuroscience of learning, and an incentive for the physical implementation of such models) analysis of *simple systems, is that a great variety of biocomposed of a large number of interconnected computational learning systems, in different species, share ~~gen~~erational units ("neurons"). Signals are passed between several laws/rules/algorithms. This posit makes sense if neurons over connections, which manipulate the signal evolution is considered, but is definitely not itself a law, in a typical way. Each neuron applies an activation function and its generality must be scrutinized in every experiment to its net input to determine its output signal. Specimen system anew (e.g. Seligman 1970).

The most popular algorithms in the neuro-connectivity ("architecture"), the algorithm that determine science are synaptic ones, and are associated with a ~~pos~~es the weight on the connections, and the activation tulate of synaptic *plasticity dubbed "Hebb's postulate". In its original version it states the following: "When such networks could mimic various dynamic properties axon of cell A is near enough to excite a cell B andf neuronal circuits, such as *perception and learning. repeatedly or persistently takes part in firing it, some Certain subclasses of ANN use Hebbian algorithms to growth process or metabolic change takes place in oneachieve "unsupervised" learning (see above) in local or both cells such that A's efficiency, as one of the cellodes. Other algorithms refer to "supervised" learning, in firing B, is increased" (Hebb 1949; for rudimentarywhich some type of global information or "instructor" precedents see James 1890; Kappers 1917). In a Hebbianforms the node what the desired end-point is. An synapse, the increase in synaptic weight is thus algorithm of the latter type that has gained considerable function of the correlation of pre- and postsynaptic popularity is "back-propagation" (or "back-propagation activity. Hebb postulated the process to account forof errors"). Here the error for each unit (the desired experience-dependent modification of local nodes in minus the actual output) is calculated at the output of *cell assemblies. In formal notation, Hebb's postulate is the network, and recursively propagated backward into of the type $w_{ij}(t+1) = w_{ij}(t) + \alpha_i(t) \cdot e_i(t)$, where $w_{ij}(t)$ is the strength ("weight") of the connections are adjusted to approach the desired output vector connection from presynaptic unit i to postsynaptic unit j of the network (Rumelhart et al 1986a).

unit i , $\alpha_i(t)$ is the change in synaptic strength $e_i(t)$. A number of algorithms have been proposed to and $a_i(t)$ are measures of pre- and postsynaptic activityunderlie learning at the more global levels of brain (Brown et al 1990). Each step in the algorithm is thus and behaviour (Thorndike 1911; Dickinson 1980; a computation of the aforementioned type, and the Wasserman and Miller 1997). An influential one is associated algorithm consists of proceeding step-by-step over timeciated with the Rescorla and Wagner model of learning (at a more *reduced level, the Hebbian computation (1972; for precursors, see Hull 1943; Bush and itself is based on multiple subordinate algorithms, Mosteller 1951). Basically, Rescorla and Wagner posited such as summation and multiplication, but this should that in *associative learning, changing the associative not concern us here). The original "Hebbian" became strength of a stimulus with a *reinforcer, depends upon a generic term as well as a reference for many variants the concurrent associative strength of all present stimuli of synaptic modification algorithms. Terms composed with that reinforcer; if in a given training trial the of "Hebb-plus-a-modifier" to mark their relationship to composite associative strength is already high, learning the Hebbian are common, and sometimes a bit confus-will be less effective. In formal notation, RescorlaDWaging. For example, "anti-Hebb" is used to describe rather propose that $V_x - V_R = V_x - V_R$, where V_x is the different types of algorithms that culminate in decre- change produced by a given training trial in the strength ment of synaptic efficacy (e.g. Lisman 1989; 1993; *long-term potentiation, *metaplasticity). Over reinforcer R ; x and R are learning rate parameters the years multiple attempts have been made to demon(associability parameters) representing properties strate how Hebbian algorithms might be implemented in such as the intensity and saliencyX and R; R is the synapses in *development and learning (e.g. Lismam maximal conditioning supportable bR; and V is 1989; Fregnac and Shulz 1994; Buonomano and the total associative strength with respect R of all the Merzenich 1998; Lechner and Byrne 1998; but see a critisimuli present on the aforementioned trial. The expresscal review in Cruikshank and Weinberger 1996).

A discipline in which synaptic learning algorithms expectation and reality on a given trial; the smaller it is, became particularly popular and useful is that of the weaker is the learning. In other words, as many

Algorithm

a reader might have concluded from their own experience, the amount of learning is proportional to the adverse effect of certain types of brain injury and amount of surprise (see also *attention). Here again, mental trauma on memory was recognized long ago. each step in the algorithm is a computation of the But the systematic analysis of amnesia started only in aforementioned type, and the algorithm consists of the nineteenth century, with Ribot (1882) and proceeding step-by-step over time. The Rescorla-Wagner model can explain multiple behavioural neuroimaging, the study of amnesia has been the phenomena in conditioning, including cases of *cue only practical approach to the investigation of brain revaluation (Dickinson 1980; Wasserman and Miller 1997; *classical conditioning).

could be also obtained from electrical stimulation of

Over the years multiple attempts have been made to patients undergoing brain surgery, but this was very account for the operation of selected brain regions by limited in scope and controversial in interpretation proposing identified synaptic and circuit algorithms (*engram). The investigation of amnesia is still a very (For notable examples, see Marr 1969; Albus 1971) powerful, unique approach to the analysis of human Zipser and Andersen 1988). At the current state of the memory: whereas the application of functional art in brain research, synapses and model circuits neuroimaging could identify correlations between the still provide a more suitable arena than whole real-life activity of distinct brain regions and the *performance circuits to identify and test learning algorithms, because on memory tasks, the study of amnesiacs could potentially identify those brain structures that are obligatory the input-output relationship of real-life brain circuits is seldom understood in reasonable detail, if at all. for normal memory (*criterion, *method).

Still, advances are being made at more global levels. Amnesia is not a unitary syndrome (Whitty and of brain function as well; for example, Schultz Zangwill 1966; Parkin 1987; Mayes 1995). A *taxonomy based on etiology distinguishes among Ôorganic (1997) report that in the course of multitrial instrumental training, *dopaminergic activity in the primate brain amnesiaÕ, Ôsubstance-induced amnesiaÕ, and Ôfunctional encodes expectations and prediction errors for reward amnesiaÕ. These subtypes of amnesia are also known by The dopaminergic neuro-modulatory system may thus other names, as explained below.

be part of a circuit that performs computations of the type $R^T V$ in the Rescorla-Wagner model.

New classes of algorithms are expected to emerge at the cellular, circuit, and system levels with the intensification of the mechanistic revolution in biology. One of these days, much of descriptive neurobiology is bound to give way to a science of biological engineering, in which algorithms and quantitative relations will become the rule rather than the exception. This has profound implications concerning the proper education of future neurobiologists (e.g. Alberts 1998).

Selected associations: Lear~~Models~~ Level Plasticity
Synapse

-
1. **Organic amnesia** is a consequence of damage to the brain inflicted by injury, disease (e.g. tumour, stroke, viral infection), or surgical intervention (DSM-IV 1994).
 2. **Substance-induced amnesia** results from the intake of poisons, drugs of abuse, or medications with amnestic side-effects (for example, certain anxiolytics, *lotus). Chronic excessive consumption of alcohol could result in vitamin deficiency and encephalopathy (brain inflammation), which is manifested in Korsakoff's amnesia, at which stage it is also categorized as organic amnesia (Shimamura et al 1988).
 3. **Functional amnesia** develops after severe mental stress or trauma, or as a result of certain affective disorders. This type of amnesia is also termed ÔpsychogenicÕ, or ÔdissociativeÕ (Ôdissociative disorders in general are disruptions in the integrated functions of *consciousness, perception, personal identity, or memory).

The amnestic syndrome impairs learning and memory while leaving other cognitive faculties relatively intact. It is hence distinguished from *dementia, which involves multiple cognitive deficits, and from delirium, which impairs consciousness. Whereas some amnesia

Amnesia

1. The loss or absence of memory.
2. **The amnestic syndrome** A marked, chronic impairment in memory in the absence of other major cognitive deficits.

are modality specific (e.g. Rubin and Greenberg 1998) progressively from the unstable to the stable; the *amnestic syndrome* is *global* and independent (Ribot 1882).

sensory modality. Global organic amnesia is *transient* some improvement may be observed over time, but the amnesia is that of H.M. He became amnestic in 1953 patient does not regain normal memory. There is also at the age of 23, following a frankly experimental separate syndrome termed *postictal global amnesia*. This is a benign neurological syndrome in which the uncontrollable epilepsy. The operation removed bilateral onset of amnesia is sudden and the recovery fast (usually the medial temporal polar cortex, most of the ally 1 day). Transient amnesia could also follow head*amygdaloid complex, the entorhinal cortex, and trauma or electroconvulsive therapy.

The *classical, most widely cited case of a global amnesia is that of H.M. He became amnestic in 1953 following a frontal lobectomy (Scoville and Milner 1957) to alleviate his epilepsy. The operation removed bilateral hippocampus. The frequency of seizures, but produced a severe, permanent amnesia. Retrograde amnesia affects memory of events prior to the operation (and no effect on memory from the onset of the pathology backward). Anterograde amnesia affects memory from on more remote events). Postoperatively, H.M. scored the onset of the pathology forward. For example, in above average on a general intelligence test, showed no typical case of the amnestic syndrome, there is dense decline on immediate memory (*capacity), but was anterograde amnesia and usually only a partial, graded unable to store any new *declarative information. He retrograde amnesia. Memory of the recent past is com-was, however, capable of learning new *skills. Thus even monly affected more than memory of the distant past; in this severe case, the amnesia was not really *global*; this observation is termed "the law of regression", or "the study of H.M.", as well as of many other amnesics "Ribot's law" (it is noteworthy that Ribot regarded this then, gave rise to major insights concerning this phenomenon as the manifestation of a Darwinian human memory (Squire and Zola 1997; Milner et al 1998). These studies have demonstrated that the brain

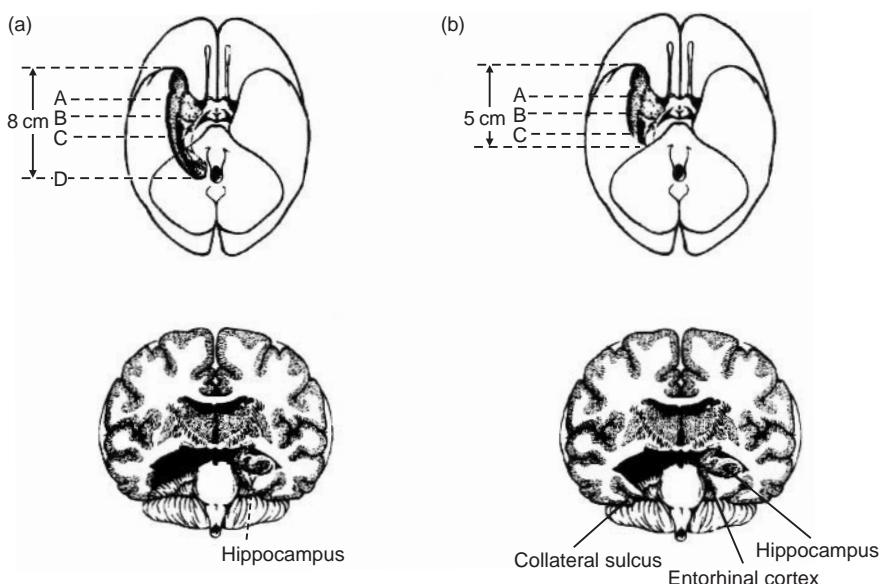


Fig. 2 The missing parts in the brain of H.M., removed in the operation that had resulted in global amnesia. (a) The planes of coronal sections in the original drawings, but only plane B is shown here. The operation was bilateral but in the hemispheres are shown intact for comparison. Adapted from (Milner et al 1997). The case of H.M. drew much attention to the role of the medial temporal lobe in general, and the hippocampus in particular, in long-term memory.

contains distinct declarative (explicit) and nondeclarative (implicit) memory systems; and that long-term integration of novel functional neuroimaging methods in the study of amnestic brains.

declarative memory is dependent on medial temporal lobe structures. Additional research has shown that nondeclarative amnesia could result from damage to a different, corticostriatal system (Mishkin et al 1984; Knowlton et al 1996; *skill). Support for the above conclusions has also emerged from studies of circumscribed brain lesions in *monkey models of human amnesia (e.g. Mishkin et al 1984; Ridley and Baker 1991; Meunieret al 1993; Zola-Morgan et al 1993; Gaffan 1994; Leonard et al 1995). Indeed, the neuroscience of amnesia is characterized by a remarkable degree of integration of human and animal research.

Selected associations: Conscious awareness, episodic memory, Dementia, Infantile amnesia, ^{Degenerative}

¹Reversible disruption of activity by transcranial magnetic stimulation (TMS) might also be used to identify brain areas obligatory for learning and memory (e.g. Grafman 1999; Ross et al 2001), but it has not yet been widely employed.

amnesia (e.g. Mishkin et al 1984; Ridley and Baker

1991; Meunieret al 1993; Zola-Morgan et al 1993;

Gaffan 1994; Leonard et al 1995). Indeed, the neuroscience of amnesia is characterized by a remarkable degree of integration of human and animal research.

Amygdala

Despite the impressive advances in our understanding of amnesia, many outstanding questions still await resolution (Warrington and Weiskrantz 1982; Mishkin et al 1997; Nadel and Moscovitch 1997; Squire and Zola-Morgan 1997; Weiskrantz 1997; Milner et al 1998; Aggleton and Brown 1999).

Among these: Is amnesia due to impairment in the *acquisition, *consolidation, storage, or retrieval of memory? Although most authorities consider acquisition of information to remain intact in global amnesics, because of the good performance of H.M. (see above), still, its shape resembles an almond (αγδα in Greek).

even subtle deficits in the way information is encoded and registered could markedly affect later retrieval. About a dozen different nuclei and specialized cortical areas are currently discerned in the amygdala, and Another question is what is the specific contribution of many intra- and extra-amygdalar connections have to different manifestations of the amnestic syndrome, such as anterograde vs. retrograde amnesia, or *recall vs. *recognition deficits? The amygdala (alias the amygdaloid or amygdalar complex), first described and named by the German anatomist Burdach in the early nineteenth century (Meyer 1971), is so called because in the primate brain the immediate memory tasks (see H.M. above), still, its shape resembles an almond (αγδα in Greek). The amygdala has been identified (Amaral et al 1992; Pitkänen et al 1997; Swanson and Petrovich 1998; Aggleton 2000). Indeed, the heterogeneity of the nuclei, areas, and pathways and the mammillary bodies), to different manifestations of the amnestic syndrome, such as anterograde vs. retrograde amnesia, or *recall vs. *recognition deficits? The amygdala as a whole is raised some doubts whether it is a discrete anatomical entity *situ*, or only an artificial construct of the human mind (e.g. Kirkpatrick 1996; Swanson and Petrovich 1998; de Olmos and Heimer 1999). Whether a well-defined natural kind or merely a convenient concept, judging by its connectivity, the amygdaloid complex fits well to serve as a central

Each amnestic subject is a unique individual, and probably in none are the lesions confined to a single representations. This is because sets of amygdaloid nuclei interconnect heavily with the unimodal and polymodal cortex, as well as with subcortical structures. Some of these pathways are asymmetrical (more extensive in one direction, e.g. from amygdala to hippocampus), and the information flows into one to warrant adaptation of the conclusions from the animal to the human. Solutions are expected to emerge from the systematic analysis of additional cases of the temporal lobe, including the amygdala, were amnesia (e.g. Reed and Squire 1998), using universally accepted batteries of memory tests; from a greater sophistication of such tests in humans, primates, and rodents; and possibly also from a more extensive literature. The overall impression was that the lesion

produced a condition resembling idiocy (Brown and others information (see also Lamprecht 1997). A Schafer 1888). A more detailed look described the different view is that the amygdala, occupying a strategic position in the network of widespread neuromodulatory lesioned animals as tamed, over-attentive but fearless position in the network of widespread neuromodulatory devoid of the ability to assess the significance of inanimate objects, and indiscriminately phagocytizes other circuits that store it (Cahill and and sexual. A similar syndrome was shown to result (McGaugh 1998). The clash between these opposing from ablations confined to the amygdaloid complex views has raised central issues concerning memory and the medial temporal polar cortex (Weiskrantz traces: is the evidence for the requirement for *protein 1956). It is indeed likely that many functions used to synthesize and gene expression in training sufficient to be attributed to the so-called *Olfactory system, including those that a certain brain area *consolidates a given control of phylogenetically primitive drives, emotions, memory? And if it is, will the memory be stored in that and elementary social interactions, are carried out by area forever after? And which parts of a circuit that subserve a memory should be considered as an integral the amygdala (LeDoux 1991).

Over the years, circumscribed lesions in monkeys part of the postulated *engram? On top of it all, there is and rodents, cases of diseased and injured amygdala actually no reason to assume that the *storage and humans, and recently *functional neuroimaging, have *modulation views are mutually exclusive. Moreover, all been employed to investigate the role of the amygdala even a close look at the Kluver-Bucy syndrome individual in learning and behaviour. The effect of amygdala dysfunctionates that there is more to the amygdala than storage, function on a number of *recognition tasks, including and that it regulates *attention and additional facets of *delay tasks and visual and cross-modal associations cognition (Gallagher and Holland 1994).

was first taken to imply that the amygdala plays a major part in these tasks; however, later studies indicated that this is a beautiful example of a cross-*level analysis that the impairment was due to damage to the adjacent rhinal fissure. The study of the role of amygdala in fear conditioning has led from the behaving organism to circuits, which was injured together with the amygdala, synapses, and molecules, and vice versa. This issue that dala in the original lesion experiments (Zola-Morgan deserves further emphasis is the ethological context of et al 1989a,b; Murray et al 1993). In contrast, concluding the findings. The amygdala fulfills an important role in sive evidence for the involvement of amygdala in learning and memory was found in other types of tasks, enabling it to construe sign-*stimuli correctly, and react which engage fear and emotional memory (Adolphs et al 1995; Maren and Fanslow 1996; Rogan and LeDoux 1996; Scott et al 1997; Walker and Davis 1997; Cahill and McGaugh 1998; Lamprecht and Dudai 2000; Parkinson et al 2000). A most popular paradigm in this context is Pavlovian *fear conditioning, a ubiquitous form of *classical conditioning. In Pavlovian fear conditioning, a conditioned stimulus (e.g. tone) is associated with an aversive unconditioned stimulus (e.g. electric shock), to yield fear (e.g. freezing, increased blood pressure and heart rate) as the conditioned response. Amygdalar nuclei, including a subset dubbed the *amygdalar basolateral complex, were specific implicated in this simple type of conditioning (the identity of nuclei recruited in fear conditioning is probably also a function of the task complexity; Killcross et al 1997; Nader and LeDoux 1997).

The meticulous analysis of fear conditioning in the amygdala had clearly paid off: it has yielded the first demonstration of *long-term potentiation induced by training in an identified pathway that subserves learning in the behaving rat (Rogan et al 1997). The cellular analysis of fear conditioning also strengthened the assumption that the amygdala itself is a structure that them emotional behaviour and learning. (Adapted from Brodal 1998)

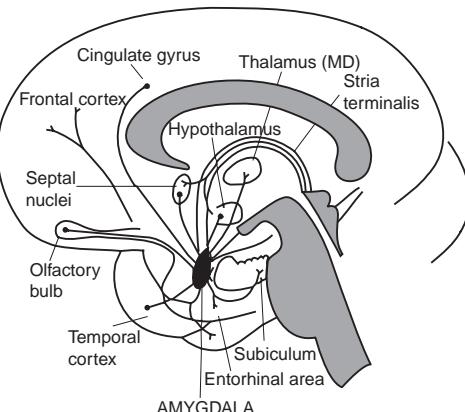


Fig. 3 The amygdaloid complex maintains extensive interconnections with multiple brain areas, including the hypothalamus, thalamus (Mediodorsal), hippocampal formation, and temporal and frontal cortex.

This schematic diagram depicts the amygdala as a single area, simplicity, but in reality it is a collection of about a dozen main nuclei and cortical areas that interconnect differentially with targets over widely distributed brain areas, and subserve diverse functions, am-

to them appropriately (e.g. see the role of amygdala in adding colour to an otherwise rather dry scientific perception, memory, and judgement of facial as well as account. To describe the behaviour of protozoa as 'verbal expression in humans, Adolphs et al 1998; Morris et al 1998; Isenberget al 1999). This is definitely a place to look for brain defects that underlie some neurotic and affective disorders and asocial behaviours.

Selected associations: Fear condition^{functional}, neuroimaging, limbic system, long-term potentiation

if they did not enjoy being alone and had passed the word along to gather and hold a mass meeting' is a matter of style only, as far as the description does not lead the reader (and even more so the writer) to assign to the unicellular organism 'declarative human-like social drives. Explanatory anthropomorphism, however, may result in embarrassing errors. A trivial example is the exposure of teeth in monkeys; what could be construed by the approaching novice as a friendly smile might actually be an expression of threat.

Possibly most relevant to current neurobiological research is our innate tendency for implicit anthropomorphism, i.e. tacitly construing the behaviour of animals in terms of problem solving 'algorithms that could have been used by the human observer. This should especially be taken into account in cases in which sophisticated cognitive faculties are suggested, for example the formation of cognitive 'maps in insects (Wehner and Menzel 1990), of 'learning sets in rodents (Reid and Morris 1993), or of 'observational learning in invertebrates (Fiorito and Scotto 1992). Implicit anthropomorphism may result not only in superfluously complex explanations but also in excessively exemplified in ancient myths, literature, and art (e.g. austere ones. As these lines are being written, hundreds Burkert 1985). Occasionally, it had also infiltrated other of diligent postdocs are running rats or mice in water social activities: throughout Europe in the Middle Ages, 'mazes, assuming that from the outset, all that the wet horses and pigs were dragged to public trial because animal has in mind from the outset of the experiment is was believed that they are 'consciously aware of the urge to learn the shortest way to the platform and own acts and hence are liable for them (Evans 1906).

Anthropomorphism

The attribution of human attributes to mythical creatures, inanimate objects, or nonhuman organisms.

The term is derived from Greek *anthropos* 'human being, morphē 'form'. Anthropomorphism owes much to anthropocentrism, i.e. our 'a priori inclination to regard ourselves as the centre of the universe and see the world through our 'biased eyes. By doing so we probably hope to gain some illusory control over reality. Anthropomorphism is intensively and recurrently exemplified in ancient myths, literature, and art (e.g. austere ones. As these lines are being written, hundreds Burkert 1985). Occasionally, it had also infiltrated other of diligent postdocs are running rats or mice in water social activities: throughout Europe in the Middle Ages, 'mazes, assuming that from the outset, all that the wet horses and pigs were dragged to public trial because animal has in mind from the outset of the experiment is was believed that they are 'consciously aware of the urge to learn the shortest way to the platform and own acts and hence are liable for them (Evans 1906).

In the early days of experimental psychology, anthropomorphism was popular (Boakes 1984), being water, in reality, some of the drives and strategies influenced by the Darwinian theory of evolution pursued by the swimming rodent are species specific that suggested a mental continuum along with the (e.g. Wolferet al 1998). physical one. The 'classics of the anthropomorphic There is, however, a twist to the story. In spite of tradition in animal psychology are books by Darwin the aforementioned caveats and reservations, the mere (1872) and Romanes (1882). The transformation of fact that an explanation has an anthropomorphic psychology into a more objective and quantitative connotation is not sufficient to demote it. In other scientific enterprise was accompanied by attempts towards, 'anthropomorphism' cannot be used as a abandon anthropomorphic anecdotes that portrayed 'criterion in refuting or accepting explanations and pets as geniuses, and to adhere to parsimonious explanatory models. The truth is that we do not really know the nations of animal behaviour, such as advocated by borders between the mental faculties of other mammals Loyd Morgan's canon ('Ockham's razor). However, those that are sometimes considered as exclusive anthropomorphism still pops out between, and occasionally in, the lines of current research articles in associate events, are they 'consciously aware of it (Clark 1992; Sullivan 1995).

Anthropomorphic accounts could be classified into two kinds: 'metaphorical' and 'explanatory'. The physiology and psychophysics of animals, the more we are metaphorical are the more innocent ones. They may become astonished to discover that even species far

remote from us on the phylogenetic scale seem to perceive some aspects of the world not so differently from us (e.g. Nieder and Wagner 1999). This raises the possibility that underestimating the capabilities of their brain is as misleading as overestimating it. There is no reason why we should not expect to find in evolution Aplysia a hind-gilled (opistobranch) marine snail (Kaneko 1979), is one of the heroes of the cellular revolution in faculties, such as *planning, *prospective memory, the neurosciences. Its external resemblance to the rabbit complex problem solving, or *insight. It is even still earned it the name sea-hare. Yet it is the inside of Aplysia that has turned it into such a highly successful *system in humans only (Walker 1983; Griffin 1984; Cheney 1988; Quinn (pers. and Seyfarth 1990).

But, whereas some anthropolike mental faculties, such as numerical competence, are amenable to neurons, 10 genes, a generation time of 1 week, and the objective measurement (Davis and Perusse 1988; Brammer 1998; Kawai and Matsuzawa 2000) this is not a faithful description of Aplysia but in the real others, e.g. subtle emotions, are not. We may therefore conclude that the sea-hare became a useful compromise. Its never be able to really know what it is like to be a bat. Main assets are a relatively simple nervous system that is (Nagel 1974). We are hence left with the humble con-readily accessible to experimentation, a simple behaviour that is Ockham's razor on the one hand, and proper appreciation that have become fascinated by the virtues of the slug. Cognition of the phylogenetic and ecological specialization of Aplysia is composed of other species' brains on the other, is delicate indeed about 20 000 nerve cells arranged in widely spaced ganglia (masses of nerve cells). Some secretory neurons are as big as the entire brain of *Drosophila*. Same neurons can be identified from one individual to another by their location, shape, and firing pattern. The system had attracted cellular physiologists (Arvanitaki and Chalazonitis 1958; Tauc and Gershenson 1961; Kandel and Tauc 1965). It was, however, the research on *plasticity and learning that has endowed Aplysia especially with its fame (Kandel and Schwartz 1982; Byrne and Kandel 1996). Following a series of reductive and simplifying steps (*reduction), the cellular and molecular mechanisms of learning in Aplysia have been pursued from the behaving animal, via preparations of isolated ganglia, to identified nerve cells and *synapses in culture (Carew et al. 1971; Rayport and Schacher 1986; Bartoshuk et al. 1995; Frost et al. 1997; Hawkins et al. 1998). This system is the epitome of the reductionist approach to memory, and as such demonstrates both the advantages and the shortcomings of the approach.

Selected associations: Artefactual, Clever Hans, Declarative memory, Subject



Fig. 4 It works both ways: an apeomorphized version of Charles Darwin in a contemporary caricature. Faithful to the *zeitgeist that reinforced the theory of evolution reinforced, Darwin himself anthropomorphized animal behaviour *The expression of the emotions in man and animals* (1872).

Like all organisms with a nervous system, Aplysia displays a repertoire of defensive (e.g. withdrawal) and appetitive (e.g. feeding) reflexes. The analysis of learning in Aplysia has focused mainly on the defensive reflexes (Kandel 1976; Byrne 1985). These can be illustrated by the gill-and-siphon withdrawal reflex (GSWR). The gill is the external respiratory organ of Aplysia. It is housed in the mantle cavity on the dorsal side of the animal.

The cavity is a respiratory chamber covered by the

Aplysia

mantle shelf. At its posterior end, the shelf forms a of the cellular analysis of learning has been performed fleshy spout, called the siphon. The siphon protrudes in the central nervous system, particularly in the out of the mantle cavity between wing-like extensions abdominal ganglion. This ganglion was found to sub- of the body wall, called parapodia. If a tactile *stimulus serve a substantial portion of the habituation, sensitiza- is applied to the siphon or mantle shelf, a two-compo- tion, and classical conditioning of the GSWR. Multiple nent reflex is elicited. One component is contraction of sites of plasticity have been identified in the abdominal the siphon and its withdrawal behind the parapodia. ganglion, but the attention has been focused primarily The other is contraction of the gill and its withdrawal on one site: the synapse between the sensory neurons into the mantle cavity. The GSWR can be *habituated and the gill or siphon motor neurons (Kandel and by repetitive monotonous tactile stimuli to the skin; Schwartz 1982; Byrne and Kandel 1996; Figure 5). It has *sensitized by noxious stimuli to the tail or head; and been proposed that part of the behavioural plasticity of undergo *classical conditioning. This is achieved by the GSWR could be accounted for by use-dependent pairing a gentle stimulus to the siphon or gill (the con- modifications in this synapse. In brief, the cellular ditioned stimulus) with a noxious stimulus to the tail or analogue of habituation was portrayed as presynaptic head (the unconditioned stimulus), so that the condi- depression, induced by repetitive monotonous firing. tioned stimulus comes to evoke intense withdrawal (theAs this depression involves only the modified synapse, it is said to be ÔhomosynapticÕ. Sensitization was portrayed conditioned response).

In intact Aplysia the GSWR is controlled by both the as synaptic facilitation, induced in the presynaptic central and the peripheral nervous systems. Most terminal of the aforementioned sensory-to-motor

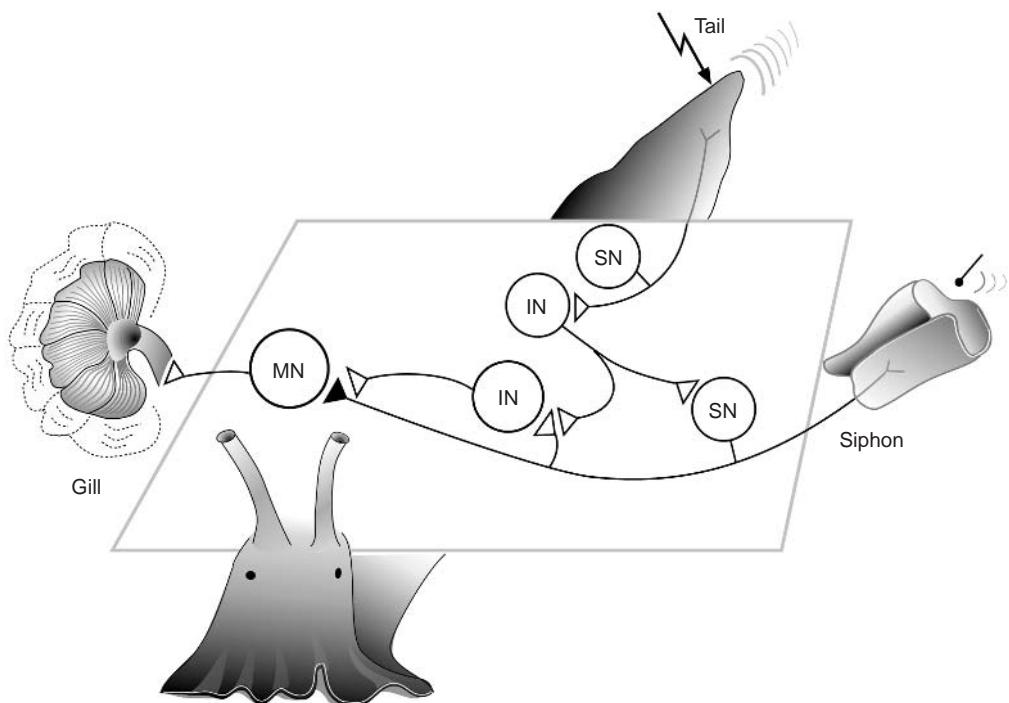


Fig. 5 A highly simplified scheme of a fragment of the circuit that subserves the gill-withdrawal reflex and its modification by Aplysia. The reflex could be elicited by a tactile stimulus applied to the siphon skin. Repetitive, monotonous tactile stimuli result in the reflex. A shock to the tail results in sensitization of the reflex. Classical conditioning is obtained by pairing the shock to the tail with a tactile stimulus to the siphon, so that this tactile stimulus comes to evoke intense withdrawal on subsequent applications in the absence of the shock. Probably hundreds of nerve cells and thousands of synapses subserve the reflex in the intact animal; only a selection of types of synapses are depicted in the scheme. IN, interneuron; MN, motor neuron; SN, sensory neuron. The presynaptic terminal of ~~sensory-to-motor~~ synapse denoted by a black triangle (left-hand side), was so far the focus of much of the cellular and molecular analysis of the reflex. *Phases of memory in the reflex contributes both to the short- and to the long-term *phases of memory in the reflex. For further details see text.

synapse by *neurotransmitters that are released from interneurons and encode the sensitizing stimulus the Aplysia system has increased, and the highly simplified (Figure 5). As this facilitation involves multiple types of models gradually matured into more realistic ones of synapses, it is ÔheterosynapticÕ. Classical condition (Ganzman 1995; Byrne and Kandel 1996; Fischbach of the GSWR was portrayed as sharing cellular mechanisms (Ganzman 1995; Byrne and Kandel 1996; Fischbach 1997; Baet al 1998; Lechner and Byrne 1998; Royer 2000). Attempts are also being made to elucidate presynaptic facilitation; however, in contrast with sensitization, which enhances the responsiveness to subsequent stimulation of the skin at any location, the *instrumental conditioning (Lechner 2000), as well as of a more complex form of learning, the cellular bases of appetitive reflexes (Lechner 1999).

facilitation in classical conditioning is specific to the Aplysia still our main source of information about the pathway that has mediated the conditioned input (*coincidence detection). This is hence a pathway-specific few days after training (*long-term potentiation activity-dependent presynaptic facilitation. Multiple addresses a shorter time window). This is evident molecular mechanisms have been suggested to account among others from the references made to it in many for the *acquisition and short-term retention of the entries in this book. Admittedly, the memory feats of synaptic facilitation. They include activation of *intracellular signal transduction cascades by the facilitatory neurotransmitter(s), phosphorylation (by *protein kinases) of a pre-existing behaviour and not acquisition of a novel of synaptic proteins (e.g. *ion channels), and modulation one). But no doubt, without the remarkable work on transmitter release (Kandel and Schwartz 1982) the molecular and cellular biology of neuronal These simplified cellular *models were later extended plasticity, learning, and memory would have been enriched, and modified to include additional synaptic sites and mechanisms (e.g. Byrne and Kandel 1996). that is worth mentioning here. The analysis of neuronal

Because of lack of space, we will not concern our plasticity in Aplysia has unveiled an impressive interselves here with the fine details of Aplysiastory, but and intra-cellular molecular complexity that keeps rather with a few generalizations only. The cellular growing. This should be noted by orthodox reductionism of Aplysiareflexes has shown that a significant component of the circuit that subserves simple learning implies simplifying it. The opposite might be the case. could be pinned down to the *level of identified neurons and synapses. This analysis was the first to demonstrate the central role of cyclic adenosine monophosphate in memory (Cedea et al 1972;

*CREB), and the multiplicity of time- and *context-dependent mechanisms of plasticity in a single cell. It has also demonstrated that at least part of the loci that

subserve short-term memory also subserve long-term memory. Further, analysis of plasticity in the GSWR has provided much support for the *zeitgeist proposal that long-term memory storage relies on modulation of gene expression (Goette et al 1986; Martinet al 1997a,b;

*consolidation, *immediate early genes, *protein synthesis). It is noteworthy that in recent years, much of the analysis of learning in Aplysia has practically merged with the cellular biology of *development. This may reflect a genuine homology between learning and development.

Yet the focus on molecular and cellular mechanisms, which are shared with other disciplines in the life sciences, may also attest to the current difficulty in switching, even in a *simple system, to the more global level of analysis, which is critical for understanding memory, i.e. Artefact stems from the Latin Ôsomething made with that of concerted circuit activity that ultimately encodes skillÕ, but occasionally, in science, the major skill at *internal representations in the behaving organism.

Selected associations: CREB, Synapse

¹The major driving force behind the Aplysia project, Eric Kandel, shared the 2000 Nobel prize for Medicine.

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1. Man-made object.

2. A phenomenon, process, or mechanism that does not normally exist in nature but is introduced by experimental manipulation of the *system.

3. A phenomenon, process, or mechanism that does not exist in nature but is believed to exist, due to erroneous interpretation of data or theories.

Artefact

phenomenon. Artefacts have haunted the experiments. Probably hundreds of Ph.D. theses interpreted the sciences since the emergence of the latter, much before pecking of pigeons in a Skinner box as an "instrument". The term was introduced into English at the beginning of the twentieth century. In biology, "artefact" was first used to denote aberrations produced in histological evaluation. It might not have been instrumental but rather specimens by the fixation methods used to prepare the classical conditioning (Jenkins and Moore 1973). tissue for microscopic examination. However, with time, it came to embrace many types and tokens of artifactual constructs, either concrete or conceptual, which iours in order to escape from puzzle boxes; but some of are confused with the real thing.

the typical behaviours, such as rubbing the flank or

It is useful to distinguish two major classes of artefacts: technical (definitions 1,2) and conceptual, or specific feline greeting reactions, emitted in response to interpretation (definitions 1,3). A harsh fixative or an unreliable stain leading to the appearance of an imaginary brain structure could be the cause of technical artefacts. Similar illusions may result from non-specific smell, allowing the observer to affect the behavioural antibodies in an immunoblot, sloppy development of an autoradiogram, or tricky electrophysiological set-up. The master and prune the potential sources of artefacts. Expert scientists come to this day in many labs; it would be of interest to enquire about their trade, but new methods and techniques generate artefacts. For example, with more and more data of new perfume or after-shave or an admiring visitor. analysis being relegated to fancy computer systems. Anthropomorphism is another potential source of the computers themselves become a source of interpretation artefacts, confusing innate ("a priori") cognitive artefacts before the data even reach the scientist. It takes a careful team leader to identify the problemfaculties ("clever Hans, *Ockham's razor").

(e.g. Katz et al 1998).

Interpretational artefacts could also be due to vari-

A common potential source of interpretational artefacts is the so-called *post hoc ergo propter hoc* argumentation. This means arguing that because one event followed another, the second must have caused the first. This could sometimes be as simple as noting that a rat's hippocampal neurons were correlated later in time with another, the second having been transferred to a new environment they explore and learn it. It happened because of the first. This could sometimes be as complex as noting that such exploration is accompanied by performing control experiments by hippocampal plasticity, including persistent facilitation in which the order of events is altered or the suspected causation of evoked neuronal responses (Green 1990). cause omitted from the protocol. For example, suppose we are tempted to conclude that a receptor for the neurotransmitter glutamate in the rat hippocampus is smaller than first reported. The reason: fluctuations of is phosphorylated (protein kinase) as a consequence of a shift in brain temperature, occurring during the learning to navigate in a maze, because the receptors modify neuronal properties *in vivo*. This molecule appears phosphorylated after the experience and account for a substantial part of the observed effect. This might be a post-hoc artefact rather than a real consequence (Andersen and Moser 1995). The aforesaid might be a post-hoc artefact rather than a real consequence (e.g. see criterion).

Interpretational artefacts could also result from lack of expertise in, or awareness of, a domain of knowledge. The artefact was not a waste of intellect; its exploration that is relevant to the finding. This is a risk encountered by investigators who other words, it is absolutely possible to learn even from shift from one field to another. A study of conditioning artefacts illustrates the case. In the first half of the last century, many operant conditioning paradigms ignored the species-specific behavioural repertoires of the experimenter. This led to questionable conclusions.

Whether the suspected artefact is of the technical or species-specific type, the first-law-of-the-artefact frequently holds: the more important is the message, the faster is the artefact exposed. Artefacts that lead

to boring conclusions gain immortality in obscure neuroanatomical, *system, and behavioural. In considerable journals. But if the news is smashing, for example, thatering levels of analysis, one should note differences in specific memories can be transferred from one individ-the dialects of the scientific *culture. The term ÔassayÕ usual to another in brain extracts (Babiel et al 1965;) is mostly popular in molecular and cellular studies. Ungar and Oceguera-Navarro 1965), the scientific Neuroanatomists prefer to use ÔtechniqueÕ or Ômethod community does its best to sort the facts out, even if the(which, as noted above, is better reserved for a more causes of the artefact, or at least what appears to be ~~a~~omprehensive activity). Psychologists cling to ÔtestÕ. artefact to the contemporary eye, do not always become clear in the process (Byrne et al 1966; Nicholls et al 1967; Smalheiser et al 2001).

Selected associations: Anthropomorphic control, Red herring Scoopophobia

¹On ÔtypesÕ and ÔtokensÕ, see *system.

Assay

A procedure or technique for the analysis of a phenomenon, process, or mechanism; a test.

Assays (from *exagiere*, Latin for Ôto weigh outÕ) are ~~ndär~~, and system assays, behavioural assays used in the merely research tools. They play a decisive part in the field of learning and memory are unique to this field: development and workings of scientific disciplines. they are specific Ômemory assaysÕ or ÔtestsÕ. They are also important in shaping the feasibility, Some memory tests were groundbreaking at the time progression, and outcome of particular research of their introduction. For a field of knowledge to programmes. Sometimes they even play a decisive part become a scientific discipline, research techniques and in moulding the fate of individual academic careers. assays are required that permit quantification of phe-

Scientific assays are the nuts and bolts of scientific phenomena addressed in that field: Ôthe forces and actions *methods and *paradigms. In experimental science, of bodies are circumscribed and measured either by they are the end instrument used to embody the objec-spatial intervals, or by moments of time, or by concen-tives of a ÔmethodÕ and test the concepts of a ÔparadigmÕ of quantity, or by predominance of power; and They are thus more specific than ÔmethodsÕ. The ~~sam~~ess these four are accurately and carefully weighed, method may be implemented by using a variety of the sciences concerned will be elegant speculations assays. For example, one could employ a correlativ~~e~~ perhaps but of no practical useÕ (Bacon 1620). A handful methodo probe the role of an *immediate early gene in of tests, by the mere fact that they had enabled for the memory in a given brain region, but use different assays first time the quantification of memory, had trans-to determine whether the expression of that gene is conformed the study of memory into a science. A promi-related with the behavioural change. A useful assay example is provided by tests involving *recall of yields results that are then subjected to analysis andries of so-called ÔnonsenseÕ syllables, introduced by construed according to selected *criteria.

The spectrum of assays used in the neurosciences 1887). This type of experiment is considered to have rich and heterogeneous. Practically all these assays opened the scientific era in research of human memory. could also be incorporated into research programmesSimilarly, introduction of *classical and *instrumental that target learning and memory. One useful classifica-conditioning has permitted the systematic experimental tion of assays (*taxonomy) is by the *level of analysisinvestigation of animal learning (Thorndike 1911; involved. Other classifications are of course possiblePavlov 1927; for more on the history, see Boakes 1984). for example, by the method that guides and utilizes the Still another class of assays includes those that alter assay (i.e. correlation, intervention, etc.). Straightfor- and reroute the course of a discipline. Here are some ward classification by level is into molecular, cellular, examples: Introduction of the *maze (Small 1901;

The latter term commonly carries the connotation of ÔsuccessÕ or ÔfailureÕ in *performance; ÔassayÕ does ÔTestÕ can also be used to denote particular instantiation of a type of assay in an experimental protocol.

Molecular assays, such as binding of drugs to *recep-tors or measuring enzyme activity, are shared by many branches of molecular and cellular biology (R. Martin 1997; e.g. *development). Cellular, neuroanatomical, and system procedures are shared by many subdisci-plines of the neurosciences and are not unique to the study of plasticity and memory. One notable exception that comes to mind is *long-term potentiation, which under certain circumstances may be regarded as an assay to determine induction and maintenance of cellular *plasticity, although it is also a method, and moreover, a *paradigm. In contrast to molecular, cellu-

lar, and system assays, behavioural assays used in the merely research tools. They play a decisive part in the field of learning and memory are unique to this field: development and workings of scientific disciplines. they are specific Ômemory assaysÕ or ÔtestsÕ. They are also important in shaping the feasibility, Some memory tests were groundbreaking at the time progression, and outcome of particular research of their introduction. For a field of knowledge to programmes. Sometimes they even play a decisive part become a scientific discipline, research techniques and in moulding the fate of individual academic careers. assays are required that permit quantification of phe-

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Assay

*classic) has paved the way to research on spatial learning, cognitive maps, and other facets of memory. Another caveat that should be considered is that occasionally, an assay becomes a prison to imagination. A popular descendent of those original mazes is the water maze (Morris 1981). This problem runs in two versions: individual and extensive use of the delay task (Hunter 1913) has permitted even a single assay, throughout their career, from their analysis of recognition and working memory, and Ph.D. thesis on. Being inflicted with some unique development of monkey models of amnesia. Very version of separation anxiety, they refuse to give up a useful versions are the trial-unique delay tasks, such procedure that has worked for them, and entrust their trial-unique delayed non-matching-to-sample (Gaffan 1974; Mishkin and Delacour 1975; *delay task). In some cases, adaptation of a well-known type of memory assay could open a whole new field. An emerging discipline of mammalian neurogenetics has example is provided by olfactory conditioning in the followed as a routine a very limited number of standard fruit fly, *Drosophila*. Sophisticated neurogenetic versions of the otherwise very useful water maze assay. analysis of memory became feasible only after classical. This was also occasionally accompanied by the simplification that conditioning had been adapted to the special needs of interpretation of performance in the maze, probably the fly (Quinn et al 1974). And, of course, there are resulting in neglect of some intriguing effects of mutations. Those many assays that are variations on a theme, introduce variations on behaviour (on some of the complexities already existing methods.

It is likely that in due time, memory research will

Lack of an appropriate assay may hinder the development of memory-specific assays based on direct observation of a field or the resolution of a major research problem. For example, some types of behavioural representations of the nervous system (*map, hippocampus and are sensitive to functional neuroimaging; example in *honeybee). hippocampal damage. However, at the time of writing there is still no satisfying behavioural assay to tap exclusively into hippocampal function in primates. Such a task will be very useful in clarifying the role of the hippocampus in memory. The hippocampus can also be invoked to illustrate a potential problem in the use of assays. This is the problem of circular argumentation.

Thus, given that a hippocampal lesion impairs performance on task X under condition A, some investigators are quick to use task X under conditions other than A to determine whether the hippocampus is involved,

Selected associations: Delay, task, Method Paradigm

Associative learning

1. The formation of new mental links among events! as if task X is an established probe for hippocampus. Learning that depends on the parameters of involvement. Failure or success on task X, however, may result from parameters specific to condition A that do not generalize to other conditions of the subject or the experiment. The problematics are further augmented when inference is made from one species to another. Here is an example that relates not only to the hippocampus but also to a profound issue in the evolution of the mind: the notion of association. The notion of association is central to both the philosophical and the experimental study of the mind. The notion of association, as it can be traced back to Aristotle, who proposed that similarity, contrast, and contiguity of images subserve recollection (On memory and the imagination; De memoria et sensu 1972). Associationism, the philosophical doctrine that classical conditioning is sensitive to hippocampal damage and involves conscious awareness in normal individuals (Clark and Squire 1998). However, empiricism in the seventeenth century (Warren 1921), this by itself is insufficient to propose trace conditioning. Hobbes (1651) talks about "the train of thoughts" and of the mind as a cross-species assay for awareness, because other potential explanations (*Ockham's razor) must first be scrutinized, such as a failure to hold information in our mind. It was, however, off-line irrespective of awareness.

Locke (1690) who first used the phrase "association of

ideas, as the title of a chapter *Essay concerning human understanding*. more *reductive and mechanistic analysis of associations at multiple *levels of analysis. One paradigm was *classi-

When psychology became an independent empirical discipline towards the end of the nineteenth century, and his school. The other was *instrumental conditioning, associated mainly with Ebbinghaus (1885) was influenced by it when Thorndike (1911) and later Skinner (1938) and their designed the first quantitative recall experiments, schools (*behaviourism). In both types of paradigms, involving perceptual atoms and their associations, the subject learns relations among events (definition 1). Similarly, Wundt (1896), the founder of the first laboratory of experimental psychology, advocated the study of stimuli, whereas in instrumental conditioning, these elementary mental elements and their association irrelations are among actions and their consequences. learning, recollection, and thought (Boring 1950a). The availability of *controllable protocols of association Over the years the integration of associationism into learning in animals has provided a fertile ground psychology has also been accompanied by the development and test of multiple types of laws ment of theories that kept the centrality of associations and theories of associative learning. These theories dif- yet disposed of the assumption that the mind works for the identification of the associated variable and of solely bottom-up from simple ideas and *psychic atoms. principles of association. Main types of associated (e.g. James 1890; Freud 1901; Hebb 1949; Tversky 1977) variables considered in these theories are stimulus-D

Associations play a part in all the faculties of the stimulus (SDS), stimulus-response (SDR), response-mind: learning (the formation of new associations, response (RDR), and response=reinforcer (e.g. see definition 1); recollection (the use of associations as*instrumental conditioning). Stimulus in these theories *cues, *priming, *retrieval); and thought (which is commonly an external, sensory stimulus. Note, how- involves both the generation of new *internal representations, that in definition 2, ÔstimulusÕ is more general and tations, definition 1, and recollection of old ones). refers to any event that triggers a response in the brain. Here we refer to one aspect only, that of *learning. A whether of an external or an internal source, hence it popular *taxonomy of learning is based on a dichotomy includes also the feedback of motor response. Further, between ÔassociativeÕ and ÔnonassociativeÕ learning, those are of course not the stimuli themselves contrast with associative learning (definition 2), in that are associated, but rather their on-line *percepts or nonassociative learning, i.e. *habituation and *sensitization stored representations. Principles of associa- zation, learning is assumed to depend solely on theions that are considered in theories of associative parameters of the unconditioned stimulus. Whether in learning are the frequency of occurrence of the events, *real-life this is indeed the case, is questionable. Even their co-occurrence in time and space (contiguity), the habituation and sensitization involve associations not probability of linkage (contingency), and the effect or only with the history of the subject and its interaction reinforcement (Dickinson 1980; Bower and Hilgard with the stimulus, but also with the *context (Hall and 1981; Mackintosh 1983).

Honey 1989; Rankin 2000). Incidental learning and At least in one basic assumption the original British *insight are occasionally depicted as nonassociative associationism clearly went wrong. This is the depiction well, but again, this is a great simplification, as in both of our mental life as dependent only on postnatal asso- cases associations are formed in the mind. Incidentiations. Many associations in our brain have innate learning involves associations between an input and predispositions. Some authors would even go further to saliency or motivation. Insight is expected to involve propose that all the associations in our brain are pre- sequential implicit associations of internal representations, and therefore all learning is ÔpreparedÕ to some- tions and their *binding. All in all, therefore, it is possi- degree or another. This could be due to the existence of ble to conclude that associations of some kind or certain neural pathways but not others. The generation another are universal, and instrumental in learning in over time of endogenous pre-representations, which even the simplest organisms and tasks. are partially independent of external-world experience

The study of associative learning has gained tremenbut selected by it (Heidman et al 1984), could also be dously from the use of animal behaviour *paradigms. constrained by *a priori patterns of connectivity in the At the beginning of the twentieth century two major brain. An example of a simple type of prepared learning types of paradigms emerged, which permitted for theis provided by the form of classical conditioning called first time the investigation of elementary forms of asso- conditioning, in which the modified response is ciative learning in laboratory animals, and hence apre-existent. Other examples of prepared associations

are *imprinting and *conditioned taste aversion. postulated inner faculties of the mind, including attention. Whether learning is ÔpreparedÕ or not should be taken into account in the search for the cellular and molecular mechanisms of learning. For example, presynaptic facilitation of active synapses in the circuitry, to the cognitive sciences (Broadbent 1958). A large body of work on attention has been accumulated since then, both in psychology and neurobiology. It ranges from investigation of the orienting reflex (*sensitization) to auditory and visual perception. A substantial part of what we currently know on attention stems from the analysis of vision in primates, at levels ranging from behaviour via *functional neuroimaging and neuroanatomy to single cell activity (Posner and Petersen 1990; Desimone and Duncan 1995; Egeth and Yantis 1997; Kanwisher and Wojciulik 2000).

Selected associations: Classical conditioning, instrumental conditioning, Priming, Taxonomy

¹This definition also fits certain artificial systems, such as robots, if ÔmentalÕ is construed *metaphorically.

²As noted in *algorithm, these are not genuine theories in the mathematical sense of the term, but rather conceptual generalizations. The same is true for ÔlawsÕ below.

³For the role of associations in completing memories from input in artificial neural networks *models, see Hopfield (1982), Amit (1989), and Mehrotra (1997).

Attention refers to multiple mental states and activities, involving vigilance, orientation, and selection of information. The spectrum of activities thus ranges from the distributed to the selective and to the focused degrees on-line information (percepts of sensory attributes, location and timing) as well as off-line information (i.e. lasting internal representations). Similarly, attention could be *stimulus-driven (a bottom-up process) or task-driven (a top-down process). The latter dichotomy is illustrated in vision. Here selective attention was explained in terms of two consecutive, partially overlapping processes. The first is stimulus-driven, automatic, instantaneous and transient. The second is task-driven, slower, sustained and requires cognitive effort (Sperling and Weichselgartner 1987). Early stimulus-driven processing is frequently referred to as ÔpreattentiveÕ (Neisser 1967), because it involves parallel processing of primitive features over the sensory space in the apparent absence of mental-resource limitation (Julesz 1981; Treisman 1985). Indeed, central to the notion of attention is resource-limited ÔselectionÕ (Norman and Bobrow 1975), which

is detected at multiple points between post-receptor input and response (Desimone and Duncan 1995). Hence, lack of resource competition is taken by some authors to indicate lack of ÔrealÕ attention. More recent findings suggest, however, that even ÔpreattentiveÕ vision (1890) was convinced that Ôeverybody knows what constrained by mental resources (Joseph 1997).

attention is Ôthe taking possessionA common connotation of attention is *conscious by the mind in clear and vivid form of one of what seem awareness (definition 2). Does this mean that attentive several simultaneous objects or trains of thoughtÕ. Jamesonhuman species can be consciously aware of their was right in stating that intuitively we know what attention did, and if so, which species? Definitions 1 and 3 above is, but, probably because the concept is so inclusivefit situations in which conscious awareness cannot be a consensus on its definition is not easy to attain. proven or even assumed. Another definition, suggested

Not always was attention at the focus of attention by Hebb, also does not specify consciousness: Ôcentral of psychology. *Behaviourism intentionally ignored facilitation of the activation of one assembly by the

previous one— (Hebb 1949); this view of attention Cowan 1988; Baddeley 1993). Attention identifies depends, however, on the validity of the notion of *cell where the action is (a popular *metaphor likens it to a assembly. As far as the relationship of attention to con-searchlight, Crick 1984) a working memory then scious awareness is concerned, it is noteworthy that oimmediately takes note of that action for further use. By the one hand, even humans may not be aware of activity so doing, it not only permits an instantaneous *plastic in a cortical area assumed to be involved in some attenresponse, but also prevents superfluous exploitation of tional tasks (Crick and Koch 1995); on the other hand, attentional resources. Whereas some of the automatic-some degree of conscious awareness is expected to extin stimulus-driven attention is innate (*a priori), it is in other species as well (example in *classical condiclear that the system has to be capable to quickly comtioning). It is therefore useful to regard attention as pare stimuli with use-dependent internal representa-involving a spectrum of awareness. Attention has beertions in order to decide whether focused attention and proposed to be the *binding agent of consciousness further processing and action are warranted. This inter-and it is tempting to speculate that it has been a drivingplay of attention and memory takes place within a frac-force in the emergence of consciousness. Seen that wajon of a second of perception. Working memory is one could not escape the humble conclusion that thetherefore also Ôworking attentionÕ (Baddeley 1993). most precious niches of our inner world owe their exis- At the cellular level, attention was found to increase tence to the emergence in evolution of the primitive, the magnitude of the response of neurons in higher-elementary orienting reflex.

Developments in two *methodologies have con-receptive field; when multiple stimuli are within the tributed much to the contemporary research on receptive field, the activity is larger when attention is brain mechanisms of attention. One is cellular physiol-directed at the target stimulus (Moran and Desimone ogy, used in the *monkey, the other is functional 1985; Reynolds et al 1999). This gain and gating control neuroimaging, used in research on human *subjects could involve multiple circuit and system mechanisms, (Desimone and Duncan 1995; Kawashita et al 1995; Kastner et al 1998; Reynolds et al 1999; Kanwisher and Wojciulik 2000). The combination of both methodologies has led to the identification of brain involve regulation of gain and gating control as well; circuits and cellular processes that are engaged i hence at the *synaptic level, certain molecular mecha-attention either correlatively or casually (*criterion). nisms of learning and attention merge.

At the system level, research on visual attention shows that areas in the frontoparietal, inferotemporal these are parietal and frontal lesions (Shallice 1993), and occipital *cortex are involved. Among the visual schizophrenia (Andreas et al 1994), and attention-processing areas, high-order cortex is particularly deficit/hyperactivity disorder, one manifestation of engaged, but there is also evidence for attentional actiwhich is learning difficulties (Shaywitz et al 1997). It ity already at the primary visual cortex. Attending a has been suggested that attention and memory are also stimulus modulates the activity in cortex, even when co-impaired in chronic fatigue syndrome, and the the subject only expects to attend the stimulus beforehypothetical Ôcentral executiveÕ was implicated@loyce stimulus onset(Chawla et al 1999). This is taken to al. 1996). In *real-life, multiple methods could be used reflect the task-driven, top-down attentional facilita- to enhance attention, and, good news, some of these tion of the processing in the area that expects the signalmethods are clearly devoid of any side effect: a compar- There is also evidence for hemispheric lateralization on of memory for humorous and non-humorous ver- with a right hemispheric bias for tasks involving atten- sions of sentences shows that the humorous ones are tion to locations in space and left hemispheric bias for remembered better, probably because they are associ-tasks involving attention to timing (Coull and Nobre 1994).

1998). As to the frontal cortex, it is considered to sub-serve a Ôsupervisory attentional systemÕ or Ôcentral exec-utive systemÕ, which co-ordinates and prioritizes attention across sensory and internal modalities

(Shallice 1988; Baddeley 1993). This is the same cortexExpecting to attend is actually an Ôattentional setÕ; for more on involved in *working memory. This should not be is meant by ÔsetÕ, see *learning set.

surprising, since clearly, attention and working mem- 2A receptive field is that sector of the sensory space that could ory are complementary and closely related (James 1890) sensed by the neuron.

Selected associations: Binding, Punctum, Metaphor, Percept, Working memory

Behaviourism

1. The conceptual framework and the school of psychology that consider only overt behaviour as the subject matter of scientific psychology.
2. The philosophical stand that considers propositions about mental states identical to propositions about behavioural dispositions.

The tenet of behaviourism is that behaviour rather than mind or brain is the subject matter of psychology, and terms of classes and types, and its variants incorporate that only publicly observed behaviour can be used as not only stimuli, responses, and reinforcers (i.e. operant psychological datum). Although its roots can be traced to earlier materialistic philosophy and physiology, the variables that are not directly observable but thought to be necessary for explaining behaviour (see *algorithms), associated with a manifesto entitled *Psychology as the Behaviorist Views It* (Watson 1913):

Psychology as the behaviorist views it is a purely objective experimental branch of natural science. Its theoretical goal is the prediction and control of behaviour. Introspection forms no essential part of its methods, nor is the scientific value of its data dependent upon the readiness with which they lend themselves to interpretation in terms of consciousness. The behaviorist, in his efforts to get a unitary scheme of animal response, recognizes no dividing line between man and brute.

Several points deserve special attention in Watson's manifesto. First, the rejection of introspection as a valid scientific method, opposing a major trend in psychology at the turn of the twentieth century (Boring 1950; Boakes 1984). Second, the rejection of *consciousness (Chomsky 1959).

as the subject matter of psychology, again, in contrast to contemporary trends (ibid.). Third, the emphasis on the phylogenetic continuity, drawing from Darwinism both, see Carnap 1933; Ryle 1949; Zuriff 1986; Collins and legitimizing animal psychology as an approach to 1987; Todd and Morris 1995). Methodological behaviourism advocates the aforementioned principle that fourth, aiming at control of behaviour. The latter objective is clearly not a necessary element of behaviourism but did recur in the history of the field, occasionally endowing it with Orwellian connotations. The above). In contrast, philosophical behaviourism does pragmatic attitude (Watson ended up in commercial advertising) culminated on the one hand in rather which comes in at least two versions: *Metaphysical* outrageously experimentation on *fear conditioning of and *Logical*. Metaphysical behaviourism makes life human babies (Watson and Rayner 1920), and on the easy by denying mental phenomena, period. Logical other in attempts to convince pigeons to guide missiles behaviourism considers propositions about mental across enemy lines (Skinner 1960). In a more practical endeavour, it also set foundations for behavioural psychotherapy (Wolpe 1963).

Despite recurrent premature elegies, behaviourism retained its vigour over many years. Like other influential concepts, the original notions mutated. Several *taxonomies are noteworthy. One of these classifies behaviourism by period or school. *Classical behaviourism* is Watson's. It is also dubbed *Molecular* because it treats behaviour in terms of individual atoms of *stimuli, responses, and single stage stimulus-response operations. *Neobehaviourism*, itself a mixed bag, is associated mainly with Tolman (1932), Skinner

is called *Radical behaviourism*, although the same term was initially used to denote classical behaviourism (Calkins 1921). It intentionally ignores mind and brain processes (in his later writings Skinner said that brain sciences are indeed relevant, but not useful in analysing behaviour; Skinner 1988). Radical behaviourism advocates a world view in which behaviour is explained in terms of responses to stimuli and modification of probability of responses by contingencies with reinforcements. It dispenses of mental causes; the unobservable *Mind* is replaced with mechanistic responses of various complexities, selected either in the species evolution (*a priori), or by the reinforcement

history of the individual *subject. The pinnacle of Skinnerian behaviourism was the attempt to explain human language (Skinner 1957), an attempt ardently resisted by linguists and cognitive psychologists (Boakes 1984).

Another taxonomy distinguishes *Methodological* behaviourism (on either one or the study of human behaviour (Boakes 1984). And behaviourism advocates the aforementioned principle that fourth, aiming at control of behaviour. The latter objective is clearly not a necessary element of behaviourism but did recur in the history of the field, occasionally endowing it with Orwellian connotations. The above). In contrast, philosophical behaviourism does pragmatic attitude (Watson ended up in commercial advertising) culminated on the one hand in rather which comes in at least two versions: *Metaphysical* outrageously experimentation on *fear conditioning of and *Logical*. Metaphysical behaviourism makes life human babies (Watson and Rayner 1920), and on the easy by denying mental phenomena, period. Logical other in attempts to convince pigeons to guide missiles behaviourism considers propositions about mental across enemy lines (Skinner 1960). In a more practical endeavour, it also set foundations for behavioural psychotherapy (Wolpe 1963).

Over the years, behaviourism has experienced fiercelasses of ÔidolsÕ (illusions) that beset the human mind: attacks from biological and cognitive psychology, lin- Idols of the ÔTribeÕ (inherent in the *a priori limited guistics, and philosophy (for arguments related to the capacity of the speciesÕ senses and mind), of the ÔCave insufficiency of behaviourism to account for learning, (resulting from the individualÕs education and experience Dickinson 1980). As noted above, behaviourismence), of the ÔMarket-PlaceÕ (originating in social influence excluded itself from the biological arena in which much ence and public opinion), and of the ÔTheatreÕ of the excitement of modern memory research takes(stemming from dogmas and illusory knowledge). The place. Nevertheless, even with the recent developments¹ analysis of error and bias in science has since became in the neurosciences, behaviourism is still highly rele-richer and more sophisticated, but the basic illusions want to basic concepts addressed in this book. Fostill haunt us: those that stem from the senses, faulty example, the mere definition of *memory raises the logic, acquired prejudices, and suffocating *paradigms. issue of the relevance of observable facts to inferre\$science has learned to cope with the shortcomings of processes. Behaviouristic definitions of learning andthe senses, yet finds it rather difficult to struggle with memory cannot guide neurobiological research other faults of human nature, be them conscious or not. because they are not expressed in biologish. But simi- Bias could be explicit (definition 1) or implicit (defi-larly, data on *ion channels and *synapses cannothitions 1 and 2). But even if explicit, it should definitely advance memory research unless they are expressed iba distinguished from explicit distortion, which falsifies behaviourally relevant language. Skinner (1988)the data. The latter deplorable disease will not be pointed out that ÔSherrington never saw the action odiscussed here further. At the other end of the spectrum the synapse about which he spoke so confidently. stand the Ôidols of the tribeÕ, the elementary sensory and do see it now. An aim of modern neuroscience is to cognitive illusions that bias reality and usually trans-observe neuronal function in the context of circuits and scend culture, education, and profession (Gregory neuronal populations (*cell assembly) that encode 1966; Kahneman and Tversky 1982); they will not be *internal representations and guide behaviour. The referred to here either.

*level of internal representations, which the classical In the context of the present discussion, it is method- and radical behaviourist tabooed, is hence expected to logically useful to distinguish four major domains in bridge the organismic and the molecular approaches towhich bias could emerge: The behaviour of the experi- memory. We distanced ourselves long ago from the hegemonic *subject, that of the experimenter, the inter-mony of introspection that the fathers of behaviourism action between the subject and the experimenter, and so much distrusted, but we are still striving to reach the the scientific community that judges the research stage in which brain activity will provide accountable, reliable, and objective measures of behaviour.

Selected associations: Culture, Instrumental conditioning, Paradigm, Performance

¹On Sherrington, see under *synapse.

Bias

1. A preference or inclination that impairs impartial judgement.
2. The favouring of some outcomes over others as a result of systematic errors in procedures or interpretations.

Frances Bacon, trusting that Ôthe subtlety of nature iexperimenter (*Clever Hans), and sometimes attempts greater many times over than the subtlety of the sense\$comply with a perceived goal (Pierce 1908). The cues and understandingÕ (Bacon 1620), distinguished fouthat convey an experimental ÔhypothesisÕ to the subject

and hence influence the subject's behaviour are termed **Odemand characteristics** (Orne 1962). Their influence on the behavioural outcome of an experiment were mostly studied in humans, but they clearly exist in experiments involving other species as well. Demand characteristics may lead to biased responses by the subjects and to potential artefacts on the side of the experimenter. And finally, the experimenter is itself a potential source of bias (Rosenthal and Rubin 1978; Martin and Bateson 1993). An almost trivial source is self-deception, motivated by a wish to obtain certain results but not others (a potential negative spin-off of *scoophobia). In such situations minor acts of sampling bias and even data selection throughout the experiment could accumulate to a significant impairment in the overall outcome.

Proper *controls in the experimental design are a must if one wishes to minimize bias due to the subject, experimenter, or experimenter-subject interactions. For example, the potential for some facets of bias could be excited by strictly following a **Oblind** design, in which the person making the measurements does not know the constituents turn-over with time, such as the self treatment each subject has received until after the experiment is over. In human experiments (such as those that test the effect of drugs on behaviour), a **Odouble-blind** focus on a distinct type of the **Obinding problem**, which design should be followed, in which the subject as well refers to the ability of the brain to bind, within a fraction of a second, the features of a complex *stimulus does not know the treatment. Furthermore, experimenters must be well aware of their own behaviour. For example, the location and the bodily gestures of the experimenter could markedly bias the behaviour of a rat or *mouse in a *maze. The design and execution of laboratory experiments is a complex mixture of science and art, and at least the science part of the experiment has a long history (e.g. neuroscience and the philosophy of mind presently interest in this type of problem has a long history (e.g. Hume 1739). Neuroscience has dragged it into the consideration of vision: different types and combinations of visual attributes are processed in the brain in multiple streams (Knierim and Van Essen 1992). How do they

But the ordeal of overcoming bias in the experimental design and in its execution is not over even when the manuscript is finally ready for publication. This is the **OHumpty Dumpty** problem: **OHumpty Dumpty** sat on a wall/ Humpty Dumpty had a great fall/ All the King's horses and all the King's men/ couldn't put Humpty together again (Carroll 1872). The attitude of referees and editors is sometimes biased by *zeitgeist, by a prevailing conceptual paradigm, or, even worse, by the fame of the senior author or the institution in which the work had been done. The refusal over years to accept papers that defied some ideas about what conditioning should be/ there are trees, flowers and grass/ There are rivers and example of referees and editors being biased by a conditioned taste aversion, because it had seemed to speak of/ That there are hills, valleys and plains/ That a true and real ensemble/ Is a disease of our own perceptual paradigm. In other cases, the wish of referees and editors to appear politically correct in their scientific milieu or in society at large may also introduce bias into the scientific literature.

Selected associations: Control, Paradigm, Subject

Definition: Binding

Binding

1. The phenomenon or process in which elements in space and time cohere into a perceived whole.
2. The phenomenon or process in which perceptual features integrate into a coherent sensory *precept.
3. The phenomenon or process in which representational elements fuse into a coherent *internal representation.

Binding is related to the coherency of all kinds of internal representations (definition 3), not necessarily in the context of sensory perception. Hence it

surfaces, either implicitly or explicitly, in discussions of present there at that point in time. The features are *memory (Squire et al 1984; Teyler and DiScenna 1986; integrated, or ÔgluedÕ by the attentional ÔbeamÕ (*metaphor Damasio 1989; Hommel 1998; Dudai and Morris for critical discussions of Ôfeature integrationÕ, see 2000). These discussions usually refer to *declarativeM. Green 1991; Van der Heijden 1995; Treisman 1995). memory, but sometimes generalize to simple stimulusD The neurobiological approach attempts to identify response representations. Clearly, although the main computations and algorithms relevant to binding stream interest in the Ôbinding problemÕ is still in the brain and their physiological implementation. context of perception, whatever will be gained there will focus on the *cortex and on thalamocortical contribute to the understanding of memory as well. interconnections; in discussions of the role of binding

The binding problem binds several subproblems. in memory, attention is also devoted to the *hippocampal formation and to its role in coherency of internal representations. Two major types of solutions come up

1. Parsing: How are the relevant elements selected in neurobiological models of binding. The first type among other elements in the perceptual or mental of solution is that binding is based on place code space (Treisman 1999)? And how much of this (*map), and is performed by hierarchical combination selection is constrained by *a priori rules? of coding units, which converge anatomically on a
2. Encoding: How is the binding marked, maintained, and read by other systems in the brain; *cell master location (*homunculus; Barlow 1972; also assembly)? discussions in Singer and Gray 1995; Grossenbacher 1997; Bartels and Zeki 1998). The second type of
3. Mapping: How are the elements, once bound, kept in the correct structured relation(s); *map)? code (Eckhorn et al 1988; Hardcastle 1994; von der
4. Flexibility: How are the bound elements reused in binding without lingering interference of the previous binding(s)? Malsburg 1995; Engelt al 1997). The basic idea in this case is that feature-detecting neurons are bound into coherent representations of objects if they fire in synchrony. Neurons in the cortex have been indeed

Each of these questions could be tackled at multiple levels, from that of the computational theory, via the of 30D70Hz, and this has specifically been proposed *algorithms that implement the computations, down to as a candidate mechanism of binding. It also fits the biological hardware that implements the algo-psychophysical data, which suggest 20D30 ms as the rhythms. Discussion of binding in cellular neurobiology time scale of a Ôcognitive beatÕ (*capacity, *percept). is still rather uncommon. The main focus is on the At this stage, the temporal synchrony hypothesis is higher levels of neuronal circuits, brain systems, and still mostly phenomenological. It is not yet clear cognition. At these levels, it is methodologically whether the oscillations represent a causal mechanism, convenient to distinguish two types of approaches: top-a phenomenon, or an epiphenomenon (*criterion). To down or cognitive, and bottom-up or neurobiological. understand whatÔs going on, one would wish to identify The *classic top-down approach is that of the Gestaltthe semantics of the representational code(s), the source School (Gestalt, from German ~~shape~~; Koffka 1935; of the oscillations (i.e. intrinsic, emergent ensemble properties; Hochberg 1998; *insight). This school of psychology, tries, top-down induction or executive control), and the founded in Germany in the early twentieth century, has hardware components (e.g. *coincidence detector). promoted the view that the nature of perceptual parts is So is ÔbindingÕ as defined above a problem, or a determined by the whole, and that enquiry into the mind pseudoproblem? The same question applies to other should consider global organization and proceed top-*enigmas of the brain. What distinguishes ÔbindingÕ down. Unfortunately not much top-down analysis of the from some other unresolved brain processes and mechanisms was possible during the formative years of theanisms, and occasionally endows it with a mystic Gestalt. In more recent cognitive psychology, an influential flavour, is probably its association with major philosophical model is that of Ôfeature integrationÕ (Treisman andopical aspects (or some would say Ôspin-offsÕ) of the Gelade 1980; Treisman 1993). This model considersneurosciences. These include the mindDbody problem *attention as the binding agent. It proposes that simpleand *consciousness (e.g. Crick and Koch 1990). Many perceptual features are registered in parallel across the scientists hesitate to touch these issues, others do it visual field, in a number of specialized subsystems rather enthusiastically. Crick (1994) remarks on the Focused attention scans serially, within milliseconds, Ôbinding problemÕ that Ôit is not completely certain that through a Ômaster-mapÕ of locations, accessing the features is a real problem or the brain gets around it by some

unknown trick¹. Sure the brain does its trick, and the processes in learning (see **a priori*, **stimulus*); and the problem is hence only ours to solve. *ÔThat wonder is the* role of neurogenesis in the adult brain. effect of ignorance has been often observed² (JohnsonA song is a series of sounds with silent intervals 1751). It is therefore likely that with time, the ÔbindingÔ between them. It is different from a ÔcallÔ that is a simple, will stay but the ÔproblemÔ dissipate.

Selected associations: Algorithm¹ Attention Cell assembly
Coincidence detection Percept

brief vocalization uttered by both species in all seasons in response to particular stimuli such as a predator. Calls are not unique to birds. Birdsongs are. The most elementary sound in a song is a note, lasting 10–100 ms. Notes form syllables, syllables phrases, and phrases songs. Songs are commonly 1–5 s in duration. Different songs form a repertoire. The size of the repertoire ranges from one to many hundreds songs, depending on the species. Repertoires of geographically distinct populations of the same species often differ, and are termed dialects³ (Baker and Cunningham 1985). Some species perform all or most of their repertoire in cycles that takes many minutes to complete (Marler 1984). Terms such as ÔdialectÔ should not lure us to regard birdsong as an analogue of human language, as there is much more to language than structured stereotyped vocalization. But still, the song repertoire provides the bird with a complex expressive and communicative system, which may require special strategies to ensure prompt **retrieval* and correct response (e.g. Todt and Hultsch 1998).

The ontogenesis of song involves discrete stages. Take the wild chaffinch as an example (Nottebohm 1970). In the spring, immediately after hatching, chaffinches begin to emit various food-begging calls. Within a few

Birdsong

Complex, stereotyped vocalizations, accompanied by characteristic body postures, produced predominantly by mature male birds during the breeding season.

Male birds sing to selected audiences. The male is weeks, the male starts to emit a loose, rambling aggregation landlord and potential warrior, notifying other males that it is ready to defend its territory. It is also a charm- vocal pattern is called ÔsubsongÔ. The subsong keeping troubadour attempting to convince females that it is the best in town. The song occupies such a cardinal song, gradually emerging. These passages are called role in the maleÔs life that it may even dream about Ôplastic songÔ. During the breeding season the subsong (Dave and Margoliash 2000). Whereas we humans vanishes and the plastic song crystallizes into the full could enjoy the song repertoire regardless of gender/adult song. The singing posture typical of the adult also the male and the female of songbirds are probably eachnatures. The final crystallization takes place before the tuned to understand only that part of the song that end of the winter.

speaks to their heart (Williams and Nottebohm 1985). Although there are remarkable species differences in The **plasticity* of birdsong has been well known to bird song development, data from experiments involving fanciers in the Orient since ancient times, and experts sensory and social isolation (e.g. Marler and Tamura manipulations of song were exploited for aesthetic 1964; Konishi 1965) generalize to portray the following and commercial purposes (Konishi 1985). This neu-*model of song ontogeny: the bird is born with a song ronal and behavioural plasticity has also long attracted motor-control system that needs input in order to scientistsÔ attention (Darwin 1871; Mertfessel 1935) generate a normal song. This input is provided in two Koehler 1951; Thorpe 1954). In addition to being a stages, ÔsensoryÔ and ÔsensorimotorÔ, which may partially overlap, depending on the species. First comes the the study of birdsong taps into several central issues in Ôsensory stageÔ, during which the bird listens to a tutor. brain research. These include the role of genetic constraints on learning (Ôprepared learningÔ, see **a priori*, prefer a conspecific tutor. Thus, even if we raise a *imprinting); the interplay of **development* and learn- chaffinch in PavarottiÔs house, the chances that it will ing; the contribution of ÔinstructionÔ and ÔselectionÔ learn to sing La Bohème very slim indeed. In the

sensory stage, elements of the tutor's song are confined to memory. In the sensorimotor stage, which corresponds to the subsong, plastic song, and crystallization, the bird must listen to itself to match its vocal output with its innate template as well as with the memorized template of the tutor's song. The entire process combines elements of instruction (by the tutor) and selection (among endogenous innately constrained song templates; see Marler 1997). In the absence of tutor, only the innate information is used. Some species can generate species-specific song solely on the basis of an innate template, in the absence of tutors and auditory feedback. Species differ also in the stability of song.

In some age-limited learners, such as the zebra finch and white-crowned sparrow, learning is limited to the first year of life, and crystallized song is maintained throughout adulthood. In open-ended learners, such as the canary, new songs are added in adulthood. Even adult age-limited learners retain a significant amount of plasticity, and use auditory feedback in adulthood to maintain the stability of song structure (Leonardo and Konishi 1999).

One of the advantages of birdsong as an experimental system is the well defined and quantifiable behavioural output that provides a convenient and faithful assay to determine whether learning has occurred. Moreover, song is generated by a single organ, the syrinx. This facilitates the tracing of pathways from central motor centres and ultimately identification of brain circuits that subserve acquisition and execution of the motor programme. Over the years, in series of elegant studies combining anatomical and cellular methods, a picture has been generated that depicts the development (Margoliash 1997).

major elements of the central song system as composed of two major forebrain pathways (Figure 6). The posterioremedial pathway is traditionally termed the motorament, learning and recognition. It is not obligatory for pathway, and includes, in ascending order, the nucleus Uva, the nucleus NIf, the higher vocal centre (HVC), feedback evaluation and adaptivity of singing in the originally so abbreviated because it was thought to be adult bird (ibid; Brainard and Doupe 2000). This hyperstriatum ventrale, and finally nucleus RA, that pathway indirectly connects HVC to RA via area X, innervates the tracheosyringeal portion of the hypoglossal nerve nucleus (nXIIts), itself innervating the syrinx. This pathway is fed by auditory input, and is and circuits, and no single site stores the entire score obligatory for both song development and production (*engram, *metaphor). Furthermore, a clear-cut dissociation between central sensorimotor and learning in silent song: upon noticing a female, the lesioned male adopts a singing position but emits no song, becoming a very sad bird indeed. The HVC and RA are organized hierarchically, with HVC neurons representing syllables and RA neurons representing notes. Uva and NIf may help organize syllables into species that sing. However, in songbirds, it is prominent higher units of song. Some of the sites afferent to Uva in HVC, and correlates with seasonal variations in

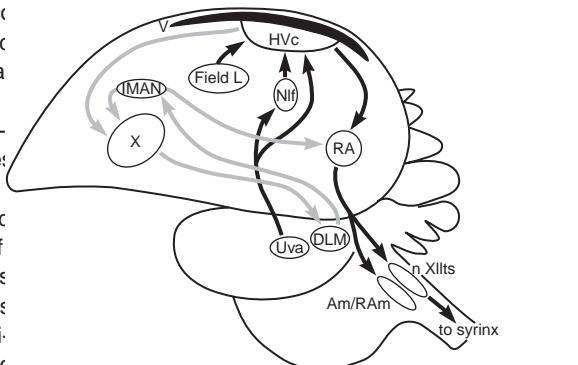


Fig. 6 A schematic representation of the songbird brain, showing the brain centres and pathways that subserve the development, learning and production of song. The system is composed of two major forebrain pathways. The posterioremedial pathway (includes the nuclei Uva, NIf, HVC, and RA. The RA innervates the tracheosyringeal portion of the hypoglossal nerve nucleus, which in turn innervates the song organ, the syrinx. The anterior forebrain pathway, which is obligatory for song development and learning, connects the HVC to RA via area X, the thalamic nucleus DLM and nucleus IMAN. Also shown is the auditory area L, which feeds the HVC. Abbreviations: AM, nucleus ambiguus; DLM, medial portio of the dorsolateral nucleus of the thalamus; HVC, higher vocal centre in the neostriatum; IMAN, lateral portion of the magnocellular nucleus of the anterior neostriatum; Field L, auditory region in the neostriatum; NIf, nucleus interface; RA, robust nucleus of the archistriatum; RAm, nucleus retroambigualis; Uva, nucleus uvaformis in the neostriatum; X, area X; n XIIts, tracheosyringeal part of the hypoglossal nerve nucleus. (Adapted from Brenowitz et al. 1997.)

Calcium

song and sex hormone levels. (Sex hormones play a part especially noteworthy in the context of plasticity are the in moulding song circuits and behaviour; Bottjer and studies on the role of Ca^{2+} mediating and modulating Johnson 1997.) The role of neurogenesis in song memory excitability and integrative properties in dendritic ory, if at all, is not yet clear. In recent years neurogenesis compartments (Markram et al 1995; Magee et al has also been noted in the adult mammalian brain, and, 1998); control of *neurotransmitter release (Matthews furthermore, reported to be enhanced in learning 1996; Goda and Sudhof 1997); modification of (Gould et al 1999; *hippocampus; but see concerns in membrane *receptors (Barria et al 1997); and modula-Rakic 2002). Neurogenesis in birds in general and song of gene expression (Biro et al 1996; Dolmetsch birds in particular may therefore reflect a more generalet al 1998).

process. This is surely a finding that can defeat the popular notion that old brains only fade out.

Selected associations: Developmental Imprinting, Observational learning, Skill

The ubiquitousness of Ca^{2+} -signalling in the nervous system makes it impractical to mention all its major functions in experience-dependent neuronal modification. These functions are performed at locations ranging from neuronal subcompartments to circuits, and on time-scales ranging from milliseconds to days and more. Ca^{2+} is required for elementary short-lived processes of *synaptic plasticity (Thomson 2001), and for the induction of *long-term potentiation, a popular cellular model of longer-term neuronal plasticity (Nicoll and Malenka 1995). A few examples will serve to illustrate the role of Ca^{2+} in *acquisition, retention, and consolidation of learned behaviours. In the circuits that subserve *classical conditioning of defensive reflexes in *Aplysia*, Ca^{2+} encodes information about the conditioned stimulus (CS). Furthermore, convergence of the CS and the unconditioned stimulus (US) takes place on a Ca^{2+} /calmodulin-activated adenylyl cyclase (*coincidence detection; *intracellular signal transduction cascade). The optimal activation of the enzyme learned about the ways in which calcium ions (Ca^{2+}) encode and modulate neuronal information, but the picture is far from being comprehensive.

A metallic element that comprises about 3% of the earth crust and is essential for many biological processes, including neural *plasticity.

Calcium (calx, Latin for lime) fulfils many regulatory, computational, and representational functions in the brain. Furthermore, it is instrumental in translating information across *levels and time domains in the brain (see below). In recent years much has been learned about the ways in which calcium ions (Ca^{2+}) encode and modulate neuronal information, but the picture is far from being comprehensive.

In resting cells, intracellular Ca^{2+} is in the range of 10–100 nanomolar. Upon stimulation it could rise by several orders of magnitude. In many cases the infortype II (CaMKII ; Braun and Schulman 1995; De Koninck and Schulman 1998), was found to be patterns of change rather than a tonic increase in concentration. Changes in cellular Ca^{2+} due to influx from the extracellular milieu and release from intracellular stores. Both mechanisms generate all-or-none Ca^{2+} signals, which are brief and localized changes in intensity, timing, and location of the primitives of the language generate a reper-mechanism immune to molecular turnover (Miller 1997). The latter control cellular metabolism, structural dynamics, protein kinase, PKC, was also implicated in learning signal transduction, hormone release, differentiation, (e.g. Scharenberg et al 1991.) In addition, Ca^{2+} is involved in cellular consolidation: it regulates the introduction of novel technologies of molecular biology, cellular electrophysiology, and imaging has opened new vistas in the analysis of neurons.

Experience-dependent autophosphorylation of the enzyme complex was proposed as a molecular storage of the postsynaptic density. It phosphorylates and modifies receptors, channels, and cytoskeletal elements. Ca^{2+} codes (Bootman et al 1997). The latter and Kennedy 1986). Another family of Ca^{2+} -regulated control cellular dynamics, protein kinase, PKC, was also implicated in learning signal transduction, hormone release, differentiation, (e.g. Scharenberg et al 1991.) In addition, Ca^{2+} is involved in cellular consolidation: it regulates the introduction of novel technologies of molecular biology, cellular electrophysiology, and imaging has opened new vistas in the analysis of neurons.

Why is it that Ca^+ , rather than any other ion, plays such a key part in cellular activity in general and in plasticity in particular? Though in essence a teleological question with speculative answers, it does

warrant consideration, because it could illuminate interesting properties of signalling systems. Possibly the physicochemical parameters of Ca^+ when considered in combination with those of critical

Capacity
1. The ability of a *system to receive, process, store, represent or transmit items.

2. The measure of this ability.

3. The upper limit of this ability.

Ca^+ binding sites in the cell, had from the early days of Pondering the capacity of our memory carries with it evolution fitted the demands of cellular function and the risk of being enslaved to the common *metaphor of plasticity better than those of other ions. The problem memory as a static storehouse (Roediger 1980). This with this line of reasoning is that it is of the egg-misconception should be avoided at the outset. and-the-hen type: was the cause the abundance of Furthermore, in the case of the nervous system, even the Ca^+ , or the availability of the biological binding sites? definition itself evokes cardinal issues: What is the This inherent issue notwithstanding, one appealing meaning of Ostore (definition 1)? Are *internal representations stored as such, reactivated, or reconstructed evolution is that the affinity of Ca^+ for important macromolecules in the cell is strong enough to allow rapid binding but not too strong to prevent rapid dissociation. This is important in cellular signalling however, something must eventually be stored as, in general and in fast plasticity in particular. For example, magnesium binds stronger to phospho-groups than calcium. And as if all this is not enough, it is likely that different, monovalent ions are in general much worse in getting bound to biological macromolecules. The problem is highly complex, because, as mentioned above, it is not tonic, but rather transients, which are most important in signalling. The life-span of these transients may not be sufficient for Ca^+ to equilibrate with binding sites in the cell (Markram et al 1998b). Analysis of Ca^+ signalling, therefore, requires gigantic calculations of nonequilibrium Ca^+ dynamics. For our purpose suffice it to remember that the real-life role of Ca^+ neuronal plasticity must be considered in the context of the simultaneous interaction of this ion with the network of the many Ca^+ binding molecules in the neuron.

It is also noteworthy that overall, the actions of Ca^+ in the neuron span orders of magnitude in time, space, and complexity (Bootma et al 1997). This endows Ca^+ with a unique position to bridge molecular, cellular, and system levels of brain action (Dudai 1997b). The spatiotemporal pattern of Ca^+ is therefore a candidate parameter for future equations of the not-yet-available interlevel correspondence rules.

$\text{O}10^{13}$ to 10^{17} bits (reviewed in Dudai 1997a; Obit is the basic unit in information theory; see *system). In considering the information that becomes available to the brain, we must take into account not only the information that is obtained from the external world, but also that information that is generated endogenously by the brain (**a priori*, *internal representation, *stimulus). We do not yet have the bases to estimate the magnitude of contribution of this type of information

Selected associations: Intracellular signal transduction, cascade, channel, Plasticity, Reductio, Stimulus

*Modelling of artificial neuronal networks of the estimated size of the human brain yields an upper representational capacity of 10^{13} (Palm 1982) to 10^{15} bits (Amit 1989). There have been also attempts

Capacity

to estimate the representational capacity of parts of the brain, such as *cortex (Gochin et al. 1994; ~~Robins~~ long-term memory stores 1997). The conclusion was that the available representational capacity is probably more than required to store subserve our actual mental and behavioural repertoire.

	Size	Reference
Words in language (mother tongue)	25 000–50 000	Nagy and Anderson (1984)
Pictures recognized	10 000	Standing (1973)
Game patterns by the bits of the formal models to vague, almost impressive-a chess master sionistic units. The most popular estimate is that our working memory can hold only seven-plus-minus-two chunks of information at one time. This estimate stems from experiments in psychology (Jacobs 1887; Miller 1956) and from observations in anthropology (Wallace 1961; Berlin 1992).	10 000–100 000	Chase and Simon (1973)
Facts by mnemonists	100 000	Yates (1966)
Core personal episodes	Thousands	Dudai (1997a)
Items in expert databases	500–2000	Levi-Strauss (1966)
in orally-reliant societies		Berlin (1992)

But how much of this information could be stored in our memory over time? Some agreement exists only on the maximal capacity of short-term, or better, *working memory (*phase). The discussion digresses here from the bits of the formal models to vague, almost impressive-a chess master sionistic units. The most popular estimate is that our working memory can hold only seven-plus-minus-two chunks of information at one time. This estimate stems from experiments in psychology (Jacobs 1887; Miller 1956) and from observations in anthropology (Wallace 1961; Berlin 1992).

Despite the catchy title of Miller's classic article, seven-plus-minus-two is not a sacred number. There are lower estimates as well (down to

only three separate registers; Broadbent 1975). Miller called a unit of memory, but formally is very unsatisfactory.

The idea was not to determine a precise value, but rather to theorize indeed (Dudai 1997). It is pointed out that the brain is an information processing system of limited capacity, which had evolved to recode doubt of interest, but it would do no harm to scrutinize information into chunks in order to be able to deal with the assumptions that underlie this interest. One it efficiently (Baddeley 1994; Shiffrin and Nosofsky 1994). Attempts have been made to estimate the size of, is that the bigger, the better. The capacity of memory chunk in terms of digits, syllables, words, and patterns is the outcome of the interplay among (Simon 1974). Some individuals develop a remarkable multiple drives and elements. These include the functional skill for chunking, and by combining it with efficient retrievals that this memory system is supposed to accommodate from long-term stores, can handle huge amounts of information simultaneously (e.g. more biological machinery; the feasibility of algorithms; than a 10-fold increase in the normal digit span; Chase and Ericsson 1982).

It has been estimated by Simon (1974), on the basis of evolution of the system. Here is but one concrete example from the contemporary psychological literature, that 5–10 bytes is phylogenetically advantageous for the system of are needed to transfer a chunk from short- into long-term stores. When it comes to both the maximal and the capacity? Not necessarily (see in *false memory).

actual capacity of the latter, the issue of magnitude. It would be naive to expect real advances in the becomes even more evasive. In what units should long-term memory be measured? Which chunks should materialize. First, we must decipher the codes of inter-used to estimate the size of, say, an episodic scene or personal representations, in order to be better equipped to motor skill? Furthermore, how can one compare the requirements for representational and capacity of different long-term memory systems? A computational space in the brain. Second, we must gain variety of experimental methods have been deployed a much better understanding into the processes and ranging from introspection (Galton 1879), via controlled mechanisms of persistence, forgetting, relearning in recalling of personal experience (Wagenaar 1986), to extinction, and particularly, retrieval of memory. measurement of *real-life capabilities such as picture retrieval that tolerates liberal reconstructions of inter-recognition, language, or the feats of mnemonists. These representations, and is heavily dependent on (Table 1). There are no definite answers, only estimates. Information, is expected to place different demands expressed ad-hoc, somewhat fuzzy units. A conservative estimate is that a normal human long-term memory retains 10^6 items, where item means a word, a fact, a capacity is hence intimately associated with some of the an autobiographical episode—what might intuitively be most profound *enigmas of memory research.

Selected associations: Episodic memory representation
Persistence/Working memory

¹This issue is further discussed in *persistence.

²By the way, the working-memory capacity of the chimpanzee is not much less: 5 items, the same as preschool children (Kawai and Matsuzawa 2000).

remained viable in both experimental and theoretical research on perception, learning, and memory (e.g. Palm 1982; Crick 1984a; Dudaal 1987; von der Malsburg 1987; Gerstein et al 1989; Sing et al 1990; Nicolelis et al 1997; Sakurai 1998).

The platonic cell assembly has the following attributes: (a) it encodes internal representations in a spatiotemporal code; (b) a representation is distributed over many units in the set; (c) each unit may be a member of several assemblies; (d) the units in the assembly become coactive and hence actualize the assembly and what it represents, in brief time-locked pulses; and (e) the assembly is plastic meaning that the representations could change over time, either in response to input or by endogenous rearrangements. That the cell assembly uses a distributed, alias ensemble, alias population code means that in big-enough assemblies, no single neuron is essential to any percept or memory; put in other terms, the assembly denies the existence of single-cell

Cell assembly

A hypothetical concept referring to *phasic sets of coactive neurons that are assumed to encode *internal representations and perform computations over representations.

In 1949, Hebb published *The organization of behavior*

later to become the most influential book in the history of modern neuroscience (*classic). In this book, as the case with other great ideas, this one as well stood he wrote, "I have tried to bridge the gap between the shoulders of giants." The possibility that sensori-neurophysiology and psychology. In essence, Hebb's monograph was about how the brain *perceives and represents the world. It has yielded important insights into brain function, as well as two major concepts. Typical of Hebb's integrative view of the brain, these have the representational complexity to account for concepts related to two *levels: the *synaptic and the higher properties of the nervous system (Sherrington *system. At the synaptic level, Hebb coined a postulate (1941). Hebb was a student of Lashley, who attempted in of use-dependent synaptic *plasticity (see *algorithm). vain to localize memory traces to specific brain regions, At the system level, he proposed the existence of neuronal assemblies as vehicles for perception, *attention, *association, memory, and thought. Hebb (1949) No (1938), himself relying on earlier observations, envisaged that in the brain

"homunculi."

Hebb's assemblies did not emerge out of the blue. As the case with other great ideas, this one as well stood he wrote, "I have tried to bridge the gap between the shoulders of giants." The possibility that sensori-neurophysiology and psychology. In essence, Hebb's monograph was about how the brain *perceives and represents the world. It has yielded important insights into brain function, as well as two major concepts. Typical of Hebb's integrative view of the brain, these have the representational complexity to account for concepts related to two *levels: the *synaptic and the higher properties of the nervous system (Sherrington *system. At the synaptic level, Hebb coined a postulate (1941). Hebb was a student of Lashley, who attempted in of use-dependent synaptic *plasticity (see *algorithm). vain to localize memory traces to specific brain regions, At the system level, he proposed the existence of neuronal assemblies as vehicles for perception, *attention, *association, memory, and thought. Hebb (1949) No (1938), himself relying on earlier observations, singled out the role of neuronal loops and recurrent circuits in information processing in the nervous system.

This was contrary to contemporary naive switchboard metaphor, which described the brain in terms of many yet rather simple (sensory) input/(motor) output connectors. Hebb took the aforementioned ideas further. He formulated a comprehensive conceptual framework of brain function in which populations of neurons represent information about the world. As representations (and hence memories) are distributed over many nodes, localized lesions could fail to abolish memory. Furthermore, assemblies according to Hebb are dynamic entities. They form, *develop (first in the immature and

É stimulation will lead to the slow development of Ôcell assemblyÕ, a diffuse structure comprising cells in the cortex and diencephalon É capable of acting briefly as a closed system, delivering facilitation to other such systems É A series of such events constitutes a Ôphase sequenceÕ/the thought process. Each assembly action may be aroused by a preceding assembly, by a sensory event, or ñnormallyñ by both. The central facilitation from one of these activities on the next is the prototype of ÔattentionÕ.

Although with time Hebb's synaptic postulate may have gained more popularity (despite being regarded by calls for synaptic plasticity; Hebb's famous synaptic Hebb himself as less original; Milner 1986), it is the Ôcell postulate, mentioned above, was his solution to the assemblyÕ that was at the heart of his seminal book. mechanism of use-dependent modifications in local the past 50 years or so, the concept of Ôcell assemblyÕ has in the assembly. The first attempts to model

Cell assembly

neuronal assemblies on a digital computer were carried out a few years after Hebb's book was published to prove or refute it. Such tools now available: sophisticated cellular physiology, functional models have been suggested for the representation of information in neuronal assemblies, based on the analysis, and, preferably, all combined. The hunt for the principle of ensemble encoding; some of these models *reduces the search for the engram from gross incorporate Hebbian local modification rules.

neuroanatomical cartography to the analysis of func-

Do cell assemblies exist in real life? Many attempts have been made to identify them and observe their circuits and their interconnections. This by itself has been instrumental in advancing our understanding of action. These attempts have involved combinations of memory,

cellular physiology, neuroanatomy, *functional neuroimaging, and behaviour. The *zeitgeist is that population coding, which is in line with the assembly notion, plays a part in higher brain function (Jones 1972; Lee

Selected associations: Cerebral cortex, Homunculus, Internal representation Model

et al 1988; Singe et al 1990; Hurlbert and Derrington 1993; Tanaka 1993; Arieli et al 1995; Goldman-Rakic 1996; Nicolelis et al 1997; Sakurai 1998; Stopfer and Laurent 1999; Tsodyks et al 1999). Time-locked phasic activity of large neuronal populations is also detected (e.g. *binding).

Yet the inference that these are cell assemblies that encode and control behaviour requires more than that. One must establish a necessary, causal, and sufficient link between the coactive populations and specific instances of perception, memory, and behaviour (*criterion). Taking the devil's advocate stand, one could claim,

'During this period, the system can be said to become locked in a quasi-stable state of an energy minimum.'

²For a fascinating history of this aphorism, commonly attributed to Newton, including some lessons on the intricacies of *culture and collective memory, see Merton (1993).

Cerebellum

A brain organ at the rear of the brain overlying the brainstem, composed of a cortex and a core device, or a process permissive for coding but not of white matter, which contains deep nuclei, code itself, or a step on the road to another type of interconnected with all major subdivisions of coding, even on the road to the elusive homunculus. the central nervous system, and involved in sensorimotor and cognitive function.

Suppose cell assemblies do indeed encode internal representations; in that case, how big are the assemblies? The minimal number of neurons that is needed to encode and transmit physiologically meaningful information reliably in the cortex was proposed to be 100 (Shadlen and Newsome 1998). Similarly, it has been estimated that the number of neurons required to

this was soon rejected: this marvelous instinct, collectively encode a meaningful aspect of a visual scene which is developed by education into mind, and which is closer to 10^{10} than to 10^{11} (Crick and Koch 1998). The lower limit attests at most to 10^6 (Cochran 1998). But a postulated assembly representing a complex scene could bind together many such mini-assemblies (Mettrie 1748). Others thought that the spirits which each encoding an attribute of the representation. In such a case, the overall number of coactive neurons could reach $\gg 10^6$. Each coactivation phase of the hypothetical assembly is expected to be in the millisecond range. Limits on the coactivation time can be deduced from the observation that 40–150 ms are sufficient for unconscious movements (Hoffmann 1695, cited in Brazier 1984). This latter proposal (spirits excluded) was not too far from certain more recent notions of cerebellar function. But the picture is changing. And so is the view of the role of the cerebellum in learning tasks (Thorpe et al 1996; Van Turennout et al 1998).

The cerebellum in mammals constitutes only about

The cell assembly illustrates a fruitful concept in 10% of the total volume of the brain, yet contains more than half of all the neurons (Ghez 1991). It is composed

of a thin cortex and a core of white matter containing pairs of deep nuclei (the fastigial, anterior and posterior interposed, and dentate nuclei; Figure 7). The cerebellar input and output pathways course through the cerebellar peduncles that connect the cerebellum to the brainstem. The cerebellar input is carried by two connections to the deep nuclei, which relay the cerebellar output further.

reach the cerebellar cortex and send collaterals to the deep nuclei. The mossy fibres originate in the brain-stem. The climbing fibres originate in the inferior olive and the cerebellar cortex has a wide variety of investigators, ranging from in the medulla, itself receiving input from the spinal neuroanatomists to cell biologists to theoreticians, to cord and the cerebral cortex. The cerebellar cortex is neatly organized in three layers, containing only a few types of neurons (Figure 8): Purkinje cells (large GABAergic neurons), granule cells (small glutamatergic neurons), Golgi cells (GABAergic/ glycinergic), and stellate/basket cells (GABAergic) to propose models for cerebellar function (e.g. Braatenberg 1967; Marr 1969; Albus 1971; Ito 1972, 1984; Raymond et al 1996; Braatenberg et al 1997). Two points concerning these models are particularly noteworthy. First, the models consider the cerebellum to be either an orchestrator of motor function, (Voogd and Glickstein 1998). Each Purkinje cell a motor learning machine, or a clock. It is now evident

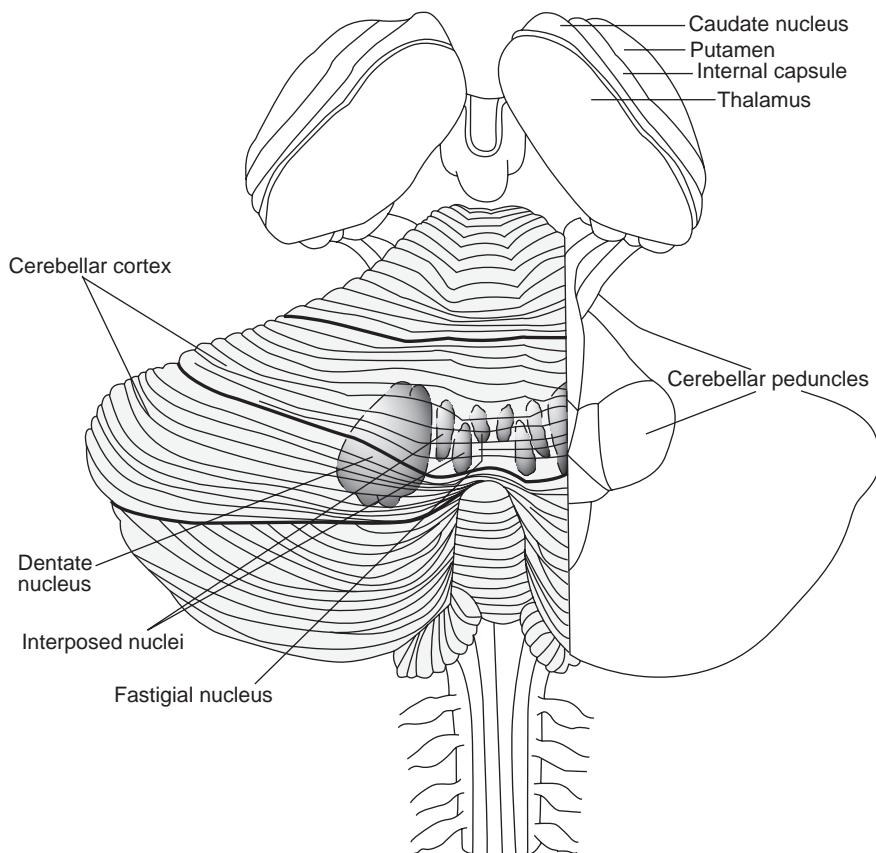


Fig. 7 A simplified macroscopic view of the exposed cerebellum. In this dorsal view, the cerebral cortex is depicted as transparent, showing the underlying deep nuclei, and the right hemisphere is cut out to show the underlying cerebellar peduncles. (Adapted from Jansen 1986, J. W. Wenhuys)

Cerebellum

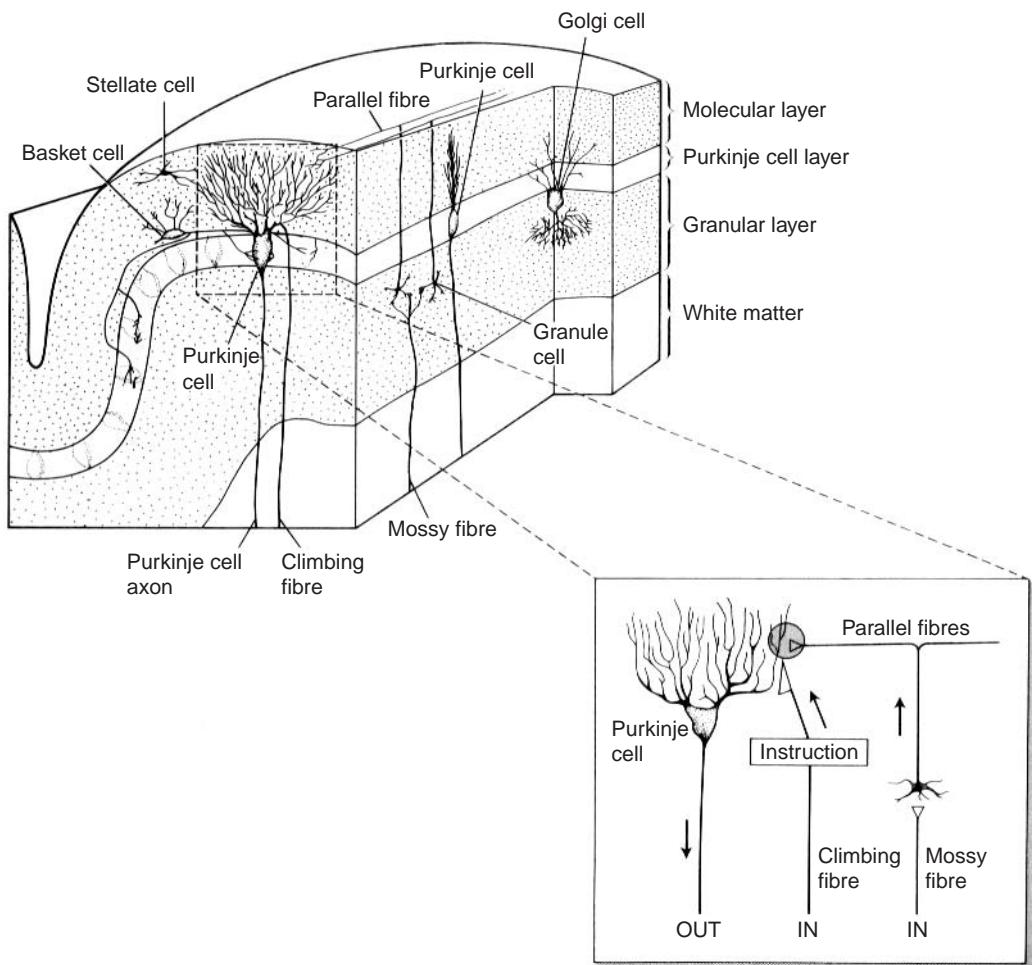


Fig. 8 A simplified microscopic view of the cerebellar cortex. Only five types of neurons (Purkinje, granule, Golgi, stellate, and basket) are localized into the three layers of the cerebellar cortex. The sole output, which is inhibitory, is provided by the Purkinje cell layer via two excitatory fibre systems, the mossy and the climbing fibres. Each Purkinje cell receives converging input from a large number of parallel fibres via many parallel fibres that are sent by the granule cells. In contrast, each Purkinje cell receives input from only one climbing fibre. A scheme depicting the convergence of the two major cerebellar inputs on the Purkinje cell. The influential Marr-Douglas-Albus model (Marr 1969; Albus 1971) proposed that the climbing fibre instructs the Purkinje cell to respond specifically to the concurrent pattern of parallel fibres. The modified synapse is encircled. (Adapted from Ghez 1991.)

that these possibilities are not mutually exclusive. Much of the data on the role of cerebellar circuits in learning and memory is based on studies of the cerebellum in non-human primates. Second, a highly influential model has proposed a locus of plasticity and learning stems from two systems. One is of plasticity in the cerebellar cortex as the key to the adaptation of the vestibulo-ocular reflex (VOR; du Lac et al 1995; Ito 1998); the other is classical conditioning of the eyeblink reflex (Yeo and Hesslow 1998; Figure 8). The basic idea is that information arriving via the climbing fibre conditions the Purkinje cell to respond specifically to the concurrent pattern of parallel fibres. Certain lines of experimental evidence support this prediction.

movement. It stabilizes vision, by keeping images from slipping across the retina. The reflex is capable of remarkable adaptation, e.g. after wearing reversing prisms, eye movements go with, instead of against, head movement. The visual information and the vestibular information involved in this adaptation converge both in the deep cerebellar nuclei and in the cerebellar cortex. Although significant pieces of the puzzle are still missing, it is now believed by most authors that both these sites are involved in the adaptation. Furthermore, it is proposed that the convergence on the Purkinje cell of the visual information, mediated by the climbing fibres, with the vestibular information, mediated by the mossy-fibre-parallel fibre, induces long-term depression (LISBERGER 1998; ITO 2001). This LTD is considered to contribute to the behavioural change of the VOR.

The other system that has contributed tremendously to our knowledge about the role of the cerebellum in behavioural plasticity is classical conditioning of the eyeblink reflex, in which the subject blinks in response to a noxious stimulus applied to the eye area. This is one eyelid. The cerebellar cortex and the interpositus nuclei are sites of the most studied cases of simple learning in mammals. It has been studied in multiple protocols and instead of delay conditioning, or complex protocols of classical conditioning are used, additional brain organs, such as the hippocampus, become obligatory as well (*criterion). ->, excitatory synapse; Dl, inhibitory synapse. (Adapted from Thompson and Kim 1996.)

Studies using cellular physiology, anatomical, pharmacological, and neurogenetic lesions, and electrical stimulation of discrete brain sites (*criterion, while the others add adaptability. This is particularly *method), have identified the cerebellar cortex and the interpositus nuclei in the cerebellum as sites of *associocomplex forms of conditioning engage additional brain areas. In both cases, the conditioned input (vestibular learning-related plasticity changes can, however, begin the VOR, auditory in the standard protocol of eye-detected in other sites in the brain, particularly if the blink conditioning projects in parallel to the cerebellum) conditioning protocol becomes more complex than elemental delay conditioning. In both cases, the mental conditioning. Furthermore, when a trace conditioning protocol is used instead of delay conditioning, the hippocampus becomes obligatory (Figure 14, p. 46), the hippocampus for conditioning (e.g. Moyer et al 1990). There is also cortex and the deep nuclei (*coincidence detector). In evidence that trace conditioning of the eyeblink reflex, both cases, the convergence in the cerebellar cortex as opposed to delay conditioning, requires *consciousness could result in modification of the Purkinje response to awareness (Clark and Squire 1998), which should be the conditioned input. The modified Purkinje output, expected to engage cerebral cortex as well.

Though controlling different behaviours, and involving different brainstem nuclei, cerebellar cortex cases, the relative contribution of the cerebellar nuclei

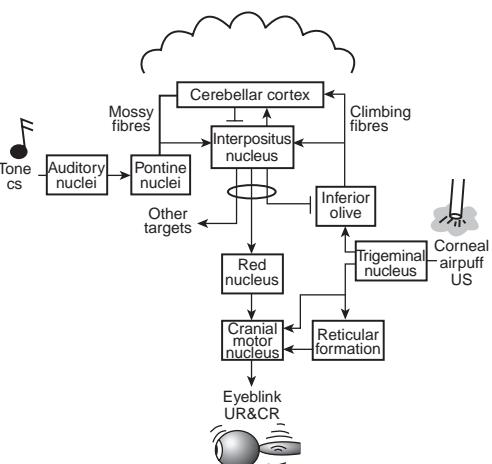


Fig. 9 A flowchart diagram of the circuits that subserve classical co-

ditioning of eyeblink in the rabbit. In a typical protocol, tone is the

conditioned stimulus and periorbital air puff the unconditioned stim-

ulus. The unconditioned stimulus elicits closure of the eyelid as well

as extension across the cornea of the nictitating membrane (the inter-

mediate eyelid). The cerebellar cortex and the interpositus nuclei are sites

of the most studied cases of simple learning in mammals. *association and *plasticity in this type of learning. When tra-

ditioning is the conditioned stimulus and instead of delay conditioning, or complex protocols of *classical co-

ditioning are used, additional brain organs, such as the *hippocam-

pus, become obligatory as well (*criterion). ->, excitatory synaps-

Dl, inhibitory synapse. (Adapted from Thompson and Kim 1996.)

Cerebellum

and the cerebellar cortex, respectively, to learning, and discerned: archicortex ("hippocampal formation), the site(s) of the lasting memory trace, are still debated paleocortex (olfactory, entorhinal, and peri*amygdala).

Recent evidence, including *functional neuroimaging, and data, unveils cerebellar involvement in declarative memory, *working memory, and language (Levitin 1993; Desmond and Fiez 1998; Thach 1998; Wiggs 1999). The role of the cerebellum in these higher brain functions is possibly based on the same computational model (White 1984–94; Mountcastle 1997). First and abilities, such as the spatiotemporal orchestration of movement, the cortex can be described as composed of strings of events, which contribute to the adaptive control of simple motor reflexes. Whatever the computations are, it becomes clear that depiction of the cerebellum merely as a motor centre is outdated.

Selected associations: Acquisition, Classical conditioning, Engram, Performance, Skill

for the most advanced mental abilities of our species.

Multiple macroscopic and microscopic criteria are used in the cartography of the cortex (Jones and Peters 1984–94; White 1989; Mountcastle 1997). First and et al, and occipital (Figure 10a). The cortex can also be mapped on the basis of function and functional hierarchy (sensory, motor, and association cortex; or primary and higher-order cortex; or unimodal, polymodal, and supramodal cortex). Finer parcellation into areas is based on cellular architectonics. The most popular map, containing 52 areas, was introduced by Brodmann

about 100 years ago. The cytoarchitecture of the cortex is usually described in terms of laminar and columnar organization. A six-layer classification, I–VI, first introduced by Brodmann, is conventionally used to describe the laminar structure of the neocortical sheet (Figure 10b). Further subdivision of the major layers is added, e.g., layer Ia in

The layers contain pyramidal cells, which are the most abundant neurons in the cortex, and various types of pyramidal neurons. The arrangement of afferents and efferents in each layer depends on the area and the species, but in general, thalamocortical afferents end predominantly in the middle layers, whereas cortico-cortical afferents synapse on to neurons in layers I–IV. Several diffused neuromodulatory systems (e.g. *acetylcholine, *dopamine, *noradrenaline) reach the cortex mostly in layers I and VI. In most cases, cortical neurons in layers II–III project to other cortical areas and those in deeper layers project to subcortical structures.

The other organizational principle in the cortex is the division into columns. The column, 0.1–0.5 mm wide, is regarded by many authors as the universal organizational and computational unit of the cortex (Mountcastle 1997). Most of the axonal arbor of cortical neurons lies within the cortical column (Douglas et al 1995). Even in layers that are major recipients of thalamic input, the great majority of the synapses still mediate information from within the column (Ahmed et al 1994). Another interesting observation is that about 85% of the synapses of the excitatory neurons synapse on to other excitatory neurons. The computational theory and algorithms and about the same number of glia cells. From a (*level) beyond all this gigantic collection of recurrent phylogenetic perspective, three types of cortices are in circuits is still mostly an enigma.

¹GABAergic neurons are so called because they release the inhibitory neurotransmitter *γ*-aminobutyric acid (GABA). Glycinergic cells release glycine (see *glutamate).

²Proposals that the cerebellum is involved in the control of posture and movement surfaced in the literature already in the seventeenth century (Brazier 1984). These proposals were augmented and substantiated in the nineteenth century, and validated after the First World War by reports on the behavioural consequences of cerebellar injuries (e.g. Holmes 1930). Though most current models consider the cerebellum to control movement, there is also the view that it is the inferior olive in the medulla rather than the intrinsic cerebellar circuits that is the pacemaker and spatial organizer of movement (Welsh and Llinás 1999).

³For examples of additional experimental systems that are used to investigate cerebellar function and plasticity, see Ulfhake (1998), Thach (1998).

⁴On LTD, see *long-term potentiation, *metaplasticity.

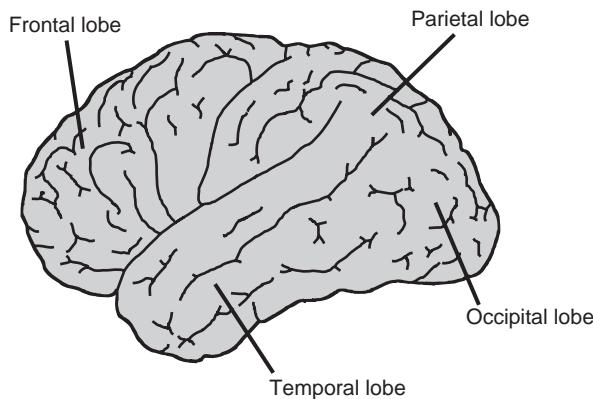
⁵The nictitating membrane is an internal eyelid, a curved plate of cartilage covered with glandular epithelium, which is drawn from the inner canthus laterally across the cornea when a noxious stimulus is applied to the eye. The movement of both external and internal eyelids is controlled by nuclei in the brainstem.

Cerebral cortex

The outer layer of the cerebral hemispheres of the brain.

The cerebral cortex (Latin *f*oam, *b*ranch, *s*hell) is a multi-layered, convoluted sheet of tissue overlaying the cerebral hemispheres. In humans it is 3–4 mm thick, covering 2600 cm². It contains at least 10¹⁰ neurons and about the same number of glia cells. From a phylogenetic perspective, three types of cortices are in

(a)



(b)

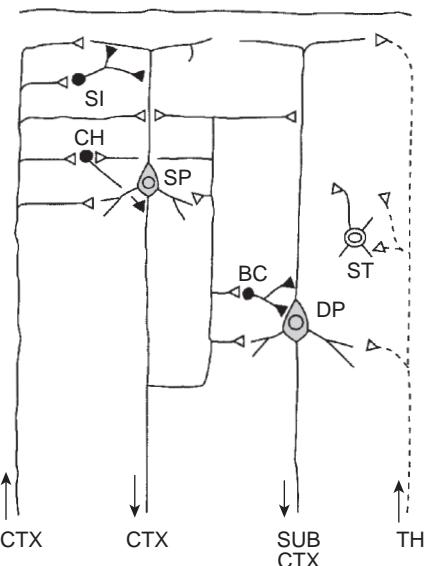
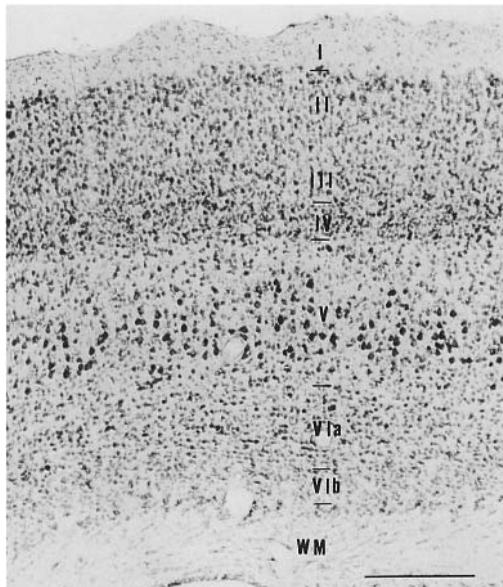


Fig. 10 (a) A macroscopic view of the cerebral cortex: simplified drawing of the lateral surface of the human brain, showing cortical lobes. The primary visual cortex is in the occipital lobe, and higher-order visual areas reside in the occipital, temporal, and parietal lobes. The primary and higher-order auditory cortex is in the temporal lobe; primary and higher-order somatosensory areas in the parietal lobe, and higher-order motor cortex in the frontal lobe. The primary taste area is in the insular cortex, which is in the medial wall of the cerebral groove (groove) that separates the frontal from the temporal lobe, and is invisible on this lateral view, and higher-order taste cortex is in the insular cortex. The olfactory (piriform) cortex, on the ventrolateral surface of the brain, which is also invisible in this view, is an ancient cortex (paleocortex). Areas that subserve higher cognitive functions, including *planning, *prospective memory, and *working memory are in the frontal lobe. (b) A microscopic view of the ~~left~~ ^{posterior} frontal section of the rat primary visual cortex, showing nerve fiber bodies in different cortical layers. WM, white matter. (From Peters 1985.) Simplified diagram of elements of cortical circuits. BC, basket cell; CH, chandelier cell; DP, deep pyramidal neuron; SI, superficial inhibitory neuron; SP, superficial pyramidal neuron; ST, stellate cell; also are major afferent and efferent pathways. CTX, cortex; SUBCTX, subcortical areas; TH, thalamus. Open triangles represent excitatory synapses. The great majority of the connections of cortical cells are formed with other cortical cells (Shepherd 1988.)

Cerebral cortex

A few *generalizations that emerge from the functional neuroanatomy of the cortex are of potential relevance to memory. First, although different areas of the cortex share the basic design of local circuits, the particular afferent and efferent destinations of discrete cortical areas turn the cortex functionally nonhomogeneous. This differentiation, evident already from the macroscopic functional map of the cortex (Figure 10a), imposes gross limits on the distribution of storage of each item in memory, especially if this item is modality specific, such as a visual scene, tone, or taste. The adult cortex is hence not really equipotential, as was inferred from certain early attempts to search for the *engram. Second, at the same time, long-range connections in the cortex provide it with the potential to subserve rich associativity, potentially permitting the same item in memory to be ultimately accessed and *retrieved via different *cues. And third, the configuration of afferents and efferents of cortical columns fits neatly to subserve processing of target information (thalamic input), *context (diffused systems input, corticocortical connectivity), and *associations (corticocortical connectivity). However, the relevance of this hardware configuration to the computation and encoding of discrete *stimuli, context, and associations, respectively, is yet unclear.

Ample evidence shows that the cortex indeed subserves some types of learning and memory. This evidence is either suggestive, or correlational, or proves necessity, but in no case so far does it prove sufficiency and exclusiveness (*criterion). Sufficiency and exclusiveness, we should remember, are hardly to be taken as standing requirements, among others, deciphering the expected: the cortex interacts with other brain systems in locating, associating, construing, and assessing information about the world.

animals or by observing the effect of brain damage in human patients (e.g. Luria 1966; Penfield and Rasmussen 1968; Shallice 1988; Squire and Zola-Morgan 1991; Suzzuki et al 1993; Mishkin and Murray 1994; *amnesia, *planning, *working memory).

The activity of specific cortical areas is altered in *acquisition and retrieval of memory. This can be shown by *functional neuroimaging (e.g. Nyberg et al 1996; Karniel et al 1998; Kelley et al 1998; Wagner et al 1998a,b; Wheeler et al 2000).

The activity of cortical neurons correlates with the acquisition and retention of memory. The activity of nerve cells in unimodal, polymodal, and supramodal cortex in the *monkey and in the *rat was found to be specifically correlated with mnemonic performance in a variety of tasks (e.g. Funahashi et al 1989; Schoenbaum and Eichenbaum 1995; Fuster 1995; Quirk et al 1997; Zhou and Fuster 1997; Erickson and Desimone 1999; Super et al 2001). Two general types of findings are noteworthy (Eichenbaum 1997b): (a) cortical neurons can modulate their response to the target stimulus over the course of learning, and retain the change afterwards, and (b) cortical neurons can sustain or reactivate responses over the task in the absence of the stimulus (Figure 11).

The particular role(s) of the cortex in learning and memory is far from being understood. Such understanding requires, among others, deciphering the neuronal code(s) used by the cortex in registration and reactivation of *internal representations (for a selection of approaches, see Abeles 1991; Gawne and Richmond 1993; Konig et al 1996; Shadlen and Newsome 1994;

*cell assembly). In the meantime, it might be useful to think about memory in cortex in the following way: *percepts are formed in modality specific cortex, or in a combination of such cortices, and are registered in collaboration with activity in supramodal cortex and extracortical circuits, such as limbic circuits in the case

1. The cortex is highly *plastic. Remarkable morphological and functional plasticity is evident in *development as well as in the adult brain in response to sensory stimuli and injury (e.g. Krebs et al 1960; Wiesel 1982; Sadato et al 1996; Buonomano and Merzenich 1998; Crair et al 1998; *map). This plasticity is a candidate vehicle for learning and memory.
2. The cortex is rich in synaptic components that serve learning. These components can be shown to be altered with learning, and further, their disruption in cortex blocks learning, *consolidation, and *experimental extinction of memory (e.g. Berman and Dudai 2001; *coincidence detector; *CREB, memory). The representation may become independent of some of the circuits that were obligatory for its encoding and registration (e.g. hippocampus in declarative memory). The representation may also invade new *immediate early genes, *glutamate; *long-term potentiation; *protein kinase; *receptor).
3. Cortical lesions impair learning and memory. This can be shown by inducing circumscribed lesions in cortical areas. Retrieval of the information may require

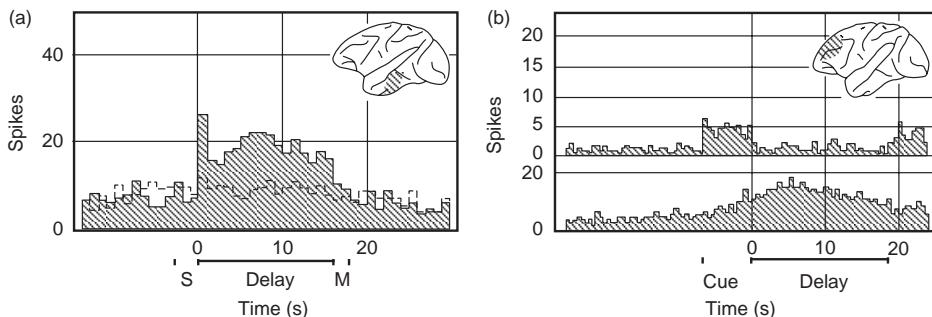


Fig. 11 Mnemonic performance of cortical neurons in the monkey. (a) Spike frequency histogram (i.e. activity level measure) of inferotemporal cortex during a delayed matching to sample task (*delay task). The *subject selected one of several colours to be presented before the delay. The unit increased its activity only during the delay if the sample was red (solid line, shaded histogram (broken line, superimposed on the red response histogram). S, sample, M, match. (After Fuster and Jervey 1982.) (b) Spike frequency of two units in the dorsolateral prefrontal cortex during a visuospatial delayed response task, in which the monkey learned which wooden blocks covers a baited food well. The upper unit increased firing in the *cue period, during which the monkey observed covering of the wells, and in the choice period, following the delay. In contrast, the lower unit increased activity during the delay (After Fuster 1973.) One interpretation of the data is that the neurons in both cortici (which are depicted in the insets, respectively) retain information.

activation, co-ordination, and monitoring by the supramodal cortex, particularly the prefrontal cortex. In retrieval, cortical areas that have subserved the acquisition of the information in the first place, may become activated again. This reactivation, however, is unlikely to generate a representation identical to the one at the moment of acquisition. This is because the information has been pruned and associated over time and, furthermore, is affected by the context of retrieval, which is contributed by exogenous stimuli as well as by the spontaneous, endogenous activity of the cortex at the moment of retrieval. Hence, we may use many *metaphors to describe the cortex, but a hard disk is

³The concept of cortical column is based on structural and functional observations. Neuroanatomy has shown that columns of nerve cells are discrete structural units. Cellular physiology has shown that local aggregates of cortical neurons could be discerned on the basis of their response to a certain *stimulus *dimensions. Columns can also be detected nowadays by *functional neuroimaging (Kim 2000). The concept of cortical column appeals to *reductionism because it reinforces the notion that cortical function can be dissected into elementary modules. There are, however, voices who oppose an atomistic approach to cortical function (e.g. Fuster 2000a).

Classic

Selected associations: Cell assembly, Conscious awareness, Engram, Functional neuroimaging, Recall

1. Of acknowledgeable excellence.
2. Serving as a standard or a model.

¹For the sake of convenience, ÔcortexÕ will be used throughout this chapter to refer to the neocortex, or the neocortex and paleocortex (archicortex). The latter is discussed separately under *hippocampus). The accurate term is, however, cerebral cortex, as the *cerebellum also has a cortex.

²Modal refers to sensory modality. As to the notion of association cortex, it can be traced back to the observation that some cortical areas did not display sensory or motor response in lesion or stimulation experiments. These areas were first called Ôsilent areasÕ because it was thought that they associate the sensory and motor information. The term association cortex is losing favour, and in any case should not be taken to imply that only these areas perform associations; all cortical areas are probably capable of some or another type of associations.

ÔClassicsÕ in its classical sense is borrowed from the Romans. ÔClassiciÕ were citizens who possessed a substantial income. The word was used also to refer to the armed forces, and ÔclassicusÕ was the trumpet call signifying the battle. The Latin author Aulus Gellius (second century AD) was probably the first to refer to writers of worth and distinction as classic writers (Saint-Beuve 1850). The French philologist Littré later adapted the term to refer to literary works Ôused in the classes of colleges and schoolsÕ (Harvey 1937). ÔClassicalÕ became the adjective used when reference was made to the arts and literature of ancient Greece and Rome;

with time it also came to denote formative periods in Skinner (*behaviourism), and Konorski (*plasticity). Yet other segments of *culture, such as Western music in the list does not refer to the corpus of authors, but rather the last half of the eighteenth century, or physics before selected, individual papers or books; and in any case, relativity and quantum mechanics. Strictly speaking, one must make decisions, even if painful. The list is ÖclassicsÖ are works of letters produced in the ÖclassicalÖ period, arranged chronologically:

Greek-D Roman period, and ÖclassicÖ is a signal work in

any discipline and period (Burchfield 1996), but this 1. St AugustineÖs philosophy of memory, book 10 in distinction is not usually honoured in daily language.

What are the *criteria for a ÖclassicÖ? High quality is of course a must, but is not enough. The work must also exert a strong impact, either explicit or implicit, on later generations. Hence, it must withstand the test of time. It is therefore good practice to refrain from crowning pieces of work as ÖclassicÖ, be they as impressive as they are, before they pass the judgement of at least a few scientific generations. A reasonable estimate of a generation time in the neuroscience is 8-D10 years; a time window of 30 years seems therefore sufficient to judge the impact of publications on the field. Admittedly, by choosing to label as ÖclassicÖ signal works published least 30 years ago, one surely minimizes the number of enemies among his or her contemporaries. But the latter argument is of course merely a fringe benefit.

Not all selections of ÖclassicÖ publications in the life sciences follow the test-of-time rule. M.H. Green (1991) compiled ÖclassicÖ publications in molecular biology over the period 1958-D88, i.e. up to 2-D3 years earlier. Peters (1959) covered genetics during the period 1865-D1955, i.e. up to 3-D4 years earlier. And Shaw (1990), compiled a reprint volume of 82 influential publications in the neurobiology of learning and memory, including papers published only a year or two earlier. The stand taken here is that there is no need to rush.

The method of choosing ÖclassicÖ publications in science is another issue. One way is öhypopopuli, i.e. citations. This is now common in other areas of culture as well, e.g. poetry (Harmon 1998). However, citation indices have their own pitfalls, including the tendency to cite Ötrendy spikesÖ or mundane methods in overcrowded fields. At the end of the day, selection of a short-list of ÖclassicsÖ in a scientific discipline boils down to a mix of a few unchallenged choices, strong professional *bias, and an unavoidable touch of idiosyncrasy. It does mean, of course, that different people will generate somewhat different lists (e.g. Baddeley 1994). But this only adds to the fun. Having said all that, here is a biased canonic list, limited *a priori to 10 items 4. only, although a few additional ones are actually sneaked-in in the process. This selection unavoidably leaves aside very important publications by very influential authors, including, among others, Pavlov (*classical conditioning), Thorndike (*instrumental conditioning),

his autobiographical Confessions (400). Augustine (354-D430), a prominent Christian philosopher (Colish 1997), and a marvellous writer, composed his autobiography in the service of theology. Embedded in it is a gem of introspective psychology. Augustine was not the first in antiquity to write about memory, but his treatise is probably the most readable and surely the most poetic. Those who take the joy of reading AugustineÖs philosophy of memory, especially chapters 8-D19 in book 10, will encounter reference to issues of *taxonomies, *metamemory, *binding, problems of *retrieval and *forgetting, *atmaging, and more. Augustine is included in this list to remind us that as far as the phenomenology of memory is concerned, although we have perfected it tremendously, we did not invent the wheel.

James ÖThe principles of psychology (1890). The bible of Western psychology, James ÖThe principles of psychology (1890) provides not only an object of intellectual admiration but also a rich source of inspiration. When many later works in psychology are analysed, they appear to contain *palimpsestic fragments that trace back to James. In three studies conducted to establish a consensual list of psychologyÖs great books, polling colleges and professional psychologists ÖThe principles received the highest rating (Norcross and Tomcho 1994).

Experimental study of the mental processes of the rat by Small (1901). Fans and slaves of *mazes, please note: here it all started, in a small-scale model of the Londonian Hampton Court Labyrinth, copied from the Encyclopaedia Britannica (Fig. 46, p.156). This is a perfect example of the importance of matching a *subject with an *assay in the field of memory research. In such matching, ethology could always provide the guide to success: as Small put is, to rodents, maze experiments are Öcouched in a familiar languageÖ. Since then, mazes have become the most popular tool to measure the memory of the most popular species of laboratory animals.

Remembering study in experimental and social psychology by Bartlett (1932). This is the epitome of the attempt to understand human memory in real life. Bartlett became disappointed with the investigation of the memory of nonsense material under artificial conditions, a *paradigm introduced by Ebbinghaus

(1885) at the birth of quantitative experimental psychology. Instead, he started to use *methods that unveil how the memory of meaningful items works in normal conditions and surroundings. *Remembering* is a function of daily life. So our memories are constantly mingled with our constructions, are perhaps themselves to be treated as constructive in character. It is true that they claim the confirmation of past, perceptual, personal experience; but the claim must not, psychologically speaking, be taken too seriously (Bartlett 1932, p. 16). It took almost half a century before this view has started to infiltrate the **zeitgeist* of memory research at large (*false memory, *real-life memory, *retrieval). By the way, part I of *Remembering* a source of inspiration for perceptual and memory experiments to try on family and friends.

5. Hebb's *The organization of behavior* (1949). Another holy scripture of modern neuroscience, and probably the most cited and influential publication on neural *plasticity and memory in the past 50 years. Judging by the trends in the field, it is likely to remain the most cited classic for generations to come. A uniquely coherent conceptual statement, *The organization of behavior* maintains an extensive dialogue with earlier literature (with primary sources as well as the excellent textbook of Hilgard and Marquis, 1940). The organization of behavior is mostly cited for two notions: *cell assemblies and their maturation, and, most of all, Hebb's postulate of learning (*algorithm). Hebb was rather astonished to see that this postulate gained so much popularity, as he himself did not consider it as his most original contribution (Milner 1986). Nevertheless, the crispness of the formulation, and its integration in a creative exposition of a theory of brain function, clearly justify the naming of the postulate as *ÖHebbianÖ*.
6. The formation of learning sets, by Harlow (1949). This is an outstanding example of the ability to extract new *levels of information from a seemingly simple experimental set-up. No big grants were required to make the breakthrough here. Harlow shows how by using discrimination tasks, one could unveil not only the ad-hoc performance of the *subject, but also learn about the ability of that subject to learn how to learn and form rudimentary concepts (*learning set).
7. The magical number seven, plus or minus two: Some limits on our capacity for processing information (Miller 1956). Here is a title that has become a legend. This work is a decendent of earlier attempts to quantify universals of human memory (e.g.

Ebbinghaus 1885; Jacobs 1887). It is anchored in the concepts and measures of information theory, and demonstrates that the brain is an information processing system of limited *capacity. Although Miller's intention was not to determine a precise value, his estimate of short-term memory capacity of seven-plus-or-minus-two chunks became almost a mantra (not without challenges; e.g. Baddeley 1994).

8. Loss of recent memory after bilateral hippocampal lesions, by Scoville and Milner (1957). This is the beginning of a major chapter in the research on *amnesia, on the role of medial temporal lobe in *consolidation and memory, and on the *taxonomy of memory. The real hero is the amnesic patient, H.M., unfortunately unaware of his profound continual role in modern neuroscience. The incentive for many studies on human amnesias, primate models of amnesia (*delay task, *monkey), and the role of the *hippocampus in learning, could be traced to Scoville and Milner's report. It is a classic case of a fruitful interaction of the clinic with basic research (Code et al 1996; Corkiret al 1997; Milner et al 1998).
9. The information available in brief visual presentations, Sperling (1960). In this condensation of his Ph.D. thesis, a beautiful example of a smart and focused experimental design and execution, Sperling demonstrates the existence of an *Öiconic memoryÖ* store, or *phase, which lasts for a fraction of a second to a few seconds at most. The giants on the shoulders of which this study is standing are duly accredited in the monograph, something to be longed for in many papers nowadays. Sperling's paper boosted the whole field of *ÖimmediateÖ* or *ÖsensoryÖ* memory (for a perspective 40 years later, see Dosher and Sperling 1998).
10. This place is reserved to three papers, each published by an independent research team. These papers promoted what was later to become a most productive chapter in the molecular biology of learning: investigation of the role of macromolecular synthesis and growth in consolidation and long-term memory. Taken together, the studies of Flexner et al (1963), Agranoff and Klinger (1964), and Barondes and Cohen (1966), have demonstrated that inhibition of protein synthesis during or immediately after training prevents the formation of long-term memory, without affecting short-term memory. These papers complement each other in their experimental details. They have paved the way to decades of research on neuronal proteins, genes, plasticity, and memory. By doing so, they have contributed remarkably to an important ingredient in the current neurobiological



Fig. 12 Authors of some classic classics: Auguste Comte (*Sociology*, 1851); William James (*The principles of psychology*, 1890); Donald Hebb (*The organization of behavior*, 1949; courtesy of Peter Milner).

zeitgeist (*CREB, *development, *immediate-early genes, *late response genes, *protein synthesis).

Close contenders for this slot are McGaugh (1966), a well-cited epitome of the view that the *engram is not completed when training is over (*consolidation); and Kandel and Spencer (1968), a manifesto of the *reductionist, cellular approach to learning and a harbinger of the highly successful research program on Aplysia.

Classical conditioning

1. Types of *associative learning in which the *subject learns that one *stimulus predicts another.
2. Types of training procedures in which two stimuli, the conditioned stimulus (CS) and the unconditioned stimulus (US), are paired with each other, so that the CS comes to evoke a conditioned response (CR), which is similar to the unconditioned response (UR) elicited by the US.

Naturally, because of the aforementioned self-imposed criterion of a 30-year moratorium on canonization, this list does not refer to many developments that have revolutionized memory research in recent years. It is indeed rather tempting to single out already at this stage Pavlov and his dogs are probably the first association some more recent papers, in disciplines ranging from what comes to mind in most people when prompted molecular neurobiology to cellular physiology, neuroanatomy, imaging, behaviour, and psychophysics. Indeed, a century after its formalization (Pavlov 1906), which are almost certain to withstand the test of time and the *paradigm of classical conditioning (alias Pavlov-conditioning) can compete for a respectable seat in the classics pantheon. At the same time, however, it is also tempting to suggest that many of the older papers cited above will retain their status in years to come. In the highly dynamic field of work of Sechenov (1862), the father figure of Russian physiology, Pavlov (Figure 13) led a systematic attempt to become only more and more difficult with time.

Selected associations: **Conditioning**, Insight, Paradigm, Persistence

¹Two other notable examples are Aristotle's *Memory* and Quintillian's *On the education of the orators* (first century AD *consolidation).

to *reduce the study of higher brain function to that of quantifiable atoms of reflexive behaviour. In doing so he relied mainly on gustatory stimuli as the US, gustatory reflexes as the UR, and auditory or visual stimuli as the CS (Pavlov 1927). Since then, Pavlovian conditioning became *classical. In the past three decades, it has accumulated renewed momentum, due to the impressive developments in behavioural, cognitive,



Fig. 13 Pavlov, assistant, dog, and Pavlov. The heavy sticks (left) are thrown at selected targets from a distance in the Russian (Ösmall townsÖ, or ÔRussian pyramidsÖ), on which Pavlov was a very proud expert. The dog seems a bit tired of being classical might merely be an *anthropomorphic interpretation. (Courtesy of K. Anokhin and P. Balaban, Moscow.)

*system, and cellular neuroscience (Holland 1993; Baconditioning of the timing and the order of the presentation et al 1998; Kim et al 1998; Pearce and Bouton 2001). tation of the CS and US. This emerged from the obser-

In classical conditioning, the subject learns relationsvation that, whereas certain conditioning protocols among stimuli (definition 1). This is different from culminate in successful learning, others do not (e.g. *instrumental conditioning, in which the subject learns Pavlov 1927; Konorski 1948; Mackintosh 1983; Figure relations among actions and their outcome) (The 14). An effective protocol delay conditioning in which behaviour of the experimenter in classical conditioning the CS is presented first and the US onset precedes the (definition 2) is almost as important as the behaviour of CS offset or coincides with ittrace conditioning in the experimental subject: it is the investigator who which the CS starts and ends before the US starts, is also chooses and manipulates the CS and the US, and selects. Effective, provided that the interstimulus interval is kept the CR from the overall behavioural response of the sufficiently short (usually in the subsecond to the sec-subject. In ÔtrueÖ classical conditioning, the CR is supond range; but see a striking exception in *conditioned posed to be a novel response to the CS, but probabl;taste aversion) Simultaneous conditioning which the more often than realized, the CR is an intensification of CS and US onset coincide in time, is less effective, unless a pre-existing (innate, *a priori) response to the CS. Thethe CS offset precedes the US offset backward condi-latter case is termed-conditioning. If random pairing tioning, in which the US onset precedes the CS onset, of the CS and US , or presentation of the CS alone, elicitand the US terminates before the CS, is usually ineffect-with time a response similar to the CR, then condition-tive. It can therefore be concluded that order depend-ing is by definition nonassociative. Nonassociative elic-ency and temporal contiguity are critical factors in tation of a CR to a previously neutral CS is termedensuring effective conditioning. Contiguity was noted pseudoconditioning. Nonassociative-conditioning is already by Aristotle as important in recollection, *sensitization. In some protocols of classical condition- and marked as a condition for association in early ing, the CS, after coming to elicit a CR, is used as a US nonassociative psychology in the seventeenth and eight-a subsequent phase of conditioning. This is termedteenth century (Warren 1921; *associative learning). second-order condition(Rescorla 1980); higher-order Classical conditioning permitted, however, for the first conditioning can be similarly obtained.

In the first *phases of its investigation, ample ral parameters involved, in a variety of species. Reduc-attention has been devoted to the role in classicationist analysis has ultimately chased *coincidence

Classical conditioning

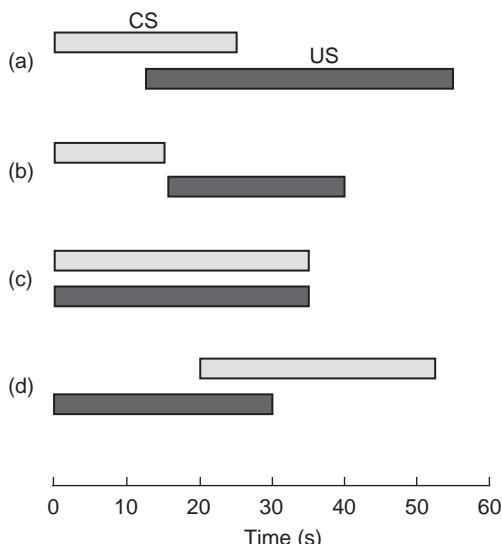


Fig. 14 Protocols of classical conditioning and their effectiveness. (a) Delay conditioning, which is usually successful. (b) Trace conditioning, which is usually successful provided the interval between the offset of the CS and the onset of the US is kept sufficiently short (but see **conditioned taste aversion* for a striking exception). (c) Simultaneous conditioning, which is not an effective procedure. (d) Backward conditioning, which is usually unsuccessful.

detectors, that could implement contiguity, down to the molecular level (Dudai 1985; Abrams and Kandel 1988; Bourne and Nicoll 1993).

As much as order dependency and temporal contiguity are important, more sophisticated conditioning protocols have demonstrated that temporal contiguity per se is insufficient, and the emphasis shifted to the role of contingency (Rescorla 1968, 1988; Mackintosh 1983; Wasserman and Miller 1997). Contingency in this context means comparison of the probability of the occurrence of the US in the presence of the CS as contrasted with the probability of the occurrence of the US in the absence of the CS; conditioning is assumed to occur only when the aforesaid probabilities differ (Rescorla 1968, 1988). Still, contingency may also not suffice to account for all the facets of conditioning (Mackintosh 1983; Rescorla 1988; Papini and Bitterman 1990; Wasserman and Miller 1997). So far, in spite of a number of sophisticated theories of associations, there is no accepted unified theory covering all manifestations and properties of classical conditioning (Pearce and Bouton 2001). There might never be, because classical conditioning encompasses multiple training protocols, behavioural phenomena, neuronal

circuits and possibly mechanisms (*algorithm). Compare, for example, trace conditioning to delay conditioning (Figure 14); whereas in delay conditioning the CS and US overlap on-line part of the time, in trace conditioning, the subject must hold off-line information about the CS before the US onset. Therefore, trace conditioning is expected to engage brain regions that are not required for conditioning that depends on on-line information only. This was indeed found (Moyer et al 1990; Clark and Squire 1998; *conscious awareness, *declarative learning). This also raises the question whether classical conditioning should be considered as a distinct type of memory system, specifically, a nondeclarative memory system, as is advocated by the current *zeitgeist (*taxonomy).

Classical conditioning is considered by the majority of scholars in the field to involve reconstruction of knowledge about stimuli, their relationships, and their predictability (Dickinson 1980; Holland 1993; Wasserman and Miller 1997; Pearce and Bouton 2001). One major impetus to this Ôcognitive revolutionÕ in the field of classical conditioning was contributed by the study of a rich set of phenomena, which show that the possibility of a stimulus to enter into association and control behaviour is altered markedly by the history of the subject with this or other stimuli either before, during, or after training. Many of these stimulus-D revaluation phenomena could be construed as reflecting interaction of the *internal representations of the stimuli involved. Here are selected examples (for additional ones, see *cûe):

1. In sensory pre-conditioning, two practically ÔneutralÕ sensory stimuli, CS₁ and CS₂, are repeatedly presented together, followed by the conditioning of CS₁ to a particular response. Sensory pre-conditioning is said to have occurred if CS₂ also evokes the response on a test trial (Brogden 1939; Kimmel 1977). Sensory pre-conditioning was demonstrated first in Pavlov's laboratory. It provides a demonstration that associations can take place among stimuli in the absence of an overt response.
2. In conditioned inhibition, a CS- that is conditioned to predict the absence of the US, later inhibits the development of the CR to a composed CS+CS+ stimulus (Pavlov 1927; Zimmer-Hart and Rescorla 1974). This is construed to imply that the subject anticipates no US in the presence of the CS-, and must overcome this anticipation to form the association of the compound stimulus with the US.
3. Uncorrelated presentation of the CS and US is used as a control for classical conditioning (Rescorla

- 1967). It also retards, however, subsequent associative conditioning of the same CS-US pair (Kremer's performance of classically conditioned behaviour as 1971). This phenomenon came to be known as the surface structure, and the dynamic interaction of learned irrelevant (Blackintosh 1973; Baker 1976).
4. Latent inhibition (Lubow and Moore 1959; Lubow 1989) is attenuation of the associability of the CS as a result of its non-reinforced pre-exposure. For example, in conditioned taste aversion, if instead of pairing an unfamiliar taste with malaise, one pre-exposes the subject briefly to that taste a few days before training, the aversion developed after pairing with the US is significantly weaker (e.g. Rosenblum et al 1997). Several explanations have been proposed to account for latent inhibition. Some of these suggest that pre-exposure reduces subsequent attention to the CS (Lubow 1989); others propose that the formation of a CS-context association during pre-exposure interferes either with subsequent acquisition of the new CS-US association, or with its expression (e.g. Graham et al 1994).
5. Pre-conditioning exposure to the US could also retard the formation of a CR (Randich and LoLordo 1979). The explanations invoke "habituation", or alternatively, again, the formation of stimulus-context associations, which later compete with the formation of new CS-US association (e.g. Cole et al 1996), or with its expression (Millet et al 1993).
6. Responding to a CS is also sensitive to post-training alterations in the ability of the US to control behaviour (Rescorla 1973; Holland and Straub 1979). This is termed US devaluation. It is construed to imply that the internal representation of the CS gains access to adjustment in the value of the US at the time of performance.
7. And, last but not least on our brief tour of the surprising world of conditioning phenomena: a CS (Wilhelm von Osten, in 1900 with the aim of reproducing) may also come to modulate the response of the conditioned subject even independently of its direct association with the US, in which case this CS is said to overshadow those of his predecessor, endowed him with to set the occasion for responding to another CS. As respectible title "Clever Hans" (Pfungst 1911), and Occasion setting was first described by Skinner earned him an honourable position in the history of (1938) in the context of instrumental conditioning. He noted that animals can use a discriminative cue, which has been present upon the occasion of a prehuman-like mental capabilities have been attributed. vious reinforcement, to decide whether to emit the conditioned response or not; the cue itself, however, did not elicit the response. Occasion setting was Caligula invited his beloved Incitatus to banquets and subsequently investigated mostly in classical conditioning (Holland 1992). It is argued that occasion setting is easier to fit into "configural theories" of imperial humour (Barrett 1990). Throughout history conditioning (Pearce and Bouton 2001; on what individuals of many other species have been regarded as configural theories see footnote 3).
- All in all, the picture that emerges is hence of the internal representations of stimuli and of the probability of their co-occurrence as the deep structure.
- Selected associations:** Associative learning, Coincidence detector, Instrumental conditioning, Taxonomy
- ¹Definition 3 in *paradigm.
- ²The truth is that the subject in instrumental conditioning learns other types of relations as well; see there.
- ³In "real-life", the CS rarely appears in isolation ("context"). A single stimulus CS is called "elemental", and the conditioning process "elemental conditioning". Otherwise, the CS is "composite". "Compound". Theories of conditioning debate whether elements composite stimuli associate with the US independently ("elemental theories") or as a unitary "internal representation ("configural theories"; Pearce and Bouton 2001). But this issue already relates to knowledge acquired in classical conditioning, which is further referred to in the text.
- ⁴Most of these revaluation phenomena could be demonstrated employed as research tools, and used to infer knowledge structures in instrumental conditioning as well.

Clever Hans

A horse in Berlin at the beginning of the twentieth century, claimed to have mastered human language and arithmetic.

Hans was purchased by a retired German schoolteacher, Wilhelm von Osten, in 1900 with the aim of reproducing the remarkable behaviour originally noted by von Osten in an earlier horse. Soon the feats of Hans II overshadowed those of his predecessor, endowed him with the occasion for responding to another CS. As respectible title "Clever Hans" (Pfungst 1911), and Occasion setting was first described by Skinner earned him an honourable position in the history of (1938) in the context of instrumental conditioning.

He noted that animals can use a discriminative cue, which has been present upon the occasion of a prehuman-like mental capabilities have been attributed. vious reinforcement, to decide whether to emit the conditioned response or not; the cue itself, however, did not elicit the response. Occasion setting was Caligula invited his beloved Incitatus to banquets and subsequently investigated mostly in classical conditioning (Holland 1992). It is argued that occasion setting is easier to fit into "configural theories" of imperial humour (Barrett 1990). Throughout history conditioning (Pearce and Bouton 2001; on what individuals of many other species have been regarded as configural theories see footnote 3).

possessing some degree or another of human reason,

Clever Hans

although they did not attend such a high respect in gov-principle to differ from any hitherto discovered (cited ernment. This *anthropomorphism was not always in Rosenthal 1965). The *enigma led to a signal research taken in the animals favour, and in some cases even ~~had~~ programme, executed by Oskar Pfungst in collabora-them to the gallows (Evans 1906). Clever Hans was ~~on~~ with Carl Stumpf (Pfungst 1911), which finally however, different in that he was treated seriously bashed light on the Clever Hand phenomenon, although respected professors, and the investigation of his alleged leaving some issues unresolved (Hediger 1981). Briefly, wit unveiled and singled out some basic issues in behavPfungst showed that Hans learned to respond to subtle joural research, which are highly relevant to memoryhuman bodily movements, unleashed unintentionally research to date.

Hans was clearly clever, however, in his own equinecame out rather stupid unless someone he could watch way. Mr von Osten trained Hans to provide answers to ~~had~~ the answers. Hans clearly knew nothing about plethora of questions by either tapping with its front math, logic, or the German language, yet knew a great hoof or pointing its snout to symbols on a board. Hans deal about human gestures. Pfungst even stepped fur- could apparently do arithmetic, including fractions, ther and became himself a ÔClever HansÕ in a *control categorize objects, and even read German (e.g. ~~in~~experiment, only to find out that with proper attention, response to the question ÔWhat is the woman holding~~he~~ he could come up with correct answers to questions her handÕ, he would gallantly reply, letter by lettermerely by observing the experimenter in front of him. ÔSchirmmÕ, i.e. parasol). His wisdom was so impressiveThe Clever Hans phenomenon turned attention to that a scientific commission was called to exclude anycritical issues in experimental psychology. These deceit, and indeed, in 1904, the committee declaredinclude: (a) the importance of a systematic research confidentially that von Osten used no tricks. But the *methodology, including appropriate controls, as well rest remained a puzzle even to the high ranking acaas Ôblind testsÕ in which the experimenter could not demics: ÔThis is a caseÕ, they wrote, Ôwhich appearsnow the relevant history of the experimental *subject

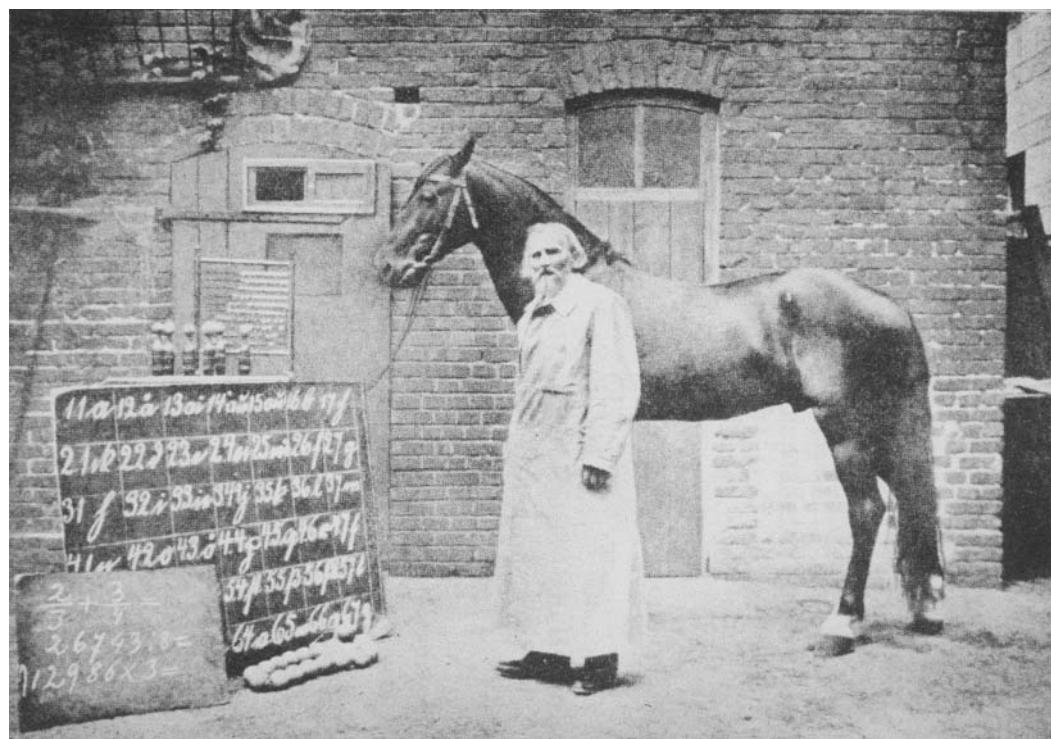


Fig. 15 Clever Hans, Clever von Osten, and blackboards in an equine classroom. The horse learned to respond to subtle human

and the expected outcome; (b) the effect of Ödemaniñ the order of magnitude of milliseconds (less than a characteristicsÖ, i.e. unintentionally influencing themillisecond to a few milliseconds in synaptic events, performance of an experimental subject by expecting æ.g. Markram et al 1997; 100 ms in perception and certain outcome (Orne 1962; *bias); (c) the importance cognition, e.g. Thorpe et al 1996; van Turennout et.al of *OckhamÖs razor, i.e. preferring a simple explanation1998; *percept). Note that if 0, the order of events to a more complex one; (d) the subtlety of innate and may also make a difference, i.e. whether it arrives before acquired communication abilities of animals (e.g. or vice versa (see *classical conditioning and below). Sebeok and Rosenthal 1981; *a priori); (e) the need toAnother type of coincidence detector generates the become well versed in the natural behavioural reper-desired output only after receiving two or more *stimuli of animal subjects; (f) the pitfalls of anthropo- uli in a number of steps within a defined, commonly morphism; (g) the lack of correlation between oneÖshort time window (Ögraded coincidence detectorÖ; defi-academic title to success in animal training (Hedigernition 2). Still another type of integrating device, which 1981); and finally, last but not least (h) the absence ofis also sometimes referred to as a Öcoincidence detectorÖ correlation between the academic statue of members ofis characterized by more relaxed temporal constraints, a site visit team to the robustness of their conclusions. and in this case ÖcoincidenceÖ refers to occurrence at the

During the early days of experimental psychology same place rather than at the same time (definition 2). Clever Hans occupied a key position in textbooks (Wat-An additional point that requires clarification is what is son 1914), but then dwindled into footnotes (though meant by ÖdeviceÖ. In the context of the present discuss-see Sebeok and Rosenthal 1981). The lesson shouls, on, a device is either a macromolecule, a *synapse, a however, be refreshed, as if forgotten, a mouse in anerve cell, or a neuronal circuit.

*maze might be deemed smarter than it is, or at least for The majority of experimental evidence for the the wrong reasons. With time, horses ceased to benvolvement of identified coincidence detectors in favourable subjects for learning research, yet not utterlylearning and memory, relates to the molecular and forgotten (e.g. Heiret al 1981; Houpet al 1990).

Selected associations: Anthropomorphic Artefact Control, Subject

Coincidence detector

1. A device that responds only on receiving two signals simultaneously.
2. A device that responds only on receiving a complete set of two or more signals.

Many brain faculties depend on the ability to detect andasymmetry in the activation of the cyclase underlies encode associations and correlations among eventstemporal asymmetry of the CSDUS pairing in the Coincidence detectors are essential for this ability. Thébehaving organism (ibid., also Abrams and Kandel most straightforward type of coincidence detector 1988, and *classical conditioning).

senses the occurrence of two events at the same time Another molecular coincidence detector with a (definition 1). However, what is meant by Öat the samproposed role in *plasticity and learning is the *glutamtimeÖ depends on the scientific discipline and on thenergic N-methyl-D-aspartate (NMDA) *receptor *level of analysis. Simultaneity in particle physics has aNMDAR; Seuburget al 1995). Here, the receptor-different meaning than in physiology and psychology.*channel complex detects coincidence of presynaptic Hence, although an ideal coincidence detector respondactivity (glutamate, which activates the receptor) only when the time difference between events & and postsynaptic electrical activity (depolarization, in practice, a response is emitted to t. It is safe which removes a magnesium block from the channel, to say that in the context of neuroscience, two eventsFigure 16). Convergence in this case is permitted within can be said to occur Öat the same timeÖ if that timetens to hundreds of milliseconds. Furthermore, at least

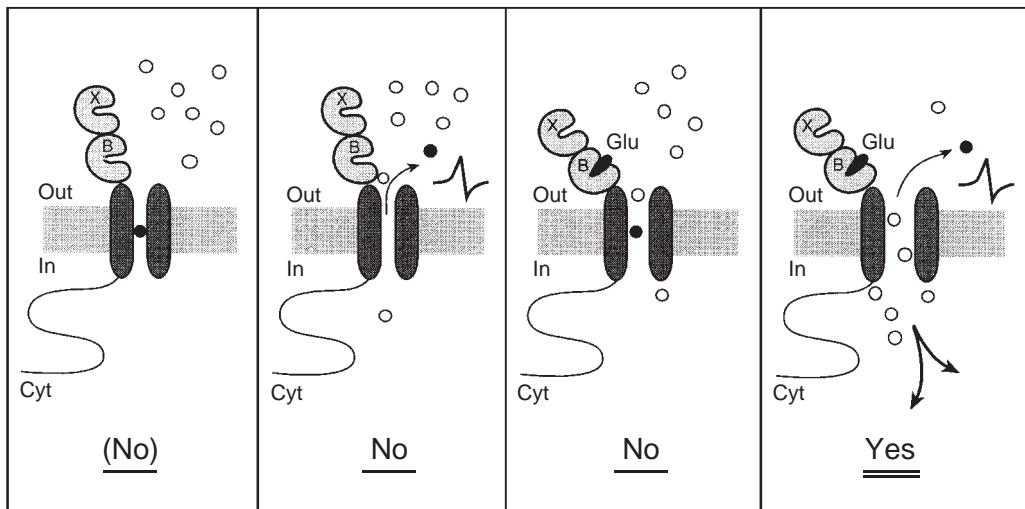


Fig. 16 The *N*-methyl-D-aspartate-type of the *receptor for the *neurotransmitter *glutamate is an example of a molecular coincidence detector that takes part in cellular *plasticity mechanisms, such as *long-term potentiation, which are assumed to subserve learning and memory. In the resting state (left panel in this highly simplified scheme), the extracellular (Out) binding site (B) for glutamate (Glu) is vacant and the intracellular (In) binding site (X) for other molecular *stimuli is occupied by magnesium (Mg). Electrical activity that results in post-synaptic depolarization can relieve the magnesium block, but this by itself is not sufficient to allow a significant calcium influx. Occupation of the glutamate receptor is also insufficient to open the channel. Only coincident activity of glutamate and depolarization (right panel) leads to calcium influx (heavy arrows, Yes), which may culminate in plastic changes in the neuron. Cyt, cytoskeleton, with which the intracellular (In) receptor interacts; X, binding sites for other molecular *stimuli.

one additional type of input, glycine, and possibly (Sullivan and Konishi 1986; Hopfield 1995; Edwards et al. 1998), although the relevance of these findings at the level of the coincidence detection properties of the circuit level to learning and memory, if at all, has not yet been determined. One of the best known examples of coincidence detection in the circuit that encodes to function as coincidence detectors (Bourne and interaural phase differences in the brainstem of birds Nicoll 1993; Carollet et al. 1995). Notable among them are transcriptional regulation elements, including transcription factors and promoters (Impey et al. 1994; Janknecht et al. 1995; Deisseroth et al. 1996; *CREB, immediate early genes, *protein synthesis). Some cells convert a code that is based on the time of arrival of sounds. In this system, coincidence detection combines the use of neuronal delay lines, which carry the auditory information from each ear separately, to *immediate early genes, *protein synthesis). Some cells convert a code that is based on the location of the firing neurons in the considered as signal integrators (definition 2). Two brain (place codes; Sullivan and Konishi 1986; also major conclusions can be drawn from the data. First, Agmon-Snir et al. 1998; *map). In general, discussion coincidence detectors exist at multiple tiers of intracellular coincidence detection at the circuit level relates to lular signal transduction cascades, from the membrane to the cell nucleus, hence yielding many and the evoked responses of the neurons in the circuit; permutations in the interaction of stimuli and as a consequence, high response specificity. Second, \hat{O} counts by the circuit (de No 1938; Hebb 1949; von der Malsburg 1987; Abeles 1991; Hopfield 1995; Konig et al. 1996; Danet et al. 1998). The neurons in the circuit integrate incoming synaptic potentials before they fire molecular networks (*reduction).

Coincidence detection has been described in several spike codes. The kinetics of this integration is a parameter of circuits that process and encode sensory information that determines whether the neuron can serve only

as an integrator (definition 2) or also *a bona fide temporal coincidence detector* (definition 1). Only if the integration time interval is shorter than the inter-spike time interval, can the neuron act as a coincidence detector for the incoming spikes. The synchronized whole, both the formation and the retention of this type of information, which is then relayed to other neurons, might encode the coherency of a sensory *percept or *reduction. Collective memory is a primitive of mental concept (Konig et al 1996).

All in all, it is difficult to envisage how without the evolution of coincidence detectors, be they molecules or neurons, or circuits, our brain would have had the capability to detect correlations and causal relations in the external world, and *bind together meaningful narratives in the internal world.

Selected associations: Algorithm → Cell assembly → Internal representation → Intracellular signal transduction → cascade

contemporary *culture of that group (Bartlett 1932; Wertsch 1985; d'Andrade 1995; *context, *real-life memory). Thus, although portions of the collective memory can be encoded in individual brains, as a whole, both the formation and the retention of this type of memory is an emergent property of the group (d'Azevedo 1972). Together with other ingredients of culture, it permits nongenetic information to transcend the limited lifespan of individuals.

The term 'collective memory' actually refers to three entities: a body of knowledge, an attribute and a process. The body of knowledge is a cardinal element of culture. It is characteristic of the given social group, yet changes over time (*plasticity). The attribute is the distinctive holistic image of the past in the group, an image which itself may be used as a definer of the group. This is a constant dialogue between individuals and their social group. By selecting ongoing information that is relevant to the group, filtering it, retaining it, and dispersing it in society, each individual could potentially alter the collective memory of the group. This in turn could affect the subsequent acquisition and use of memory in the individual, which could further affect the memory and behaviour of the group, and so forth. In other words, individuals could contribute over time to the collective memory of the group(s) to which they belong, but collective memory at any given point in time could also affect the perception and the memory in the brain of the individual members of the group. By virtue of their social affiliations and beliefs, individuals belong simultaneously to multiple groups centred on family, friends, age group, profession, hobby, politics, religion, and nation. Therefore, individual brains subservce the encoding of multiple systems of collective memory, some of which could be conflicting or even contradictory. The conflict may result in psychological and social tension.

In spite of the fact that collective memory is not a property of the individual, it is tempting to compare it with memory in individual brains. Only a few heuristic analogies will be noted here. Similarly to a popular taxonomy of human memory, over the years collective memory has been portrayed as being composed of

Collective memory

A set of historical narratives, beliefs, and customs shared by a social group over generations.

When the 'star of England', Henry V, set out to boost the spirit of his few troops before the battle of Agincourt, he recruited future history (Shakespeare 1600):

Harry the king, Bedford and Exeter,
Warwick and Talbot, Salisbury and Gloucester,
Be in their flowing cups freshly remember'd
This story shall the good man teach his son;
And Crispin Crispian shall ne'er go by,
From this day to the ending of the world,
But we in it shall be remembered;
We few, we happy few, we band of brothers;

And as the outcome of that battle attests to, the urge to enter the collective memory of a nation is at times stronger than the fear of death.

Discussion of collective memory is at the interface of explicit and implicit systems. 'Collective consciousness', a term used by Durkheim (1895) in defining 'social facts' (i.e. the subject matter of sociology), refers to the unique among the types of memory covered in this book because it is not confined to an individual nervous system. Rather, at any given moment in time it is a memory system. Jung (1969) put forward the idea encoded in a distributed system of individual brains in that humans also have a 'collective unconscious', deep in the relevant social group, as well as in elements of the psyche harbouring universal primordial

memories or images (ÖarchetypesÖ; see also Ellenberger

1970). This is an implicit memory system, which,

according to Jung, can be studied through myths. In a

scientific context, the Jungian account of collective

unconscious is vague (and see Bartlett 1932); but one

does not have to be a Jungian in order to assume a body

of implicit universals of human mental faculties, which Farmers know, probably from the dawn of farming, that has been built into the human brain in the course of its evolution (*a priori) and mould societal function. their first encounter with it. The farmers themselves Other analogies between individual and collective mem-may have probably noticed that foodstuff comes to ory can be proposed. Similarly to other types of memory,evoke disgust if consuming it results in nausea and *retrieval of collective memory involves reconstruction intestinal distress. However, common knowledge does (Halbwachs 1925), in which the representation of the not always penetrate academic barriers: it has taken original event is adapted to the context of recollection John Garcia and his colleagues several distressful years (e.g. Schwartz et al 1986). And similarly to individual to convince the referees of respectable scientific journal-real-life memory, one encounters *false collectivenals that conditioned taste aversion (CTA) does occur memory and possibly also *flashbulb collective memory(Garcia 1981). This almost became a case of CSA (Schudson 1995; Baumeister and Hastings 1997). (conditioned submission aversion).

Only little is known on the actual mechanisms of Also dubbed the Garcia Effect, Bait Shyness, or the *acquisition, *consolidation, *extinction, and *forgetting of collective memory. Retention is less of a mysteryoffer idiosyncratic terms based on unpleasant personal as noted above, the collective *engram is distributed inexperience), CTA does differ in a critical parameter the brains of individuals with overlapping lifespan that from other *associative learning *paradigms. This transmit the information from one generation to another, as well as in artefacts of culture. Adolescence time interval between the conditioned (CS) and the and early adulthood appear to comprise a Ösensitivity to conditioned (US) *stimuli. Whereas in *classical periodÖ for the acquisition and the consolidation of and *instrumental conditioning an ISI of more than the collective memory (Schuman and Scott 1989;seconds commonly renders training ineffective, CTA *development, *imprinting). In a world whose public opinion is dominated by massive deviation from the widely accepted paradigm, namely media coverage of events in real-time, the kinetics of that two stimuli must come close together in time in acquisition and extinction of collective memory is order to become associated in mind, that has led probably faster than it has ever been (Lynch 1996;respectable psychologists to doubt the early scientific Cox 2000).

The encoding and stability of collective memory are The first systematic studies of CTA were reported of extreme importance to issues of national and international policy, social policy, economy, war, and peace. Rzoska (1953) and by Garcia et al (1955). Both conducted their experiments on the *rat. Rzoska investigated Sectarian and national myths are still major powers ongoing in the national and international arenas. But not onlyquent rejection of the same bait; Garcia noticed that the there. Collective memory has a role in selecting and association of a saccharin solution with exposure to constructing our attitude toward nature and science as -irradiation, which induces malaise, suppresses subsequent (Midgley 1992; Eder 1996). One of the toughest challenges facing a scientist is to identify potential *bias in CTA by associating the saccharin with the delayed injection of malaise-inducing compounds (Garcia et al 1966). Saccharin is used to this day as a standard CS in CTA experiments. Many other tastes can be used as well; they are most effective if unfamiliar to the *subject at the time of conditioning (Revusky and Bedarf 1967). The US could also vary, from rotation and irradiation to drugs and poisons. A standard US is an intraperitoneal injection of a LiCl solution, which produces transient visceral distress within a few minutes of

Selected associations: Bioculture, Observational learningParadigmZeitgeist

¹An intriguing question is whether nonhuman social species, such as

*monkeys, have rudimentary forms of collective memory, as opposed to other manifestations of culture (Bonner 1980).

Conditioned taste aversion

A learned association of taste with visceral distress.

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injection. In a commonly used protocol, the rat (or mouse) is made slightly thirsty, and then given to drink the diluted taste solution for 10–20 min. This is followed by the correlation of neuronal events with learning, and tested for taste avoidance, either by presenting it with targeted interventions in the process by drugs or other the CS only (single-bottle test), or by permitting it to choose between the CS and another stimulus. CTA offers significant advantages for the investigator because it is highly reproducible and the resulting memory is long lasting, which permits analysis of multiple memory

On the one hand, the ISI in CTA can extend up to 6–8 h, but, on the other, it cannot be made too short: 10 s only is ineffective (Schaaf et al 1995). It seems that the brain has an a priori tendency to encode memory, from the behaviour to the molecules and distinguish ingestion-induced malaise, which requires back, is feasible. CTA has therefore become a popular assay and paradigm in memory research. Whereas the of negative reinforcers. Similarly, stimuli that act on behavioural parameters of CTA have been described in non-visceral receptors and have less intimate association with food, such as tones, visual cues, or brain circuits that subserve this behaviour. It is generally accepted that the gustatory area in the insular cortex instrumental conditioning, are ineffective in CTA plays a part in processing the detection of taste unfamiliarity (Garcia et al 1968). Odours can be used as CS in long-term memory and in encoding the taste representation; the delay conditioning (Slotnick et al 1997), but are less effective, and work best when associated with the taste with the malaise; and the amygdala subserves (Ötztal et al 1979).

rodents are involved, a multi-level analysis of learning at least several minutes to develop, from other types of assay and paradigm in memory research. Whereas the integration and expression of CTA (Figure 17)

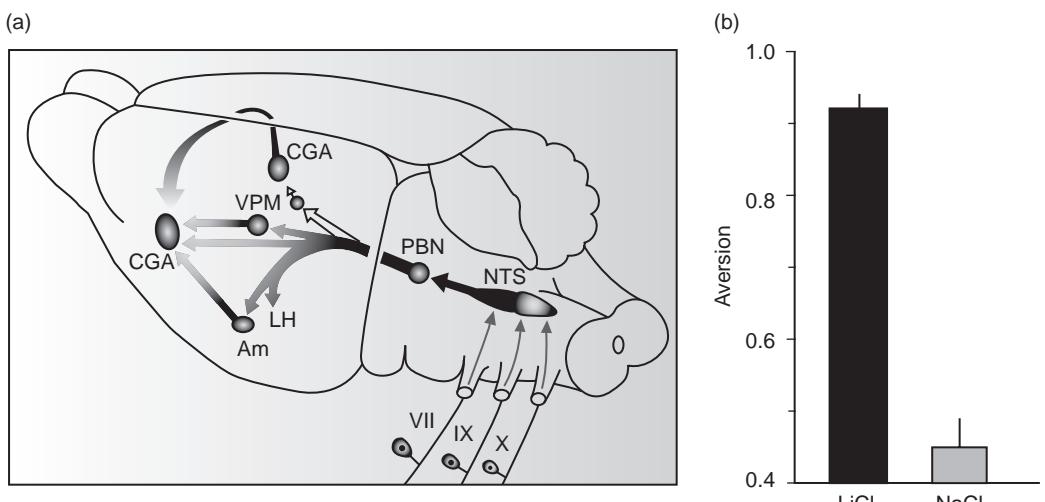


Fig. 17 (a) A scheme of the central taste system in the rat, which mediates CTA learning. VII, IX, X = cranial nerves; Am, amygdala; CGA, central gustatory area in the insular cortex; LH, lateral hypothalamus; NTS, the nucleus of the solitary tract in the pons; PBN, posterior nucleus in the pons; VPM, the ventroposteromedial nucleus of the thalamus, which contains the thalamic taste area(s). The detection of taste familiarity and in the taste memory; the amygdala in encoding the hedonic valence of the taste and in the performance of CTA; and the PBN particularly in the association of the CS with US in CTA. (b) Rats injected i.p. with LiCl an hour after an unfamiliar solution of saccharin display high aversion toward saccharin when tested 3 days later. The test involves a choice between water and saccharin. 0.5 means equal preference, and a low score means preference of saccharin. It can be seen that rats injected in the absence of malaise (*control), come to prefer the saccharin to water.

Conditioned taste aversion

(Yamamoto et al 1994; Bureš et al 1998; Lamprecht and Dudai 2000).

It is unlikely that the tolerance of CTA training to long ISI stems from unique types of molecular mechanisms that subserve CTA are similar to those that subserve other forms of learning, such as the activation of *glutamate and *acetylcholine receptors and the modulation of *immediate early gene expression.

Information gathered so far indicates that the molecular mechanisms that subserve CTA are similar to those that subserve other forms of learning, such as the activation of *glutamate and *acetylcholine receptors and the modulation of *immediate early gene expression. Probably, the tolerance to long delays results from special circuit properties, shaped in evolution to ensure that the organism is prepared learning (*a priori) of the avoidance of food

toxins (e.g. Shipley and Sanders 1982). An appealing hypothesis is that sampling a taste, especially an unfamiliar one, creates an ÔactiveÕ (*taxonomy), short-term memory trace in the gustatory cortex, and possibly in some other stations in the central taste pathway (Figure 17). This memory of the CS lasts for only a few hours and is accessed by stations in the central taste circuit that can also detect malaise. Candidate mechanisms that could encode this type of memory are the *persistent phosphorylation of synaptic proteins (Rosenblum et al 1997; *protein kinase), local *protein synthesis, and other types of tagging of the active synapses (Frey and Morris 1997; *consolidation). If malaise is sensed while the short-term taste memory is still active, the CS and the US information converge, probably in the parabrachial nucleus and possibly also in the amygdala. This in turn triggers the cellular mechanisms that register the long-lasting taste-malaise association.

Selected associations: A Priori Associative learning
Classical conditioning Paradigm Surprise

cases it is more or less coherent and internally consistent, yet false in the *context named (Talland 1965; Moscovitch 1989). Typically, the account concerns the person who tells it, who is unaware of its memory *coincidence detectors in the central taste circuit deficit.

Confabulation in its broader meaning (definition 1) refers to a wide spectrum of phenomena. Some of these that are within the normal range of the human behavioural repertoire. Minor, innocent confabulations and the modulation of *immediate early gene expression may pop-up occasionally in some individuals in stress-situations; they could be considered a sort of defence mechanism. Creative confabulations could contribute to mythology, literature, and the fine arts, as noted, for example, by Hobbes (1651):

Ôprepared learningÕ (*a priori) of the avoidance of food

Much memory, or memory of many things, is called experience Againe, Imagination being only

of those things which have been formerly per-

ceived by Sense È the imaging of the whole object,

as it was presented to the sense Imagi-

nation; as when one imagineth a man, or horse,

which he hath seen before. The other con-

poundedas when from the sight of a man at one

time, and of a horse at another, we conceive in our

mind a Centaure. So when a man compoundeth

the image of his own person, with the image of the

actions of an other man; as when a man imagines

himselfe a Hercules, or an Alexander (which hap-

peneth often to them that are much taken with

reading of Romants) it is compound imagination,

and properly but a Fiction of the mind.

Only pathological confabulations are of interest to us here. More specifically, only selected aspects of pathological confabulations. Hence antisocial personality disorder, which is expressed among others in deceitfulness (DSM-IV 1994), is not of our concern here; neither is MunchausenÕs syndrome, a psychiatric disorder in which an otherwise healthy individual seeks invasive medical treatment for feigned or self-induced symptoms (Ahser 1951). Left out is also confabulation in states of delirium and dense *dementia. To the student of memory, the most intriguing is confabulation in clear consciousness, which is adjunct to amnesia (definition 2). It fits the oxymoron Ôhonest lyingÕ. Two types of confabulations are discerned in this case (Berlyne 1972; Kopelman 1987; Schnider et al 1996a). One is ÔmomentaryÕ or ÔprovokedÕ the other is ÔfantasticÕ or ÔspontaneousÕ.

Momentary or provoked confabulation is so called In Latin confabulare is Ôto chat with a foolÕ, and because it is fleeting and provoked by questions prob-fabulae!Ñ nonsense. The confabulator indeed tells the *subjectÕs memory. It is seen in amnesics, as well story, but this story is not complete nonsense. In many as in demented patients in the early stages of their

Confabulation

1. The making up of narratives and details, or the filling in of gaps in memory.
2. Falsification of memory in the absence of deceitfulness occurring in clear *consciousness in association with *amnesia.

In Latin confabulare is Ôto chat with a foolÕ, and because it is fleeting and provoked by questions prob-fabulae!Ñ nonsense. The confabulator indeed tells the *subjectÕs memory. It is seen in amnesics, as well story, but this story is not complete nonsense. In many as in demented patients in the early stages of their

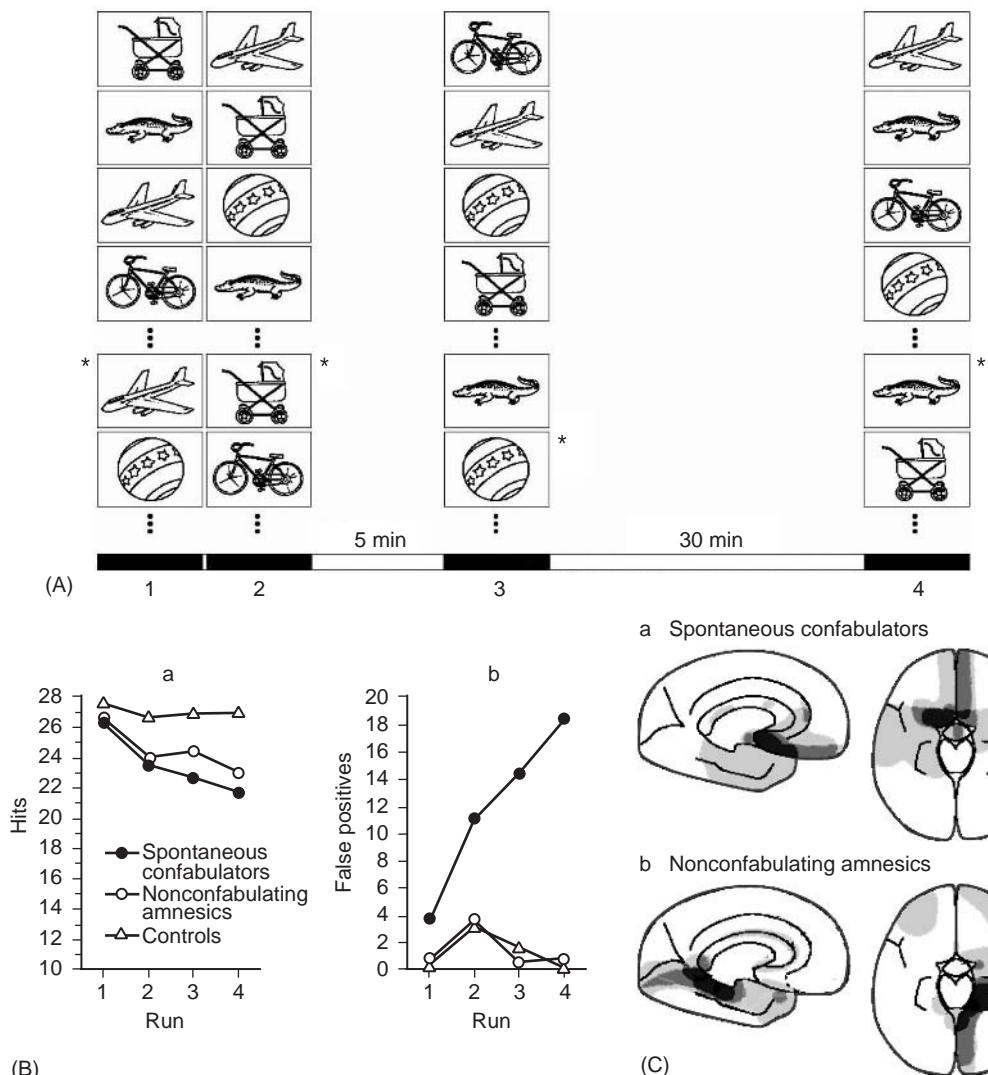


Fig. 18 A laboratory test that confabulators fail. Schnider and Ptak (1999) subjected spontaneous confabulators, nonconfabulating amnesics, and controls, to a continuous *recognition task. In each run of the task, 80 pictures were presented one after the other on the screen for 2 s each (A). Some of the items recurred (targets, marked by asterisk, total 28 in each run), whereas the other items (distractors, total 52 in each run). The subjects were requested to indicate item recurrence. Immediately after the completion of a first run, a second run was made, with a different selection of targets and distractors. At the beginning of the second run the subjects were asked to indicate item recurrence only within the second run. Similarly, 5 min after the second run, the third run was made, and 5 min after the third run, the fourth run was made. As expected, spontaneous confabulators and nonconfabulating amnesics failed to fare well in target detection (Ba); but most striking was the steep increase of false positive identification by the spontaneous confabulators (Bb). This was replicated with nonsense instead of meaningful pictures (not shown), with similar results. These data were construed to indicate that confabulators fail to suppress currently irrelevant memory traces. (C). The overlapping lesions in the brain of the spontaneous confabulators and the nonconfabulating amnesics (b). The basal forebrain and the medial orbitofrontal cortex were damaged in confabulators (a). Confabulating amnesics; in the latter, the lesions covered the posterior mediotemporal lobe and the dorsolateral prefrontal cortex. (Adapted from Schnider and Ptak 1999.)

Confabulation

cognitive deterioration. For example, a subject asked to either the retrieval set is faulty to begin with, or the recognize a picture of the British Royal couple, might proper retrieval *cues become ineffective, or improper reply that they are celebrated movie stars, and go ~~or~~ cues intrude, or the information gets mixed up in fabricating details about the last movie in which they ~~e~~phory; or the *metamemory system does not monitor allegedly starred. This confabulation is momentary, for the retrieval process properly and fails to eliminate does not significantly affect the subject's behaviour, and wrong results. The literature contains arguments for can be understood in terms of compensation for the and against any of the above hypotheses.

deficient recollection; some nonamnesics and nonde- A particularly fruitful hypothesis is that confabulated occasionally do just this, if weakness of character is a disorder of mnemonic chronology, and that the ter prevents them from simply admitting that they do confabulated account is composed of bits of experi- not remember. In contrast, fantastic or spontaneous ones taken out of their proper chronological and, confabulation is unprompted, sustained, refers to wide- hence also, factual context (Van der Horst, cited in ranging narratives, may contain elements of grandiose Berlyne 1972; Schnider et al 1996a,b). Even bizarre and has a persistent effect on the subject's behaviour. Confabulations might assimilate information that has Spontaneous confabulation is not always fantastic. It been encountered earlier, although not necessarily could include sensible reminiscences that are out of experienced, by the patient. Disorders of mnemonic their spatiotemporal context. Consider, for example, chronology are probably insufficient to explain confab- the patient who suffered from brain haemorrhage, and delusion per se many amnesics err in the chronology of who for weeks afterwards confabulated about perform-experiences yet do not confabulate¹ but it might be a ing stocktaking in a certain store, although the last time necessary condition for confabulation to occur. A vari- he was supposed to do that was years earlier (Burgess of the mnemonic chronology deficit was proposed and McNeil 1999). At the other side of the spectrum are and tested by Schnider and Ptak (1999). They com- confabulations whose source is more difficult to iden- pared the *performance of confabulating and noncon- tify, as that of the Korsakoff's patient (*amnesia) recovering amnesics on a continuous *recognition task. ering from a motorcycle accident in Britain, who came In this task, the subjects had to identify recurrent pic- to believe she was in Royal Air Force and that her accents within ongoing test sessions (Figure 18). The con- dent occurred while flying over France. Although confabulators made an increasingly growing number of time she changed some details in the story, the flying false positive responses to pictures that were presented theme remained prominent throughout for several in the former but not in the ongoing session. It seemed months (Berlyne 1972).

that they recognized information encountered many

The neuropathology of confabulation commonly minutes ago as if it had been presented in the present. involves damage to frontal structures (Figure 18), which This was construed to indicate that the confabulators could result from a variety of insults (Alexander and DeLong 1985; Freedman 1984; Stuss and Benson 1984; Shallice 1988). These include rupture of the temporal lobe, and fail to DeLuca and Cicerone 1991). These include damage to the ventromedial frontal lobe, suggesting activated *internal representations even if aneurysm of the anterior communicating artery, caus- the suggestion that failure to recall properly may result in damage the ventromedial frontal lobe, Korsakoff's syndrome (*amnesia); and physical injury. That frontal from activation or reconstruction of too many memory lobe amnesia is associated with confabulations suggests traces, rather than from the lack of traces to retrieve. that some impairment of executive function is involved. This mnemonic failure of certain amnesics reminds one (*working memory). But this by itself still doesn't explain why confabulators confabulate. amnesics, have in daily life (*mnemonics). In the stor-

So why do they? In searching for candidate neurologage (*metaphor) and recall of memory, as in so many ical causes, it is first useful to *recall the distinction between spontaneous and provoked confabulation. As

noted above, provoked confabulations may basically reflect a normal compensatory strategy (Kopelman 1987; Schnider et al 1996a). Spontaneous confabula-

tion, on the other hand, is much farther from normal, and therefore more interesting. Poor memory is not the reason, or at least is not a sufficient one, because many amnesics do not confabulate. Most investigators now believe that the problem is related to *retrieval. On defence mechanisms in general, see *forgetting.

¹A related syndrome is Munchausen's syndrome by proxy, which is fabricated by one person, usually a parent, in another, usually child (Meadow 1977). These syndromes are called after Baron Munchausen (1720-1800), a retired German officer whose stories after dinner

confabulations became a literary *classic (Raspe 1785). It is not clear³ what meaning of these terms as intended in this book should thy that Munchausen's syndromes might be facilitated by the practice of the Internet (Feldman 2000).

³The distinction between ÔmomentaryÕ and ÔfantasticÕ is noticeable⁴ along the same *dimension, whereas that between systems, which involves subjective experiencing of ÔprovokedÕ and ÔspontaneousÕ is. Most authors now prefer the latter⁵ dichotomy. Both pairs of terms are, however, mentioned here because both are still used, sometimes interchangeably, in the literature.

⁴Aneurysm is a localized pathological dilatation of a blood vessel caused by congenital or acquired structural deficiency or inflammation of the vessel's wall. An aneurysm may rupture and cause haemorrhage, or it can become sufficiently large to displace and damage adjacent tissue.

⁵Echophy is the actual act of retrieving or reconstructing the information, see *retrieval.

Conscious awareness

The mental state in which one experiences, notices, and is directly apprised of one's own *percepts, *memories, emotions, beliefs, thoughts, and actions.

Books on memory tend to shy away from the discussion of consciousness and related issues. This is surprising⁶ because the relation of consciousness to memory is of great importance in memory research and conscious awareness is a major *criterion in the discussion of consciousness.

Awareness⁷ is of great importance in memory research and conscious awareness is a major *criterion in the discussion of consciousness. This is a *reductionist use of the term. According to this use, awareness of a target stimulus can be inferred objectively from observing the thinking, and the fact that we all know subjectively what input-output relationships, provided appropriate it is, consciousness is still an *enigma. All authors point⁸ to the great difficulty in even defining it (e.g. Crick and Koch 1992; Searle 1992; Block 1995). Because we know⁹ so little about consciousness, many authors also believe¹⁰ that premature definitions are counterproductive.

The purpose of this discussion is to outline briefly non-*declarative memories, such as *habit, *skill, and only very limited aspects of conscious awareness that¹¹ are directly relevant to the discussion of memory. To do this makes sense to talk about Aplysia; it so, we must, first, and in spite of the aforementioned caveat, attempt to formulate an operational, heuristic stimulus, but it is questionable whether the slug is really definition of the subject of discussion. This definition conscious of the stimulus; so far we have no *method to does not aspire to explain what conscious awareness determine if it is and if so, to what degree.

in the context of a theory of mind and brain, it merely delineates the subject. Second, as the terms Ôconscious-To say that the subject is consciously aware of somethingÕ, ÔconsciousÕ, ÔawarenessÕ, and Ôconscious awarenessÕ¹² Gay that in addition to the nervous system of are often used interchangeably in the literature, the subject being aware of this thing, the subject is also

conscious that this thing happens. A subject may, of course, be in a fully conscious state but unaware of the conscious awareness in *acquisition and in *retrieval target information. Stating that the subject is specific of an item could differ. For example, learning to be consciously aware of the target information implies that driving a car should better involve conscious awareness, the subject is also aware of this information; however, but an expert driver can drive for hours in the absence of the solo term conscious (or consciousness) if of conscious awareness of the activation of the driving experimental science might be somewhat problematic skill. Thus, conscious awareness is not a cognitive from the point of view of pragmatics. This is because system that becomes permanently linked to particular these terms, as noted above, are used in a broad sense of memory; rather, it is a brain state which is true of conceptual frameworks, some of which do not either obligatory, or permissive, or optional for the necessarily refer to concrete behaviour. Conscious acquisition or retrieval of an item.

consciousness intends to connote a more tangible cognitive state, of being directly apprised of one's ongoing behaviour? This question is the focus of many studies that journal acts, and fits better to be used in the context of combining multiple experimental methodologies, experimental science. This is, therefore, the term occasionally augmented by a provocative hypothesis preferred in this book. Note that many authors do and by input from professional philosophers (for a equate 'conscious' with 'aware', yet still use the selection of approaches and commentaries, see Griffin 'consciously aware', which in this case becomes a red herring; Crick and Koch 1992, 1995; Nagel 1993; Bogen dancy (*Ockham's razor).

1995; Weiskrantz 1995; Block 1996; Duzel 1997;

A compact matrix of memory systems by Clark and Squire 1998; McIntosh et al 1999). Two consciousness, proposed by Tulving (1985b), illustrates major experimental methods stand out. One is the kind of interactions possible among different types analysis of conscious awareness in brain damaged of memory and consciousness. Tulving lists three vari-patients. These are patients that suffer from amnesia; or eties of consciousness, which he termsetic (not comprehending), noetic (comprehending), and auto-noetic (self-comprehending). Anoetic is similar to agnosia (the loss of ability to recognize and identify a class of stimuli in the absence of impairment in the ability to sense these stimuli; Shallice 1988); or disconsciousness as defined above; the subject is capable of neglect syndrome (a set of deficits following interruption, registering, representing, and responding to aspects of large tracts of nerve fibres in the brain, such as the present environment, but is not consciously aware the corpus callosum; Zaidel et al 1996). This type of of these events. Anoetic consciousness corresponds to approach unveils circumscribed disturbances of procedural, nondeclarative memory systems. Noetic conscious phenomena, and identifies brain sites that consciousness allows the subject privately to experience and observe these phenomena. The second approach is and operate cognitively on objects and events and or combination of functional neuroimaging with the relations among them. This corresponds to con-neuropsychology, and its main objective is to identify scious awareness as used here, and is correlated with neural correlates of conscious awareness. It seems semantic memory (*declarative memory). Autonoetic that conscious awareness depends on the activity of consciousness confers in addition the capability of distributed brain circuits; an *homunculus explanation experiencing the private phenomenological flavour of tion is currently out of favour. Thalamo*cortical personal episodes, is correlated with *episodic, autobiographical memory, and corresponds to an advanced cortex probably plays a global, executive role (*working graphical memory, and corresponds to an advanced cortex probably plays a global, executive role (*working reflexive form of conscious awareness as defined here). memory), whereas other cortici participate according

It is hence evident from the discussion so far that the type of information accessed. From studies of consciousness is not an all-or-none state, and therefore amnesics we also learn that the *hippocampal we should indeed expect to find various degrees of formation and adjacent cortici are particularly important conscious awareness in different species as well as for the access of items in memory to conscious different states of the organism. Furthermore, different awareness.

task conditions may involve different varieties of conscious awareness. Consider, for example, *classical conditioning; whereas simultaneous and delay conditioning require only awareness, i.e. anoetic consciousness, trace conditioning may already require conscious awareness, i.e. noetic consciousness (Clark and Squire 1998).

Selected associations: Attention Declarative memory
Enigma Persistence Working memory

For more on the nature of definition, see the conceptual framework of the introduction.

²These privately experienced qualities are called qualia (singular: *qualm*). Qualia are types of Ôsense dataÕ, i.e. entities that are ^{consolidated} assumed to exist only because they are sensed; see *stimulus.

³Some authors consider consciousness to always involve self-consciousness (e.g. Kant 1800), others do not (e.g. Searle 1992). Morris 2000). This is the time-dependent stabilization processes at different *levels of brain organization. Molecular and cellular neurobiologists refer to the Ôlocal cellular consolidationÕ (Dudai and Morris 2000). This is the time-dependent stabilization of information storage at local nodes, or *synapses and their cell body, in the neuronal circuit that encodes the memory. Cellular consolidation is accomplished within a few hours after training (e.g. Montarolo et al 1986). In practice, it is commonly defined as that time window during which the formation of the long-term form of the newly acquired memory can be blocked by inhibitors of *protein or RNA synthesis. Certain other drugs, or electric shock, could also be used to block consolidation. The temporal parameters of the consolidation period will, however, depend on which treatment is used. This is because cellular consolidation involves multiple phases, some of which are sensitive to some treatments but not to others (Grecksch and Matthies 1980; Rosenzweig et al 1993; DeZazzo and Tully 1995; Freeman et al 1995; Ghirardet al 1995).

⁴There is also the view that we will never know what it is like to be an *Aplysia* (Nagel 1974). Some dispute this view (Dennett 1991).

⁵In Aristotelian philosophy, meant comprehension, or intellectual intuition (Guthrie 1981).

⁶These circuits are necessary but not sufficient. Conscious awareness requires more basic forms of awareness, that depend on arousal controlled by the brainstem (Magoun 1952).

Consolidation

1. The progressive post-*acquisition stabilization of the *engram.
2. The memory *phase(s) during which this stabilization takes place.

It took the Muses, daughters of Memory, a single protein (*CREB, *immediate early genes, *late encounter with Hesiod on Mount Helicon to breathe response genes). These processes involve local synaptic mechanisms, cell-wide mechanisms, and cross-talk between the synapse, cell body, and nucleus (Frey and Morris 1997; Martinet et al 1997a; Casadi et al 1999; Kandel 1993; DeZazzo and Tully 1995; Freeman et al 1995; Ghirardet al 1995). The new proteins are believed to embody and subserve long-term modifications of the synapse. This probably involves morphological *plasticity as well (Bailey and Dudai and Morris 2000). The new proteins are believed to contribute to the fragility of our triggered, the plasticity change becomes immune to forgetting. And as if the burden of confusion and forgetfulness stemming from the continuing passage of time is not enough, the period immediately after learning also contributes its share to the fragility of our engrams. It has long been recognized that fresh molecular turnover and independent of certain signal transduction cascades, and a consequence, is no more particularly labile and prone to interference by agents sensitive to the consolidation blockers. Model neural networks can be shown to be capable of consolidation (consolidare, Latin for Ôto make firmÕ). Consolidation is a consolidation-like process solely on the basis of modulation, however, is not necessarily completed within a few hours or days. A consolidation-like process may also be the case in simple neuronal circuits. However, local, cellular consolidation is not the whole story. Rummelhart et al 1986c); this short time after learning; in some types of memory it may also be the case in simple neuronal circuits. How may continue for weeks, months, even longer.

in some more complex circuits. In the mammalian after post-retrieval interference is task and region brain, and possibly in other vertebrates, additional con-dependent (Berman and Dudai 2001). consolidating processes operate at the system level. These processes of system consolidation involve gradual recruitment and continuous reorganization of distributed brain circuits long after acquisition has occurred. System consolidation can be detected by noting the time-dependent sensitivity of certain types of memory acquisition of every percept is bound to waste brain to circumscribed brain lesions, or the change over timespace on useless items (*capacity). Another possibility in the activation of specific brain circuits in a memory is that the post-stimulus time window of consolidation, task, as revealed by functional neuroimaging, during which the new information is particularly mal-consolidation in some systems occurs within a few hours (Shadmehr and Holcomb 1995), but in other systems it can take much more time: several days (Frey and Morris 1997; Dudai (Winocur 1990), weeks (Chen et al 1993; Bontempi et al 1999), even years (Schmidtke and Vollmer 1997; Reed and Squire 1998; Teng and Squire 1999; Head 2001; but see Nadel and Moscovitch 1997). It is believed to be promoted by endogenous brain activity, sensory input, and their interactions; the triggers and the circuit mechanisms are unknown, but the cellular mechanisms are likely to be similar to those mentioned above for cellular consolidation. The most notable example of system consolidation is provided by declarative memories. These memories are assumed to be stored in the long run in circuits that involve the *cerebral cortex. But in the first period after learning, they depend on the hippocampal formation. With time, this dependency disappears (*ibid**amnesia).

An intriguing question, which has received much attention and stirred much debate in recent years, is whether for any memorized item, consolidation starts and ends just once. The data from cognitive psychologists indicate that memory traces are reconstructed with use and that *retrieving a memory item could involve mingling the internal representations of the past with the percepts of the present (e.g. Bartlett 1932; Tulving 1983; Schacter et al 1998; *false memory). This mnemonic reconstruction process raises the possibility that engrams may be reconsolidated upon retrieval. There is evidence that a cellular consolidation phase may indeed ensue retrieval (Misanin et al 1968; Spear and Mueller 1984; Nadel et al 2000; Sara 2000; but see, for example, Dawson and McGaugh 1969). It is not yet established, however, whether the entire reactivated trace could become sensitive to interference in this assumed reconsolidation, or, alternatively, whether a ÔmemoryÔ has privileged stability. What already becomes apparent is that the cellular mechanisms that consolidate novel and reactivated traces, respectively, differ from each other (Berman and Dudai 2001; Taubenfeld et al 2001); and that the stability of the retrieved trace *declarative memory tasks.

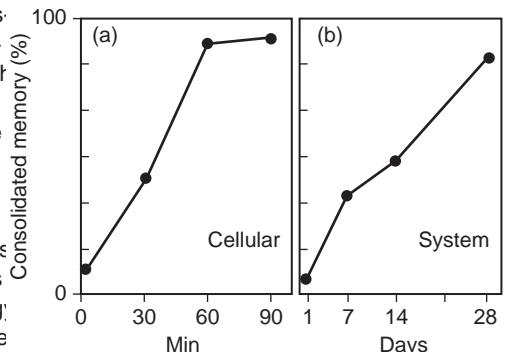


Fig. 19 Two types of consolidation windows in behaving animals. (a) The time course of cellular consolidation, determined by measuring the sensitivity of memory to the inhibition of protein synthesis. Consolidated memory is defined as treatment-resistant long-term memory. The data are from experiments on shuttle box learning in goldfish (Agronoff et al 1966; *classic). The protein synthesis inhibitor was administered to the subject at the indicated time points after training. The sensitivity of memory to protein synthesis inhibitor was over by about 1 h. A consolidation process that depends on protein synthesis during and immediately after training is a universal property of the nervous system. (b) The time course of system consolidation, determined by measuring the sensitivity of long-term memory to contextual fear conditioning to a lesion in the rat hippocampus. The lesions were inflicted at the indicated time points after training. The dependence on the hippocampus in this case is over by about 1 month. Data from Kim and Fanselow (1992). A system consolidation process that lasts weeks or even longer, during which the memory becomes independent of the hippocampus, is observed in declarative memory tasks.

spin-offs of the constraints imposed on biological meaning of the stimulus, such as the context of a figure memory systems by the design and maintenance of that a visual scene, a note in a musical score, or a word in a biological hardware, rather than functional properties sentence (Wickens 1987). Having made this distinction, it is still useful to remember Locke's gentleman: what is regarded by the experimenter as an irrelevant context may not so be regarded by the brain of the *subject.

Selected associations: Acquisition¹mediate early genes
Phase²Protein synthesis³Retrieval

¹Long-term memory may be subjected to continuous reorganization throughout life. Reorganization alone is therefore insufficient as a criterion for consolidation, because otherwise one will reach the conclusion (that some authors indeed reach) that system consolidation proceeds forever, which deprives the notion of consolidation phase of its usefulness. The criteria for system consolidation should therefore ultimately include a limited period of obligatory dependency on the activity of a specific brain region. This could be demonstrated by time-limited sensitivity to lesions or to inactivation of this region.

²On the distinction between active and inactive trace, see Lewis (1979); *retrieval, *taxonomy.

³This tension between adaptive selection and built-in biological constraints is a recurrent issue in this book; see the Panglossian paradigm, in *paradigm.

In the behavioural literature, ÔcontextÕ typically refers to environmental stimuli that are kept relatively constant in the course of the experiment, and is hence synonymous with apparatus, environment, and background stimuli (e.g. Lubow and Gewirtz 1995). In real-life, the background often varies significantly from one moment to another, but still is not usually considered the target of learning or *retrieval. The information about the time and place in which the target was acquired is referred to as Ôsource informationÕ. The context itself could, however, become the experimental variable. This is illustrated in a study by Godden and Baddeley (1975), in which divers were instructed to learn word lists both on land and underwater, and subsequently *recall the lists either on land or underwater. After learning on land, recall was better on land, and after learning underwater, recall was better underwater (Figure 20). It is likely that in this experiment, the context was not only the underwater milieu, but also the physiological state of the subject, generated

Context

The surroundings and circumstances in which an event takes place.

Events always occur in some context (from Latin *contextus* joined together, Ôwoven togetherÕ). The association between a memorized ÔtargetÕ event and context is not trivial. This is beautifully illustrated by Locke (1690): ÔÉ a young gentleman, who, having learnt to dance, and that to great perfection, there happened to stand an old trunk in the room where he learnt. The idea of this remarkable piece of household stuff had so mixed itself with the turns and steps of all his dances, that though in that chamber he could dance excellently well, yet it was only whilst the trunk was there; nor could he perform well in any other place, unless that or some such other trunk had its due position in the roomÕ. Had the young gentleman been the subject of a controlled experiment on the acquisition of dancing *skill, it would have been fairly easy for the experimenter to discern the target task (dancing) from its context (the trunk). Furthermore, in this case, the context was an innocent part of the environmental surrounds, not expected to influence the target *stimulus in any significant way. This is in contrast to another type of ÔcontextÕ, which always affects the significance

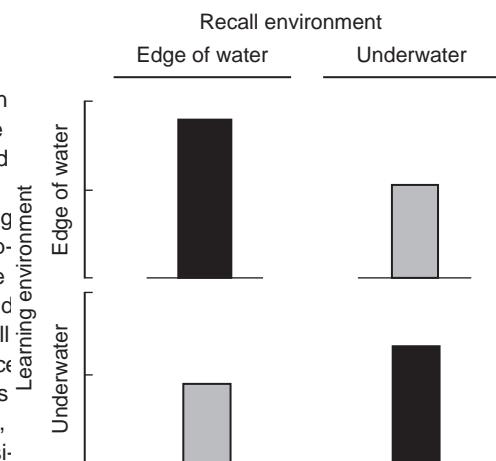


Fig. 20 A case of context-dependent learning. Godden and Baddeley (1975) instructed groups of members of a university diving club to learn lists of words either while seating 20 feet under water or while seating by the edge of the water. The *subjects were then requested to recall the lists either underwater or on land. The lists learned underwater were recalled best underwater, whereas the lists learned on land were recalled best on land. The height of each bar represents success on performance in the task. (Adapted from Godden & Baddeley 1975.)

Context

by the underwater experience. Learning that is dependent on the endogenous state of the subject is called *state-dependent learning. Distinct endogenous states are formed (Penick and Solomon 1991; Holland and Bouton 1999). This is also supported by studies of chemical substances, but could also be induced by the human subjects (Chun and Phelps 1999). Coming to external context. In such case, the distinction between think about it, this is not surprising. Since context refers to context-dependent learning and state-dependent learning combinations of features contributed by input from multiple modalities, one should expect brain circuits to become a matter of taste or professional *bias.

In their ability to reinstate context, be it internal or external, not all senses are equal. In his famous Remembrances, the hippocampus does just that. Currently, a popular *assay of contextual learning in rodents is a version of *fear conditioning. In the common (1913) retrieves his childhood memories to the flavour of madeleine cakes soaked in tea. His literary account is associated with a shock, and the subject comes to fear the mnemonic power of the chemical senses. However, as is often the case in seemingly simple to have received experimental validation: odours are classical conditioning paradigms, there is also learning superior to colours in supplying context for target of the context in which training is performed, e.g. the information (Pointer and Bond 1998). Proust's account conditioning chamber. Hippocampal lesions impair the also points to the flavour of the madeleines as a retrieval-acquired fear of context but not of the tone (Phillips *cue, i.e. a stimulus that elicits retrieval by activating anand LeDoux 1992). The effect of hippocampal damage *engram and interacting with it. Retrieval cues are on context learning is, however, detected only when certain effective to the extent that they help reinstate or recreate certain protocols or measures of fear conditioning are processes involved in the original learning (McGeoch 1932; Tulving 1983). They may hence point either to contextual learning can do without a fully functional target information, or to source information, or both. hippocampus (McNishet al 1997; Frankland et al An interesting case in which the target information 1998; Mareret al 1998; Gewirtz et al 2000).

serves as a retrieval cue to bring to mind source information is *flashbulb memory. An notable development in the study of context recent years is the large increase in the reports of cellular

Compelling evidence for the functional dissociation of target and source information in the brain comes (e.g. Zipse et al 1996; Christensen et al 2000; Shulz from the study of human *amnesia. In some types of amnesia, the patient can recall facts or events, but not populations or single neurons to target stimuli, that are when and where this information was acquired. This is affected by the surroundings and the circumstances. therefore termed "source amnesia" (Squire 1984; Mayes 1988; Lishman 1998). A classic case of source amnesia has even been reduced to the synaptic and molecular amnesia was described by Claparede (1911) in a lady with Korsakoff amnesia. Claparede used a trick that the ability of weak synaptic stimuli to establish long-term potentiation depends on the recent history of editors and readers, but still brought him fame. He struck the hand of the patient with a pin hidden between his fingers. Later, when trying again to reactivate in another (Frey and Morris 1997). But whether out for the patient's hand, she pulled it back without this intersynaptic gating of stimuli indeed subserves the being able to explain why. In another experiment, effects of context in acquisition or retrieval of memory Claparede read to her stories, which she was able to still an open question.

recollect while being totally unaware of how these stories were learned. Source amnesia has since been reconfirmed to affect Korsakoff patients, and has also been demonstrated in other amnestic and demented patients (Shimamura and Squire 1987; Braeutigam 1995; Schnider et al 1996). The pathology is considered to result from damage to multiple areas, including the thalamus and frontal cortex.

¹This applies even to the simplest of learning in simple systems. Non-associative learning, such as habituation, could involve association between the unconditioned stimulus and the context (Marlin and Miller 1981; Rankin 2000).

²Indeed, Locke's trunk-dependent dancer, mentioned above, seemingly controlled variables, and to unveil potential also be described as trapped in state-dependency, where the variables (Fisher 1966; Martin and Bateson 1993; retrieval-permissive state is reinstated in the brain by the presence of Kellinger and Lee 2000; *dimension).
the trunk. The formation of the state dependency might have been promoted by the emotions involved in acquiring the dancing skill.

Controls

The elements and protocols that are included in the experiment in order to dissociate the contribution of the experimental variable from that of other factors.

In the Middle Ages 'control' meant a 'duplicate register' or 'duplicate roll' (contrafrotulūn Latin). Rolls were the standard material for writing administrative and financial records (Clanchy 1993), and the duplicate rolls were used by one officer of the law to check up on groups of another officer. The transition from the language of bureaucracy and commerce to that of science has its roots in the methods of inquiry proposed by the British philosopher John Stuart Mill. One of these methods was 'The method of difference', whose canon reads as follows: 'If two or more instances in which the phenomenon occurs have only one circumstance in common, while two or more instances in which it does not occur have nothing in common save the absence of that circumstance, the cir-

umstance in which alone the two sets of instances differ must be the cause, or the effect, of an instance in which the phenomenon occurs'. Hence, to control for whatever possible in order to make sure that the effect is due to the independent variable (independent variable) is the cause of an effect (on the dependent variable), one should perform the experiments under two conditions, which should ideally be the other hand, multiple controls imply excessive identical except for the omission of the change in the independent variable. The condition in which the change in the independent variable is omitted came to be known as the 'control' (Coover and Angell 1907). Controlled experiments may involve multiple treatments of the same subject(s), experimental vs. control groups. For example, suppose that we set out to test the effect of a circumscribed brain lesion on long-term memory. We could include in the protocol a test of the experimental group vs. the control groups. As it is impractical to have truly matched groups, the alternative is to assign subjects in a population to groups that have an internal control for the lack of the effect of the random to smoothen variability (Fisher 1966). Statistics is then used to quantify the effect of the experimental variable, and further, to identify interactions among for a separate control group to test the effect of the

secondarily controlled variables, and to unveil potential latent variables (Fisher 1966; Martin and Bateson 1993; Kellinger and Lee 2000; *dimension).

The use of controls in experimental science has started to gain popularity in early psychophysics (reviewed in Solomon 1949; Boring 1954; Dehue 1997), and later in educational research (Thorndike and Woodworth 1901b; Coover and Angell 1907; Winch 1908). But the concept was occasionally appreciated by others as well: a 'classic example is the gedankenexperiment ('thought experiment') that proposed to test the effect of prayer on life in two groups of individuals, matched for everything except for practising Ôprudent piousÕ (i.e. experimental) vs. Ôprudent materialisticÕ (i.e. control) life-styles (Galton 1872).

In the discipline of memory research, subjecting the same group alternately to experimental vs. control conditions is inherently problematic, as the mere experience may itself affect the outcome on subsequent tests. It is therefore advisable, whenever feasible, to use separate control sider, for example, 'functional neuroimaging of complex tasks in humans, or 'delay tasks in monkeys, in which suitable subjects could be hard to get and train. Under such conditions, an experimental design with control groups often remains an Utopia, and protocols which are a blessing: those are elements embedded in the economy of controlled experiments that spare the need for separate controls. For example, suppose that we set out to test the effect of a circumscribed brain lesion on long-term memory. We could include in the protocol a test of the experimental group vs. the control groups. As it is impractical to have truly matched groups, the alternative is to assign subjects in a population to groups that have an internal control for the lack of the effect of the random to smoothen variability (Fisher 1966). Statistics is then used to quantify the effect of the experimental variable, and further, to identify interactions among for a separate control group to test the effect of the

Controls

lesion on these faculties. A protocol well-designed may include a matrix of ÔbalancedÕ or ÔreciprocalÕ controlssweet reward (*Clever Hans; Pfungst 1911)? i.e. a combination of control groups or treatments that complement each other. A classic example is provided by the Ôdouble-dissociationÕ lesion protocol (Teuber 1955). In this protocol the effect of two different circumscribed lesions, A and B, is tested on two different phenotypes, X and Y. If lesion A yields a defect in X but not in Y, while lesion B yields a defect in Y but not in X, then the defects in X and Y are not due to general damage but rather to specific dissociable contributions of A and B (see *declarative memory).

Memory research is of course not unique in benefiting from the proper application of controls in experimental design. Some elementary issues that require appropriate controls are shared by many other experimental disciplines. These issues include, for example, the need to distinguish correlation from causality (*criteria, *method). But several potential pitfalls do call for controls that to some degree or another are specific to the discipline of memory research. Here is a short list:

1. Controls for species-specific behaviour vs. learning. Motor patterns that emerge in training and testing may comprise an innate (**a priori*) response to specific *stimuli (Ôsign stimuliÕ) rather than learning (Breland and Breland 1961; Moore and Stuttard 1979; Wolfe et al 1998). In parentheses, it is worthwhile to repeat here the ever-valid advice to those investigators who mingle with the behaviour of experimental subjects*Homo included): know your subject!
2. Controls for *development vs. learning. This is especially important in behaviours whose *capacity matures gradually, or materializes in restricted sensitive periods (*birdsong, *imprinting). The rule of thumb, however, is that a definitive dissociation of learning from development could be unrealistic, as both are interwoven in the emergence and refinement of even the most elementary sensory and motor faculties (e.g. Crair et al 1998).
3. Controls for one type of learning vs. another. For example, is an alteration in behaviour that is obtained in a conditioning protocol due to the *association among stimuli, or to nonassociative processes (*sensitization, ÔpseudoconditioningÕ *classical conditioning; Rescorla 1967)? Is a particular conditioned response due to stimulus-Østimulus (*classical) or stimulus-Øresponse (*instrumental) conditioning (Jenkins and Moore 1973)? And when a horse ÔreadsÕ, is it because it has mastered human language, or because it has realized that responding

to the subtle bodily gestures of its master yields a performance due to changes in the experimental conditions. An often neglected need is to control for *state-dependent memory in studies that investigate the effect of drugs or of modulation of gene expression on memory. In such cases, if the subject flunks on the memory test, it could be a consequence of the change in its endogenous state, due to the presence of the specific drug or gene product in training but not in testing, rather than to memory failure (Overton 1964; also *context).

4. Controls to distinguish learning from alterations in performance due to changes in the experimental conditions. An often neglected need is to control for *state-dependent memory in studies that investigate the effect of drugs or of modulation of gene expression on memory. In such cases, if the subject flunks on the memory test, it could be a consequence of the change in its endogenous state, due to the presence of the specific drug or gene product in training but not in testing, rather than to memory failure (Overton 1964; also *context).
5. Controls for premature conclusions about the fate of memories. When *forgetting is detected, is it because the *engram has indeed vanished? A control test performed after a while may unveil Ôspontaneous recoveryÕ.

Other controls to unearth factors that could alter the behaviour but have nothing to do with learning and memory. For example, drug effects that result from the mere expectation by the subject that something will happen (a Ôplacebo effectÕ, Swartzman and Burkell 1998; Kvavilashvili and Ellis 1999). Or lesion effects that are actually a consequence of the surgical procedures, not of damage to the targeted brain area. This is why lesion experiments always require ÔshamÕ treatments, in which the skull is treated the same way as in the lesioned animal but no brain lesion is induced.

Occasionally what is expected to be a routine, boring control, *surprises and becomes a mind twister. Here is such a case. A subject is conditioned by a certain reinforcement. A naive expectation is that the more intensive the reinforcement schedule, the stronger the memory. A simple set of controls would include a non-reinforced group, and, possibly, a group reinforced only occasionally. Alas, the group whose behaviour is reinforced only intermittently remembers the best (Humphreys 1939). This is the kind of controls that opens a whole new field of research (see *experimental extinction). Similarly, devising innovative controls has unveiled much about the sophistication of *classical conditioning (e.g. Kremer 1971). The take home message: donÕt look for excuses, add all the control groups you can think of, they may prove even more interesting than the experimental ones.

Selected associations: Art, Bias, Culture, Method

Mars gedanken experiment finally made it, 129 years later, into a functional neuroimaging lab (Arlat 2001).

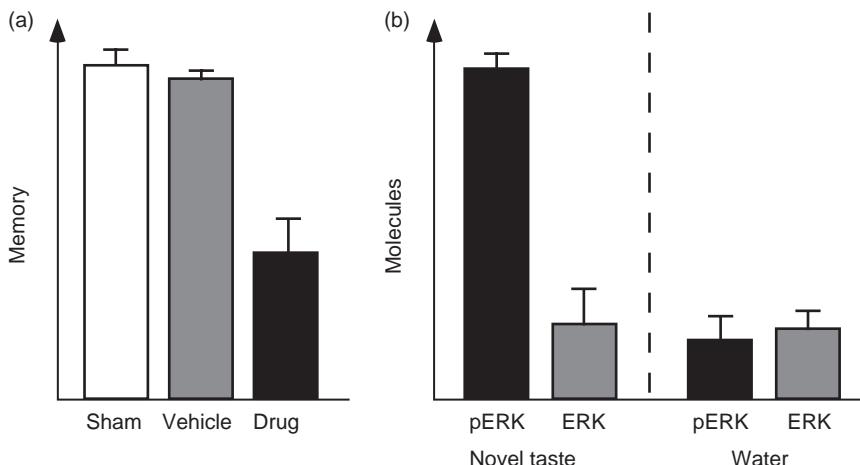


Fig. 21 Controls at two *levels of analysis of *conditioned taste aversion. (a) Microinfusion into the taste cortex, scopolamine, an inhibitor of the receptor for *acetylcholine, during training, blocks the formation of long-term memory of conditioned taste aversion (black bar). A control, in which only a drug-free solution (the vehicle) is microinfused into the taste cortex, has no such effect (grey bar). A control (i.e. surgery but no microinfusion into the brain) is also shown for comparison (open bar). Hence the effect on memory is due to the drug and not to the manipulations involved in its administration. Data from Naor and Dudai (1996). (b) Sampling a novel taste, but not a familiar taste (water), causes activation of the enzyme mitogen-activated protein kinase (ERK) in the taste cortex of the rat. This activation is due to phosphorylation of the ERK, and it can be detected by the use of specific antibodies, that bind only to the phosphorylated form (pERK, black bar). However, the population of the ERK molecules includes a certain proportion of pERK even in the absence of pERK. This implies that the increase in the number of molecules detected by the anti-pERK antibodies after the experience of the novel taste is due to an increase in the overall number of the ERK molecules (*protein synthesis), without a change in the proportion of the pERK molecules. A control is therefore necessary in which the overall number of ERK molecules is measured in parallel, with antibodies that recognize the ERK molecule regardless of whether it is phosphorylated or not (grey bar). Such a control shows that the total number of ERK molecules does not change, and that the effect of the novel taste experience is activation of the existing ERK molecules. Data from Berman et al. (1998).

CREB

A type of protein that regulates the expression of genes, and fulfils a key role in neuronal *plasticity.

In technical terms, which will be explained below, CREB, cAMP-response element-binding protein, is a protein that modulates the transcription of genes with joint regulation of multiple response elements, belonging to cAMP-response elements in their promoters. CREB is one of the most commonly used acronyms in neurobiology these days, and also one of the few words in the jargon of molecular biology that even psychologists and computational neuroscientists might have encountered. And if they didn't, they should have encountered. Because the more we advance our knowledge in molecular neurobiology, the more we realize that CREB plays a pivotal role in the response of neurons to external stimuli. CREB is a transcription factor. This means that it participates in the control of gene expression at the level of transcription, i.e. the production of RNA

complementary to a strand of DNA. Transcription factors bind to specific DNA elements in the promoter (the region that binds or facilitates the binding of RNA polymerase, which is the enzyme that synthesizes RNA), or in other regions that control transcription (e.g. enhancers; Lewin 1994). These elements, because they permit a gene to respond to regulatory factors, are called "response elements". Multiple families of response elements are known. Genes are controlled by the same or different families. One type of response elements is cAMP-response elements. One type of response elements is CRE (cAMP-response element). It mediates transcriptional regulation in response to altered levels of the intracellular signal cAMP (cyclic adenosine monophosphate). CRE is found in the promoter region of many genes. A related element is ATF (activating transcription factor element). Therefore the terms CRE/ATF, or CRE-like elements, are also in use. CREB binds to CRE, and is a member of the CREB/ATF family of transcription factors. Multiple genes encode these transcription factors, and

alternative splicing yields an even larger numbermemory research (Silva et al 1998). In recent years, factors.

multiple lines of evidence have shown that: (a) the

All the members of the CREB/ATF family have in cAMP cascade is stimulated in learning (*Aplysia* their carboxy terminus a conserved $\text{\textcircled{O}}$ leucine zipper $\text{\textcircled{O}}$ rosophila), and (b) *protein synthesis and modulation dimerization domain (i.e. a stretch of amino acids with ion of gene expression are required for *consolidation. interspersed residues of the amino acid leucine, whichCREB links these two lines of evidence. The first to interacts with a $\text{\textcircled{O}}$ zipper $\text{\textcircled{O}}$ in another polypeptide to forimplicate CREB in neuronal *plasticity were Datsal a dimer), juxtaposed to a DNA-binding domain rich in (1990), in Aplysianeurons. Subsequent studies in a basic amino acids (Brindle and Montminy 1992; variety of species have indicated that the involvement Sassone-Corsi 1995). Different CREB/ATF transcript-of CREB, and CRE-regulated gene expression in gen- tation factors are able to heterodimerize with each othereral, in neuronal plasticity and memory formation, is in certain combinations. Proteins that bind to CRE act possibly universal, and that CREB activation is corre- as both activators and repressors. For example, CREBated with, and necessary for, the formation of *long- CREM (CRE-modulator, alternatively spliced variant term memory (e.g. Bourchuladze et al 1994; Bartclet), and ATF1 are transcriptional activator, whereas al. 1995; Yinet al 1995; Bito et al 1996; Impey et al CREB-2 and CREMantagonize cAMP-induced tran- 1996, 1998; Guszowski and McGaugh 1997; Lamprecht scription. Unless otherwise specified, the common et al 1997)? The experience-dependent balance usage of the term CREB in memory literature refers tobetween the activator and repressor isoforms of CREB the activator form.

may be critical in determining the fate of a memory. On

At this point molecular biologists may already feel the one hand, it could switch on very fast acquisition that they have taken enough revenge on psychologists and consolidation of robust long-term memory (Yeh in the contest for the most graceless terminology. Yet al. 1995; *flashbulb memory). On the other, it could what should interest us is not the competition between culminate in the suppression of memory storage scientific *cultures, but rather the relevance of all this (Bartsch et al 1995; Abel and Kandel 1998). to learning and memory. There are many members in The CREB story leads us to the interface of *develop- the CREB/ATF family; unless otherwise indicated, wemental and behavioural plasticity. It is now well estab- will limit ourselves here to the discussion of CREBlished that CRE-regulated gene expression plays a key only. CREB is present in cells under nonstimulated con-part in developing tissues (e.g. Datsal 1996; Liu and ditions, mostly in a nonactivated form (some other Graybiel 1996; Pharet et al 1999). The resemblance of members of the CREB/ATF family are expressed only in CREB-related mechanisms in developmental and adult response to a stimulus, see *immediate early genesplasticity is so striking, that it was used as an argument Appropriate extracellular stimuli activate CREB by in favour of the conceptual *paradigm of long-term- phosphorylating it. CREB can be phosphorylated on memory f growth) (Martin and Kandel 1996; *zeit- multiple sites by multiple *protein kinases. Phosphory- geist). But at the same time, these shared mechanisms lation on residue Serine-133 is critical for activation, imply that we are looking at a very basic *level of cellular and is mediated via an increase in the level of intracellularresponse, which is not unique to learning and memory. lular cAMP and activation of cAMP-dependent protein CREB is probably essential in retaining cellular kinase (PKA; Brindle and Montminy 1992; Sassone-*homeostasis and in the protective response to stressful Corsi 1995), or via an increase in intracellular *calcium stimuli. It is clearly important in promoting the survival and activation of calcium/calmodulin-activated pro- of many types of cells, not only neurons (Finkbeiner tein kinase (Sheng et al 1991; Bito et al 1996; 2000; Walton and Dragunow 2000). The question thus Deisseroth et al 1998)! The phosphorylation and remains what is the relevance of CREB to memory: dephosphorylation of CREB by different intracellular Is the role permissive, supportive, or causal (see signalling pathways provides a mechanism for signa[criterion]? CREB could actually fulfil any of these convergence and *coincidence detection (e.g. Perkintorroles, depending on the physiological and molecular et al 1999). Phosphorylated CREB binds to the CREB-*context. Understanding the functional implications of binding protein, recruits other components of the the fine tuning of the CREB machinery, might also cast transcription machinery on the promoter, and initiates light on pathological conditions in which neuronal transcription, e.g. of other transcription factors (Figure homeostasis and plasticity malfunction. Such condi- 22).

tions could contribute to neurodegenerative disease

It is this initiation of transcription in response (*dementia). Future drugs that target CREB might to cAMP that has placed CREB in the spotlight of hence find multiple uses, including neuroprotection, the

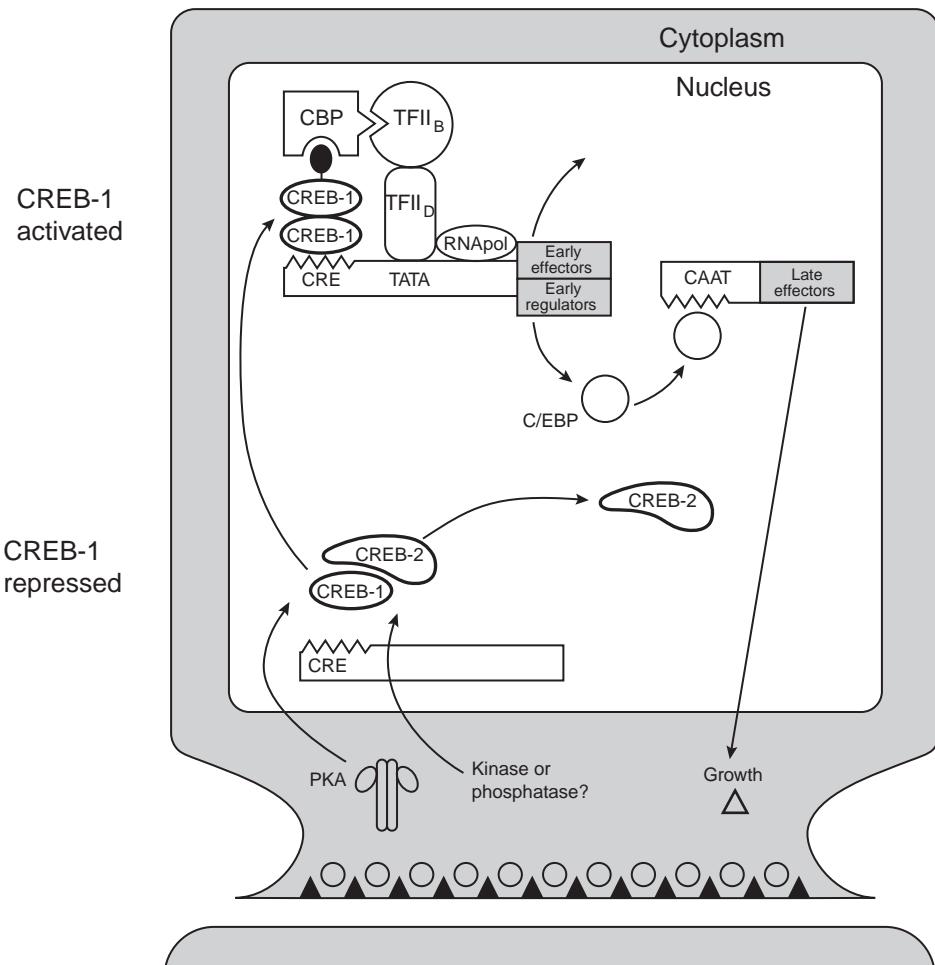


Fig. 22 A highly simplified scheme of the proposed mechanism by which CREB regulates modulation of gene expression and growth processes that accompany long-term use-dependent neuronal *plasticity. The box represents a pre-synaptic terminal; membrane is across the synaptic cleft at the bottom. CAAT, or \AA CAAT box \AA , a conserved nucleotide sequence located upstream a gene transcription unit, recognized by a variety of transcription factors; CBP, CREB-binding protein; C/EBP, \AA ATC \AA CREB, cAMP response element; CREB-1, CREB-2, activator and repressor isoforms of CREB, respectively. CREB-2 is here depicted as CREB-1, for simplicity; PKA, *protein kinase A, the cAMP-dependent protein kinase; RNApol, RNA polymerase, an enzyme that from a DNA template; TATA, or \AA TATA Box \AA , a conserved nucleotide sequence that may be involved in positioning RNApol for TF B ; TF B , general transcription factors. According to this scheme, the balance between the activator and repressor isoforms of CREB is regulated by a variety of intracellular signal transduction cascades (of which only the one involving cAMP is partially depicted determines whether remodelling of the synapse will indeed take place. Hence, certain combinations of inputs could lead to long-term memory, whereas others may not, or could even abort memory at its outset. This property may pave the way to novel specific memory-blockers that target CREB and might be used, for example, in treating some types of trauma (e.g. *fear conditioning). (Adapted from Carew 1990)

blocking of undesired memories (*lotus), or the enhancement of desired ones (*nootropics).

Selected associations: Consolidation¹ Immediate early genes² Protein synthesis³ Reduction⁴ Spaced training

¹CREB should therefore better be termed \AA cAMP/calcium response element-binding protein \AA .

²For a dissident claim that the role of CREB in neuronal plasticity is however, dispensable, see Fink (2000).

Criterion

1. A standard by which something is judged.
2. A condition considered **a priori* to provide reliable evidence for something else.

Meaning ‘standard’ in Greek, ‘criterion’ was advocated in **Aplysia* with behavioural ‘sensitization’ already by Plato, in a very capitalistic connotation: ‘You’ (Castellucci and Kandel 1976) was of the first order; but success, I admit, is fine evidence of the wisdom of the correlation of the molecular changes that take place in present generation as compared with their predecescultured **Aplysianeurons* with the sensitization is of a sors, and it is a popular sentiment that the wise manhigher order, as the events in the culture are correlated must above all be wise for himself; of such wisdom thewith the synaptic facilitation rather than directly with criterion is in the end the ability to make the most the behaviour (Sun and Schacher 1998). Correlation is a money (Hipp. Ma283b). Although to the naive mind very popular criterion, and at the same time a rather the mere notion of ‘criterion’ may look straightforwardweak one. Phenomenological correlation does not to philosophers it poses a real problem. Consider thenecessarily imply mechanistic correlation. A common following statements: in order to reach the conclusion correlative fallacy is the post hoc argumentation post that one knows a thing, one must posses criteria for the hoc ergo propter hbatin for ‘after this hence because of instantiation of that thing; but in order to know the this’), which argues that because one event was corre-criteria, one must already know what the thing is. This later in time with another, the second happened Catch-22 situation is termed ‘the problem of the crite-because of the first. Correlation nevertheless is a useful rion’. It has haunted philosophers since ancient timesguideline for the design of further experiments intended and even brought the Greek sceptics to conclude that to establish more stringent criteria (see below). we know nothing for real because the aforementioned 2. Similarity. Sometimes phenomenological similarity statements are both correct (Amico 1993). Not surpris-is used to conclude that a process or mechanism are ingly, ‘the problem of the criterion’ was dubbed as ‘related to learning and memory. For example, some of the most important and difficult problems in philos- authors promote the claim that ‘long-term potentiation ophy’ (Chisholm 1982). Modern epistemology andplays a part in memory because it displays properties philosophy of language are occupied with various facetsexpected of memory, such as ‘persistence following a brief of the meaning and use of criteria (e.g. see discussion istimulus, *associativity, order-dependency in associativ-Glock 1996). For our purpose, before taking a muchity, and localization in brain regions assumed to subserve more limited yet pragmatic attitude, suffice it to note memory (see in Dudai 1995). Such similarity is appealing, that a criterion provides indication that something is but could be misleading. Furthermore, there is no reason the case (definition 2), but unless specifically qualifiedto assume that parts of a whole should display the proper-as such, its satisfaction does not entail the occurrence dies of the whole and vice versa, hence that the molecular what it indicates. and cellular devices should display the properties of the

Now to the pragmatics. The fact that ‘criterion’ stillbehaving organism (e.g. Bechtel 1982; ‘reduction). debates among philosophers should not discourage 3. Usefulness. Are the mechanisms or processesful neuroscientists from using qualified criteria as power-for memory? There are two versions to this criterion. ful tools in experimentsand ‘models. Suppose we were The first is ‘Pragmatical usefulness’, i.e. can the proces to contemplate an elementary and pressing problem inor mechanism be used in an experimental protocol to memory research, namely, the relevance of neurobio-induce learning-related alterations in a given prepara-logical observations to learning and memory (Dudai tion. For example, serotonin is useful in inducing presy-1994b). Attempts to address this issue can benefit fromaptic facilitation in **Aplysia* (Sun and Schacher 1998), application of a number of criteria, which refer to the and ‘acetylcholine in inducing lasting plasticity following.

1. Correlation Some biological models of learning 1990), supporting the notion that these ‘neurotrans-and memory are proposed, at least at the time of theimitters play a role in memory. Experiments of this kind inception, on the basis ofrelationin space or time of occasionally merge with an attempt to demonstrate that certain biological observations with the behavioural the manipulated agent is sufficient to induce the change phenomena of learning and memory. In practice, the (see below). A second version of the usefulness criteria

correlation may be of the first or higher order. It is of the first order if the molecular, cellular, or ‘system phenomenon is directly correlated with learning and memory. It is of a higher order if the phenomenon is correlated with another intermediate phenomenon, which itself was earlier correlated with learning and memory. For example, correlation of synaptic facilita-

is Ôconceptual usefulnessÕ, i.e. can the implicated mechanism be productively incorporated into models of brane reflex in the rabbit (Thompson et al 2000); and learning and memory, leading to a more coherent microstimulation of visual cortex in order to alter the model and new testable hypotheses. An example is probebehavioural response of the behaving *monkey (Groves et al 1997). Considering the number of variables involved in any brain function, it is rather unlikely that a *protein kinase into models that attempt to explain the single molecular or cellular event will suffice to induce persistence of use-dependent *plasticity in neurons that encode memory faithfully. Nevertheless, activation or inhibition of key Ômolecular switchesÕ, such as CREB, could be suggestive, but does not prove that the process have substantial behavioural effects.

mechanism involved do play a part in learning and memory in vivo

4. Necessity

Is the mechanism necessary for learning and memory? The *methodology here is to intervene inof CREB to dare to hint that the manipulated cellular the physiological process and infer normal function process plays an exclusive part in memory consolidation from dysfunction. This is an extremely popular (e.g. Yin and Tully 1996). Again, as in the case of the approach. Many types of intervention are possible, criterion of sufficiency but even more so, the question is involving anatomical lesions (Glassman 1978), mutations (*neurogenetics), or pharmacological agents (e.g. specificity of mechanisms and parallel pathways appear to Morris et al 1986; Bermant et al 1998). Many examples be the rule in the brain systems that subserve learning. for each of the above are mentioned throughout this book. The types of caveats that typically arise involveable and useful in multiple domains of memory post hoc argumentation (see ÔcorrelationÕ above), doubt research. Here is another central question that calls for about the specificity of the intervention, and the the formulation of criteria: How should one delineate possibility that the effect of the lesion is masked by and classify memory systems? (Shettleworth 1993; compensatory mechanisms in vivo

5. Sufficiency

Does the mechanism sufficient for memory formation? In practice, this criterion is more difficult to satisfy than the previous ones. It requires mapping candidate loci of the *engram. The methodology involves mimicry experiments, resembling those mentioned in 3

above. It is common practice to infer that if event A is both necessary and sufficient for event B to take place, then B is caused by A. The following examples illustrate the use of this criterion: induction of conditioned phototaxis in the mollusc Hermissenda by altering membrane properties of photoreceptors vivo (Farley et al 1983); microinfusion of the neurotransmitter octopamine into the brain to show that octopamine encodes the unconditioned stimulus in *classical conditioning of the *honeybee (Hammer and Menzel 1998); a similar experiment with serotonin and long-term facilitation in Aplysia (Sun and Schacter 1998); switching on *glutamatergic N-methyl-D-aspartate *receptors in the *mouse in an attempt to prove that this receptor is crucial in *consolidation (Shimizu et al 2000); induction of long-term memory in Aplysia/Drosophila, or the honeybee by activation of the cyclic adenosine monophosphate *intracellular signal transduction cascade, *CREB, and modulation of gene expression (Yin and Tully 1996; Muller 2000); reversible inactivation of the *cerebellum and brainstem pathways to show that they are necessary task.

and sufficient for conditioning the nictitating mechanism be productively incorporated into models of brane reflex in the rabbit (Thompson et al 2000); and learning and memory, leading to a more coherent microstimulation of visual cortex in order to alter the model and new testable hypotheses. An example is probebehavioural response of the behaving *monkey (Groves et al 1997). Considering the number of variables involved in any brain function, it is rather unlikely that a *protein kinase into models that attempt to explain the single molecular or cellular event will suffice to induce persistence of use-dependent *plasticity in neurons that encode memory faithfully. Nevertheless, activation or inhibition of key Ômolecular switchesÕ, such as CREB, could be suggestive, but does not prove that the process have substantial behavioural effects.

6. Exclusiveness

The most demanding criterion is exclusiveness. Such a claim cannot be currently made for any candidate mechanism in learning. Some discussions lead us back to the good old philosophical Ôproblem of the criterionÕ, even if this problem is not explicitly stated

(see Sherry and Schacter 1987).

Selected associations: MetReductionSystem

An example of the use in learning experiments of a generic type criterion that fits definition 1, is Ôlearning to criterionÕ in *acquisition

This inference is not a given. Some philosophers will raise the possibility that B is merely ÔsupervenientÕ upon A. Briefly speaking, ÔsupervenientÕ, or ÔconsequentialÕ attribute comes along in addition to other attributes but is not necessarily entailed by them (Kim 1998; Davidson 1980; Hare 1984; *reduction). This is not an argument commonly employed by brain scientists. It does come up in discussions that concern the mind/body problem.

Cue

1. That aspect of the *stimulus that guides behaviour.

2. That aspect of the stimulus that distinguishes one stimulus from another in a discrimination task.

Cue

3. A stimulus that signals the need to respond.

4. A stimulus that triggers *retrieval.

ÔCueÕ originated in the medieval theatre, and is the spelled name of the letter q, the abbreviation *quendam*, Latin for ÔwhenÕ. For a while it was also spelled qu or qn. It meant a signal that prompts another event in the performance, such as the entrance of an actor (Harrison 1998). Cues fulfil fundamental roles in all the paradigms and assays of learning and memory. Definition 1 is the generic one. It refers to both learned and innate (**a priori*) cues. Definitions 2–4 are also presented because they express particular uses of ÔcueÕ in the learning literature. Definition 2 specifically refers to cues as discriminators, a particularly useful notion in *instrumental learning situations, and also in ethology (Tinbergen 1969). Definition 3 marks cues as the timing signal, again, particularly useful in instrumental tasks (for an example of ÔcuesÕ per definitions 2 and 3 see Figure 23). Finally, definition 4 refers to cues as triggers of retrieval. The role of cues in retrieval is more critical than usually meets the inexperienced eye: an influential hypothesis that binds *acquisition, *context, retrieval, and *forgetting, termed Ôthe encoding specificity principleÕ, proposes that memory is retrieved better when tested in the presence of the same cues that were present in acquisition (Tulving 1983).

Cues could be external or internal. External cues are not only those provided by the experimenter, but also those that the experimenter erroneously ignores. The latter are cues in the seemingly *controlled stimulus and context, including the behaviour of the experimenter (*bias, *Clever Hans). Internal cues are endogenous states of the organism, including circadian rhythms, which, again, are too often neglected in behaviour-control by a conditioned stimulus (CS) due to the journal experiments.

An important thing to remember about cues is that they are seldom invariant over an experiment or across subjects, even if the particular stimulus is kept constant. The behavioural significance of stimuli, their ÔcuenessÕ, is altered by the experience of the subject. Overconditioning is a trivial statement because this is simply learning that fact a trivial statement because this is simply learning that the physiological and external context, including the presence of other cues, which is much less salient than the conditioned stimulus (US) or the *reinforcement. Two subjects, even if the particular stimulus is kept constant, the behaviour shrinks with training; this is called Ôcue reductionÕ. Another important subset of stimuli making up the compound act upon different processes is called Ôcue competitionÕ (Wasserman and Miller 1997). This refers to inhibition of the behavioural

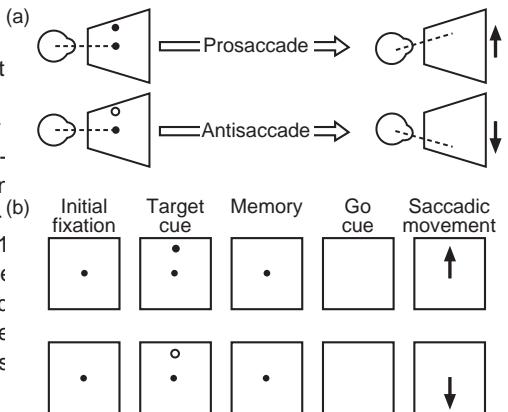


Fig. 23 Types of cues in an experiment of visual learning in the monkey (Zhang and Barash 2000). (a) The monkey was trained to make brief, rapid eye movement (a saccade) either toward the stimulus (prosaccade) or in the opposite direction (antisaccade). This was done in the course of the analysis of neuronal correlates of visual decision-making and performance in the posterioparietal *cortex, but for our purpose, only the behavioural part of the experiment will be mentioned. (b) The monkey was placed in front of a computer screen, trained in successive stages (ÔshapedÕ) to fixate on a stimulus at the centre of the visual field. A coloured stimulus, either red (full circle) or green (open circle), was then presented for 250 ms away from the fixation point. The colour was the Ôtarget cueÕ, instructing the monkey which type of saccade should be performed at the later part of the task (definitions 1 and 2). After an additional working memory interval of 1 s, the fixation stimulus disappeared. This signalled to the monkey to make the response (the ÔGOÕ cue, definitions 1 and 2). A prosaccade if the target stimulus was red, antisaccade if it was green. A proper response was rewarded (*reinforced) with juice. (Adapted from Zhang and Barash 2000.)

the others^{b(d.)}. An example of overshadowing in representations of the associated stimuli. Hence in this instrumental conditioning was provided by Pearce and respect, the cues have provided a valuable cue to the Hall (1978): two groups of rats were trained to press amechanisms underlying conditioning.

lever for food. In one group, the delivery of the food was always preceded by a brief flash of light. In the other group, the light was uncorrelated with the food. In the test, the rats that had experienced the light^Dfood corre-

lated schedule pressed the lever at a slower rate than those trained under the uncorrelated light^Dfood sched-

ule. The authors concluded that pairing the light with food retarded the development of normal instrumental

conditioning, because the light was a better predictor of

the food, and therefore the stimulus^Dreinforcer associa-

tion overshadowed the formation of the response^Dmaterial artefacts, regulations and procedures,

reinforcer association. The literature contains many *habits, rituals, and beliefs, created over time by a

other examples of overshadowing in classical andsociety or a group, and usually transmitted, both

instrumental conditioning.

Blockings inhibition of the conditioning to a stimu-

lus, CS, in a compound CS+CS₂ stimulus, by previous

pairing of CS₂ with the US (Kamin 1968). In a classical Cultura in Latin meant tilling and husbandry, and

experiment, Kamin iþid.) used a conditional emo-

culturwas a planter, inhabitant, and worshipper of gods

tional response procedure (*fear conditioning). Rats (Cassell^DConcise Latin dictionary1966). In modern

were trained to press a bar for food, and upon master-society, the agricultural connotations of culture are

ing the operant task, were further conditioned to asso-largely gone, but the sense of belonging to a physical or

ciate a CS with a fear-inducing US (electric shock). Thevirtual niche remains; some kind of worshipping, be it

fear response resulted in suppression of bar pressing ireligious or secular, is also often retained. So versatile are

response to the CS. This was observed regardless ~~the~~ uses and implications of ÔcultureÕ, that dictionaries

whether the CS was light, white noise, or a compoundgive up on defining it in a comprehensive manner. ÔCul-

stimulus of both. But in the consecutive phases of thetureÕ is widely discussed from different points of views in

experiment, an interesting phenomenon emerged. anthropology, sociology, archaeology, history, political

When the rats were first conditioned to fear the noise,science, critical theory and aesthetics, philosophy, ethol-

then conditioned to the compound stimulus, and thenogy, and sociobiology (Kroeber and Kluckhohn 1963).

tested on the light, they showed essentially no fear Three aspects of culture should interest us in the

response to the light. A similar phenomenon was notedcontext of the present discussion. The first is culture as a

when the animals were first conditioned to the light, process and vehicle for the transfer of information by

then to the compound stimulus, and then tested on the behavioural means. This involves a number of channels,

noise. Thus prior training to an element of the com- such as instruction via *observational learning, or cul-

pound stimulus blocked conditioning to the new, tural artefacts. A common manifestation of culture is

superimposed element. The interpretation is that in *collective memory. The two, although related, should

order for an association between a CS and a US to ~~be~~ confused. Members of a group can share a collec-

formed, the US must *surprise the animal. If the animal tive memory but belong to separate cultures. Culture

already knows that CSpredicts the US, addition of CS₂ also includes material artefacts as well as contemporary

does not involve much additional surprise, and there- institutions, regulations, and beliefs that do not neces-

fore association of CS₂ with the US is weak. (On the role sarily make it into the collective memory of the group.

of the unexpected in learning, see also *algorithm; onFurthermore, certain social species in addition to

additional aspects of blocking phenomena; see Miller*Homo sapiensare said to display rudiments of culture

and Matute 1996; Holland 1988.) (Bonner 1980; Whiten et.al1999; *birdsong, *monkey),

The analysis of Ôcue competitionÕ has contributed ~~but~~ it is doubtful whether the members of any of these

the compelling evidence that even apparently ÔsimpleÕspecies share even a rudimentary collective memory, in

forms of classical conditioning are actually manifesta-terms of sets of historical narratives and beliefs.

tions of rather complex information processing in the

brain, which involves interactions among the *internal to us here relate to certain anthropological and

Selected associations: Attention Clever Hans Context
Recall Stimulus

Culture

The collective body of institutions and traditions, material artefacts, regulations and procedures, implicitly and explicitly, from one generation to another.

another. Cultura in Latin meant tilling and husbandry, and culturwas a planter, inhabitant, and worshipper of gods society or a group, and usually transmitted, both implicitly and explicitly, from one generation to another. The virtual niche remains; some kind of worshipping, be it religious or secular, is also often retained. So versatile are the uses and implications of ÔcultureÕ, that dictionaries give up on defining it in a comprehensive manner. ÔCultureÕ is widely discussed from different points of views in anthropology, sociology, archaeology, history, political science, critical theory and aesthetics, philosophy, ethology, and sociobiology (Kroeber and Kluckhohn 1963). The two, although related, should not be confused. Members of a group can share a collective memory but belong to separate cultures. Culture includes material artefacts as well as contemporary institutions, regulations, and beliefs that do not necessarily make it into the collective memory of the group. The two other aspects of culture that are of interest are said to display rudiments of culture and monkeys, respectively. (Bonner 1980; Whiten et.al1999; *birdsong, *monkey),

The analysis of Ôcue competitionÕ has contributed ~~but~~ it is doubtful whether the members of any of these the compelling evidence that even apparently ÔsimpleÕspecies share even a rudimentary collective memory, in forms of classical conditioning are actually manifesta-terms of sets of historical narratives and beliefs.

tions of rather complex information processing in the brain, which involves interactions among the *internal to us here relate to certain anthropological and

sociological aspects of the concept. More specifically, to book-of-the-month shelf (for a few refreshing exceptions, of which brain and memory research are examples, see Brenner 1997; Weiner 1999; also some of the prominent part, as a culture, and to the interaction of chapters in Hodgkin et al 1977).

this culture with the rest of culture.

The culture of any scientific discipline, memory

For Geertz (1983), culture was the "webs of significance" research no exception, could be depicted as a collection of man himself has spun and in which human conceptual, pragmatic, and ritualistic attributes that beings are "suspended". These webs are composed of partially shared with other scientific disciplines. multiple types of threads, some material, some mental. They range from the philosophical to the mundane. In the world of science, "culture" is hence the physical. The philosophical include, among others, the elements procedural, intellectual, and emotional milieu, or "webstory", universal sets of the scientific methods and of significance, in which scientists are entangled during criteria. These themselves are cognitive-cultural constituents if not all their waking hours, and frequently also structures. Being so, and to the justified dismay of scientists during the rest of the day. The notion that there are two cultures, that of scientists and that of target for vicious attacks by the so-called "postmodern literary intellectuals" or "humanists" (Snow 1963), who seem to capitalize on the inherent fallibility turned over the years into a given in popular discourse of the senses and the cognition of the human individual on modern society. The question can be raised whether, yet utterly ignore the built-in safeguards that the split in the intellectual community is indeed so scientific *system as a whole has painstakingly devised deep; whether it is inherently so or due mostly to to hold a grip on reality, as well as the great successes of mutual laziness; and, moreover, whether it is static. But science and technology (for minute glimpses into these clearly, in daily life, scientists do have their typical issues, see Midgley 1992; Gottfried and Wilson 1997). dialects, *methods (not necessarily generalizable to Other attributes of the scientific culture are on the many facets of life), rituals, and worries, which also more mundane side and include laboratory practices together justifies their classification as members of a separate culture. Furthermore, within science, many overtime, lengthy seminars, international meetings, separate subcultures could be discerned, according to workshops, lecture and poster habits, manuscript and the discipline and subdiscipline.

reviewer routines, worries about priority (*scoopophobia)

As far as the scientific culture in general is concerned (dia), etc. Whoever wishes to taste these facets of the scientist one of the most intriguing issues is indeed its interactive culture and never did, is cordially invited to mingle with society at large. This has been the topic of with the crowd in the yearly meeting of the American numerous novels and movies, too many of which depict the scientist as a dangerous lunatic or a weirdo at best (prescription for agoraphobia). And then there are those (Haynes 1994). The interaction of science and society more specific elements of the culture of memory including its potential futuristic outcome, has occasionally been the topic of works of letters composed by better, subcultures—those of the physiologists and their distinguished members of the scientific culture (e.g. electrodes, the molecular biologists and their clones, the Haldane 1923; Skinner 1961). And, of course, it is also geneticists and their mutations, the psychologist and the subject matter of serious academic work (for another *subjects, the neurologists and their *amnesics, the introductory selection of scholarly themes and stands, computational people and their *models, etc., etc. see Olby et al 1990; for a provocative point of view, see Midgley 1992; and for a recent view concerning the idiosyncrasies of unwritten science—society contract, see Gibbons 1990), and folklore, a major obstacle to intercultural and

But there is another aspect to the culture of science—sometimes even to intracultural communication is the which usually gains less publicity. This is the innerlanguage barrier. Not only is the scientific jargon incomprehensible to the nonscientists, it is also frequently gibberish to scientists from other disciplines (for an informative scale of language obscurity see Hayes 1968). In recent years, unfortunately, a few frauds (1992). In this respect, there are two steps that scientists scandals and greed-driven rivalries have also attracted. First, it would be nice to stop using all these non-knows, is less heroic and more complicated thanstop awkward acronyms without explaining them; they depicted by egocentric accounts that make it to the certainly turn into a mission impossible any attempt to

follow seminars or read papers, even in the so-called or facts (ÖsemanticÖ), and memory for episodes general interest journals. How many neuroscientists (ÖepisodalÖ, ÖautobiographicalÖ; Tulving 1983; *episodic memory) can even dare to understand a sentence such as ÖKnowing thatÖ? Episodic memory, and sometimes semantic produces K-ATP in the absence of SURAÖ is memory, single-trial learning, yet could be modified ÖCSBs-CSAs-USs ISIs in DMTSÖ better? Second, it might time, either by additional facts, new experiences, or be useful to recall what Socrates said to Meno (Plato ÖretirementÖ in new contexts. Episodic memory includes Meno, 79c,d):

ÖSocrates Does anyone know what a part of a virtue is, without knowing the whole?

ÖMeno suppose not.

ÖSocrates No, and if you remember, when I replied to you about shape just now, I believe we rejected the type of answer that employs terms which are still in question and not yet agreed upon.

ÖMeno We did, and rightly.

ÖSocrates Then please do the same.

Selected associations: Birds, Collective memory
Homo sapiens, Observational learning, Paradigm

¹For another example related to the molecular neurobiology of memory, see ZENK in *immediate early genes.

memory, single-trial learning, yet could be modified information about an experience locked to a particular time and place, whereas semantic memory is not locked to specific coordinates in these *dimensions. Some authors classify ÖepisodicÖ apart from Ödeclarative (Tulving and Markowitsch 1998). Similarly, in epistemology, Öknowledge by acquaintanceÖ, i.e. of people, places, and things, is distinguished from propositional or factual knowledge (Bernecker and Dretske 2000). The term Öcognitive memoryÖ is also occasionally used for recollection with conscious awareness (Mishkin 1997). ÖExplicitÖ and ÖimplicitÖ (Graf and Schacter 1987; Schacter 1987) are sometimes used in the literature instead of ÖdeclarativeÖ and ÖnondeclarativeÖ, respectively. Others, however, prefer to consider the explicit/ implicit dichotomy to be used in the *taxonomy of learning tasks and memory tests (*assay) rather than for that of memory *systems and mechanisms (e.g. Johnson and Hasher 1987; N.J. Cohen et al 1997)³.

Support in favour of the declarative/nondeclarative distinction has surfaced over the years not only via introspection but also in *controlled experiments in normal individuals (e.g. McDougall 1923; Eriksen 1960; Richardson-Klavehn and Bjork 1988). Yet the evidence that the brain indeed honours this distinction was ultimately provided by the neuropsychological investigation of *amnesia in humans and its *models in the *monkey (Cohen and Squire 1980; Squire and Zola 1996). It has been noted for years that the memory deficits in ÖglobalÖ amnesics are not really global (e.g. Corkin 1968; Warrington and Weiskrantz 1968). A *classic study illustrates this point. Cohen and Squire (1980) subjected amnesic patients to a mirror-reading skill test, involving presentation of mirror-reflected

Declarative memory

1. The *conscious recollection of facts and episodes.
2. The *internal representations of facts and episodes that are accessible to conscious recollection.
3. The memory *system that subserves the above.

The term Ödeclarative memoryÖ, depending on the context of the discussion, refers to a faculty and experienced only once and some were repeated. The reading rience of memory (definition 1), the material stored time of the unique words was used to evaluate the ability to *acquire the procedure of mirror-reading, while system(s) (definition 3). That part of our memory is the reading time of the repeated words reflected, in directly accessible to conscious recollection but part is addition, the ability to remember specific data. Amnesic not, was first explicitly stated by philosophers (e.g. patients learned the mirror-reading skill, as indicated de Biran 1804; Bergson 1908; Syle 1949) formulated as the distinction between Öknowing thatÖ and Öknowing howÖ. Öknowing thatÖ to information that can be used in controls. Furthermore, none of the amnesics ÖdeclaredÖ, i.e. declarative memory reported that the repeated words were indeed encouraged is conventionally further subdivided into memory learned beforehand. Hence, the nonamnesics learned

Declarative memory

both ÔhowÖ and ÔthatÖ; the amnesics only ÔhowÖ. Similar conclusions were obtained in different types of tests. There are three basic approaches to the problem. ÔglobalÖ amnesics, using a variety of tasks that assay investigation in animals of the performance and ÔruleÖ (ÔhowÖ) vs. ÔdataÖ (ÔthatÖ) knowledge (Squire 1996). Some mechanisms of tasks that are declarative in Zola 1996).

The aforementioned data have been taken to indicate that amnesics can acquire nondeclarative information, human amnesia (e.g. Zola-Morgan and Squire 1985; and that mediotemporal brain structures damaged in Clark and Squire 1998; Manes et al 2000; *monkey). ÔglobalÖ amnesics (*hippocampus, *limbic system) also serve declarative memory in humans. Some pure *recognition tasks (see *delay task) could be necessary for declarative but not for nondeclarative memory in this respect. The main problem is that different tasks. But is this indeed due to the existence of different species, even different individuals and the same brain circuits for declarative and nondeclarative information, respectively? The argument could still be raised that declarative and nondeclarative memory are sub-

2. Investigation in animals of the effect on learning served by the same circuits, but there is a general impairment in the processing of information in the diencephalic brain regions that are assumed to subserve declarative memory in humans (Zola-Morgan 1985; Squire and Zola 1996; Mishkin 1997). Here the difficulties of double-dissociation experiments. First, it is unlikely that brain circuits that subserve declarative tasks in humans do only that; the hippocampus A and B, is tested on two different phenotypes, X and Y, for example, is involved in memory with or without (Teuber 1955; *control). If lesion A yields a defect in X conscious awareness (e.g. Chun and Phelps 1999), but not in Y, while lesion B yields a defect in Y but not in X. Second, the same brain regions may fulfil different functions in different species. Further, the rationale risks across-the-board damage but rather to specific damage: a task may be deemed declarative in humans in the dissociable functions of areas A and B, respectively. The ÔglobalÖ amnesics mentioned above show only a Ôsingle dissociationÖ, i.e. lesion A yielded a defect in X but not in Y. For double dissociation, patients were

3. A different approach is to attempt to identify memory systems which are shared by pre-tive tasks. Such patients were indeed identified human manifestations of declarativity. The assumption (Gabrieliet al 1995; Knowlton et al 1996). For example, Parkinson's patients failed on a task that involved prior to the ability of *Homo sapiens* experience and the acquisition of a mental *habit, i.e. nondeclarative express declarativity the human way. This assumption knowledge, in spite of being able to acquire and *retrieve taken by the followers of approaches 1 and 2 above as new declarative knowledge (Knowlton et al 1996).

Furthermore, this identifies the neostriatum, which is it searches for the deep structure of the computational

damaged in Parkinson disease, as critically involved in theory (*level) of the memory system. It is further

nondeclarative, but not declarative, memory.

assumed that ÔdeclarativenessÖ is not necessarily the decision

*Functional neuroimaging methods have further distinctive attribute of declarative memory systems. It reinforced the conclusion that in humans the mediolateral prefrontal cortex has been argued, for example, that the elementary characteristic of declarative memory is the ability to encode declarative memory, in concert with the prefrontal cortex internal representations according to relationships (e.g. Nyberg et al 1996; Wagner et al 1998; Kirchner et al 1997; Eichenbaum 1997). This, so goes the claim, among specific items, and flexibly *generalize and integrate this information in novel situations (N.J. Coleen 1997; Eichenbaum 1997). This, so goes the claim, tributes equally to both episodic and semantic memory, differs from nondeclarative memory, which is more or primarily to episodic memory (Mishkin et al 1997; Squire and Zola 1998; Tulving and Markowitz 1998). Guided by this line of argument, Ôpaired associates tasksÖ

As a hallmark of the expression of declarativeness were employed to tap into inferential, flexible memory. humans is language, the task of identifying declarative paired associates tasks, the subject learns a list of

discrete pairs of associations, denoted generically ADB, declarative or in a nondeclarative mode, and the same is true where typically A is to serve as a *cue for the recall of B information learned explicitly.

or for a response that stems from the recall of B. Paired⁴For example, it could be argued that amnesics are incapable associate learning involves multiple cognitive processes, processing information at a *level that permits proper *acquisition (e.g. McGuire 1961), including acquisition of associa- and *retrieval of declarative information, but still capable of processions among discrete *stimuli and of stimulus-response⁵ing at a ÔshallowerÔ level, presumably sufficient for nondeclarative rules. In humans, ADB could be arbitrary verbal stimuli, memory. On levels of processing in acquisition and retrieval, see whereas in laboratory animals, ADB are nonverbal sen-

sory cues. Hippocampally lesioned animals fail on⁶For the sake of simplicity, no distinction is made here between me some versions of paired associates tasks that tax flexibility of facts and memory of episodes. It is clearly possible that sity of response, for example, on the ability to associate⁷nonhuman species have declarative memory of one type but not paired elements presented in the reverse of training⁸On the hypothetical place of priming in the evolution of memo order (Eichenbaum 1997a). This was taken to support⁹systems, see also Tulving (1983).

the idea that such tasks can be used to test declarative memory in nonhuman species.

A nice spin-off of the flexibility generalization

declarativeness hypothesis is that it is in line with the

classification of *priming as an intermediate stage

between nondeclarative and declarative capabilities, with

repetition priming being less flexible and less generaliz-

able, conceptual priming being more flexible and more

generalizable, yet both still independent of conscious

awareness¹⁰But identification of the flexibility of represen-

tational reconstruction as the core attribute of declarative

memory system is only a working hypothesis. Note that if

primitives of declarative memory independent of con-

scious awareness were to be identified, the definitions of

declarative memory above will have to be modified, origy by Hunter (1913), who found that a variety of species

become a subtype of a more comprehensive definition.

can learn to respond to a light stimulus after a delay,

All this leads us to the question whether the term which in his hands ranged from a few seconds in rats to

ÔdeclarativeÔ is appropriate to be used in animal studies about half an hour in children. The procedures were later

The distinction ÔexplicitÔ/ÔimplicitÔ, despite the aforefined by Yerkes and Yerkes (1928) in their investigation

mentioned occasional claim that it fits tests better thanon mnemonic capabilities in the chimpanzee. Since then,

systems, may be more useful in animal studies, espes a variety of delay tasks have been developed and proven

cially because it does not explicitly refer to Ôdeclarati

highly useful in the measurement of short-term and

tivenessÔ with its linguistic roots and connotations. It*working memory, *recognition, and *recall.

also blunts the need for conscious awareness, which is

Delay tasks comprise an heterogeneous family whose

problematic, especially in *simple systems. We do not

members are united solely by the fact that a delay is

know at which stage of evolution conscious awareness introduced between the stimulus and the opportunity to

has entered the scene (Tulving 1983; Moscovitch 1996espond to it (definition 1).Other than that, these tasks

Eichenbaum 1999). This is definitely an issue in whichcould be used to tax different facets of learning and

the prudent use of *OckhamÔs razor to eliminate supermemory, *attention and motivation, innate response

fluous *anthropomorphism is advisable.

Selected associations: Amnesia, Episodic memory, Hippocampus, Learning, Taxonomy

Delay task

1. A task in which a delay is interposed between a *stimulus and the opportunity to respond to it.

2. A task in which response is guided by an *internal representation of a stimulus in the absence of that stimulus.

Delay tasks were introduced into experimental psychol-

declarative memory above will have to be modified, origy by Hunter (1913), who found that a variety of species

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the prudent use of *OckhamÔs razor to eliminate supermemory, *attention and motivation, innate response

fluous *anthropomorphism is advisable.

¹ÔRecollectionÔ refers here to both *recall and *recognition, see the

²In linguistics, a Ôdeclarative sentenceÔ makes a statement, i.e. informs

someone of something (Winograd 1972; Lyons 1977).

³See also on tasks of implicit vs. explicit learning, under *learning, *learning

many cases, information learned implicitly can later be used either

delayed alternation task. The subject is first rewarded for

Delay task

selecting one of two positions in a response chamber or test. In delayed comparison, additional information or a *maze. This is followed by a delay, after which the monkey must be supplied during the test, involving the correct response is choosing the alternate position. Thus, on of past and present situations. To emit a correct response the subject must remember over the delay that it had responded, the subject must recombine the information responded to position A, and master the rule that he carried over the delay with the on-line test information. next response is B, and so on (*learning set). The examples for delayed comparison tasks are provided by ory used is a combination of recall (of the last response) and delayed matching to sample (DNMTS) and the delayed and recognition (of the situation after the delay). The nonmatching to sample (DNMTS) tasks. Here the same problem with this type of spatially guided delay paradigm stimulus, usually a visual one, is presented and then again is that the subject could adopt a strategy of orient-withdrawn. After a delay, the sample stimulus is presenting toward the correct position while still in the sample sented again along with one or more additional stimuli. phase, hence eliminating the need to rely on the internal representation of the stimulus over the delay (Hunter 1913; Steckler et al 1998a).

(DNMTS). As it is not a spatially guided response to a

Indeed some authors distinguish Ôdelayed responseÓ from Ôdelayed comparisonÓ tasks (Steckler 1998a). In the current situation (compare with delayed spatial alternation above), the subject cannot ÔcheatÓ by orienting In delayed response tasks, all the information necessary for the internal representation of the correct response is available before the delay, and the behaviour could represent a *habit response that only awaits the *cue in the test.

A particularly useful DNMTS task is the unique trial-unique version of this task, each object is seen in only the whole series of tests. The trial-unique nonmatching-to-sample is appropriate for quantifying recognition memory, because an incentive to perform the task, and the ability to associate a specific object with reward does not contribute to the monkey's masters the nonmatching tasks faster than the matching tasks, because it has an *a priori tendency to explore novelty. (Modified and Appenzeller 1987; Dudai 1989.)

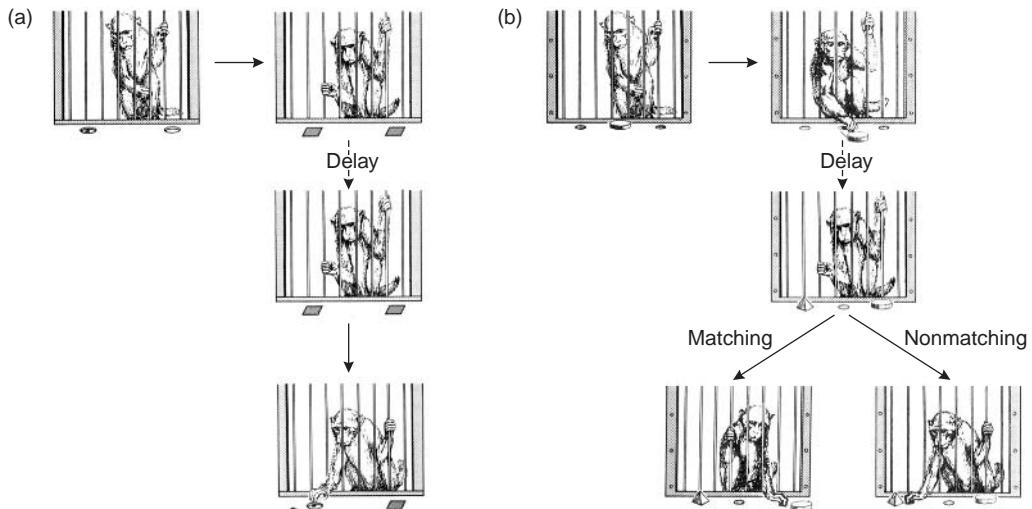


Fig. 24 Delayed response tasks are used to measure object *recognition, visuospatial memory, and working memory. (a) A visual cue is placed in one of the two wells of the cage. Both wells are then covered. After a delay (usually a few seconds or minutes), the monkey has to tell the two objects apart. This measures the ability to remember visuospatial information over the delay. (b) Delayed matching and nonmatching to sample. A conspicuous object is placed over a central reward-baited well. The monkey replaces the object to obtain the food reward. A second monkey is confronted with the same object paired with a new one. In the delayed matching-to-sample task (left), displacement of the familiar object is rewarded. This test measures visual recognition and the association of an object with reward. In the delayed nonmatching task (right), displacement of the nonfamiliar object is rewarded. In the trial-unique version of this task, each object is seen in only the whole series of tests. The trial-unique nonmatching-to-sample is appropriate for quantifying recognition memory, because it provides an incentive to perform the task, and the ability to associate a specific object with reward does not contribute to the monkey's masters the nonmatching tasks faster than the matching tasks, because it has an *a priori tendency to explore novelty. (Modified and Appenzeller 1987; Dudai 1989.)

This paradigm has been extensively used in the analysis of visual recognition in the *monkey. In brief, a monkey (Fuster 1973; Friedman and Goldman-Rakic 1994; *retrieval, is placed in a test enclosure, such as the Wisconsin General Testing Apparatus (WGTA, Figure 24) (Harlow and coworkers 1938), and presented with a visually conspicuous object over a central baited food well. The monkey learns to uncover the well and retrieve the food, indicating that frontal pathology is involved (Pantelis et al 1997).

hide the manipulation of stimulus tray from the monkey, the same object is paired with another, novel ÔjunkÔ object, each presented over a lateral well. The monkey must now avoid the familiar object and displace the new one. The procedure is repeated, with new ÔjunkÔ objects in each trial. As the objects are unique to each trial, no object-Delay taskÔ should not be confused with Ôdelay conditioningÔ, a protocol of *classical conditioning. In delay conditioning, the onset of the unconditioned stimulus occurs after the onset, but the reward here is merely an incentive to perform the test. The results could therefore be construed as representing ÔpureÔ visual recognition combined with the innately dispositioned rule of Ôgo for the new oneÔ. Furthermore, the information from one trial is irrelevant to the next, and therefore this procedure is also useful in tapping *working memory.

Dementia

Selected delay tasks are key components of test batteries used in the analysis of monkey *models of the chronic syndrome of heterogeneous aetiology human *amnesia syndrome (Zola-Morgan and Squire 1985). This is because performance on such tasks include severe memory impairment.

e.g. DNTMS, maps on to multiple features of the amnesia syndrome, including the dependence on the length of the delay, the sensitivity to interference, cognitive deficits that include severe memory impairment and the independence of sensory modality. Attempts have been made to develop reliable DNTMS procedures: aphasia (deterioration of language function); for rodents as well, to facilitate the molecular and apraxia (impaired ability to execute motor activities *neurogenetic analysis of amnesia models, but despite intact sensorimotor function); agnosia (failure interpretation of the behavioural data is still unsettled to identify objects despite intact sensory function); or (e.g. Mumby 1995); it is not unlikely that monkeys will run happily in huge *mazes in memory labs around the world before rats will be able to solve the monkeyÔs cognitive disturbances is *amnesia. Hence demented

Performance on delay tasks is subserved by multiple brain regions, including *cortical and subcortical amnesiasÔ with selective mediotemporal and telencephalic lesions are not demented. Dementia usually displays insidious onset and progressive exacerbation of symptoms. The dementias are differentiated on the basis of their aetiology (Fraser 1987; Edwards 1993; specific, e.g. inferotemporal cortex in vision (Mishkin Knopman 1993; DSM-IV 1994; Larson and Imai 1996). and Murray 1994) or somatosensory cortex in haptic tasks (Zhou and Fuster 1996), whereas the involvement of other cortical regions, i.e. perirhinal and parahippocampal cortex, is modality independent (Suzuki 1993). Visuospatial delayed response tasks rely heavily on frontal function (Jacobsen and Niseen 1937; PickÔs disease; CreutzfeldtÔJacob disease; Mishkin 1957), and the performance on these tasks is complicated by complications of AIDS. The incidence of dementia

increases with age. Estimates for the prevalence result from cholinergic deficits; and that in AD, dementia are 20% at 65 years of age, increasing the number of cholinergic neurons is reduced below 20% at 80 years of age (Joshi 1987; DSM-IV a threshold (<25%, McGeer et al 1984) that is required 1994; Price and Sisodia 1998). Dementias that become minimal cognitive function. This is the cholinergic apparent at 65 years of age are termed *early-onset* hypothesis of dementia. Drugs that increase the available those that become apparent later are *late-onset*. Ability of acetylcholine in brain were introduced as *Osseine*.

cognitive boosters in early stages of AD, so far with

In many societies there is a remarkable shift toward modest success (Giacobini and McGeer 2000; also extended life expectancy. Therefore, diseases of old ageootropics). Actually, nicotine, an activator of some that were rarely encountered only a century ago are now acetylcholine *receptors, may be the only real reason becoming an epidemic. In 1900, less than 1% of the why smokers could justify their addiction (e.g. Di Carlo world's population was over 65 years of age, in 2000, it is about 7%, and the prediction for 2050 is 20%, because smoking reduces pulmonary function, 15-20% (Olshansky et al 1993; Heilig 1997). The main depriving the brain of oxygen and impairing cognition; concern is AD. Named after the physician who first Emery (1997). The beneficial impact of cholinergic described it (Alzheimer 1907), it typically starts with activators on memory is possibly due to their effects significant recurrent lapses of *episodic (*declarative) on arousal, *attention, and *performance (Everitt and and *prospective memory. At first impaired encoding is Robbins 1997), rather than memory per se possibly more significant than increased *forgetting. Another type of potential breakthrough in understanding (Granholm and Butters 1988), and *metamemory is standing AD was made possible by *neurogenetics. relatively spared (Moulin et al 2000). The disease progresses to severe global memory deficits accompanied by other cognitive and emotional disturbances, and AD). Other, late onset variants, occur sporadically in culminates in dissolution of personality and inability to perform even the simplest of tasks (McKhann et al 1984; DSM-IV 1994). AD destroys the hippocampal formation, neo*cortex, basal forebrain, and additional brain organs and circuits. The affected brain displays two distinguishing pathologies: extracellular plaques (Sisodia 1998). To date, familial AD has been linked to and intracellular tangles. The plaques are extracellular mutations in three genes, that encode APP, presenilin-1 deposits of aggregated insoluble fragments of protein (PS1) and presenilin-2 (PS2). APP is the amyloid (peptides), called the amyloid peptides (AP). The precursor protein mentioned above. The presenilins A Ps are cleaved by enzymes, secretases, from the extracellular membrane proteins thought to affect the activity of cellular segment of a larger membrane protein, the secretases that act on APP and lead to accumulation amyloid precursor protein (APP), which normally plays a role in cell-cell and cell-matrix interactions. Tangle gene, encoding apolipoprotein E (ApoE), is related to are intracellular deposits of hyperphosphorylated tau the aetiology of AD. Together with other lipoproteins, constituents of the cellular skeleton (Kosik ApoE plays a part in the metabolism and transport of 1994; Edelberg and Wei 1996).

cholesterol and triglycerides. One of its forms, ApoE4,

We do not yet understand AD, but some candidate has been associated with increased susceptibility to cellular clues are already available. One line of incriminating evidence points to the severe loss of cholinergic neurons (i.e. neurons that secrete *acetylcholine) that is mutations that comprise a risk factor in AD has led to a detected in the basal forebrain of AD patients (Bartus et al 1982; McGeer et al 1984). As acetylcholine is produced to subserve widespread cognitive functions, the human AD pathology must yet be established (e.g. Janus hypothesis was raised that cholinergic dysfunction is set al 2000).

the cause of dementia. Furthermore, as there is some So what triggers AD? Some authors trust that the decline in cholinergic function even in normal ageing amyloid cascade is to be blamed (Hardy 1998). subjects, the suggestion was further made that others favour the idea that the pathology is initiated dementia, including modest, benign senile dementia elsewhere, and that the plaques and tangles ensue. It is

noteworthy that in the mouse, a genetic trick that reduces nerve growth factor and basal forebrain cholin-

Development

ergic activity, gave rise to age-dependent appearance of amyloid plaques and neurofibrillary tangles in the cortex and hippocampus (Capsoni et al 2000). This

1. Progression over time of a *system from one state to another according to a programme.

raises the possibility that lack of growth factors induces AD-like neurodegeneration. However, again, the relevance to the human disease is unclear. Such research is

2. Progression over time from nonspecialized to specialized structure and function.

of great interest not merely because it is expected to explain how AD happens, but also because it could

3. Progression over time from simpler to more complex structure and function.

identify drugs to prevent the catastrophe. Interestingly,

Biological development- voloperold French for

tory response to plaques, tangles, and neuronal degeneratio (Rogers et al 2000), has recently gained renewed specialization of cells and tissues. This is accompanied interest: certain nonsteroidal anti-inflammatory drugs by a change in the functional capabilities of the organ- retard the symptoms of AD (Giacobini and McGeer 2000). After all this sophisticated molecular biology, include modification of learning capabilities (Marcus we may end up swallowing aspirin to combat senility et al 1988; Hartshorner et al 1998; Stanton 2000). The (the reader is strongly urged not to regard this as a relationship of development and growth to learning practical advice).

raises some of the most fundamental issues in the neu-

Does AD research contribute to memory research? Sciences, abutting molecular biology on the one hand

To answer that, we must separate memory from *plasticity and philosophy on the other. Among these: how do

ticity. The contribution to memory researcher sees brain circuits achieve their complexity and specificity?

there, but limited. AD is not a memory-specific pathology. In this respect, it is different from the *amnesia of information that is already encoded in the syndrome, or from circumscribed dementias that result from degeneration to localized brain foci (e.g. Graham 1999). Indeed, the analysis of AD does corroborate the operation in development and growth?

\hat{O} Growth and preferential role of the *cerebral cortex, hippocampus and basal forebrain in memory. The observation that in process, to the earlier phases of which we give the one

AD, event memory is typically degraded before factname, and to the later phases we give the other. \hat{O} Memory, and declarative before procedural memory. He was not the first to suggest that. The notion that

provides additional support to the conventional when we learn our neural tissue grows was explicit in *taxonomy of memory systems. But the major contribution of AD research, and dementia research in nineteenth century. Furthermore, some of the propos-

general, is expected to be in the field of *plasticity, als referred specifically to the primary site where including the role of inter- and *intracellular signalling

growth should occur \hat{N} the *synapse, which at that time cascades in plasticity. This is because the common was not even yet known by that name: \hat{O} For every act of

denominator of all dementias might be a catastrophe of memory \hat{E} there is a specific grouping or coordination

neural plasticity (Mesulam 1999; Bothwell and Giniger 2000). Seen this way, dementia could be the heavy price of growths in the cell junctions \hat{O} (Bain 1872, cited in Finger 2000).

We risk paying at old age for our ability to learn so efficiently throughout life.

More elaborate experience-dependent growth theories emerged only later (e.g. Kappers 1917; Hebb 1949), paving the way first to the proposal (Monne 1949), and later to the discovery (Flexner et al 1963;

Agranoff and Klinger 1964; Barondes and Cohen 1966), that de novo protein synthesis, hence modulation of

\hat{O} gene expression, is required for the encoding of long-term memory (LTM).

The function LTM \sim (Growth), where \hat{O} growth \hat{O} is synaptic remodelling, is hence a *paradigmatic tenet of

¹Neurogenetics has contributed in recent years to the identification of risk factors of some other dementias as well (e.g. Garcia and Cleveland 2001).

the current neurobiological *zeitgeist. But it is more system, which may or may not be subserved by specific than that. It also provides a guideline and framework morphological configurations (see *a priori, *internal for experiments on the biological bases of lasting mem-representations). ÔInstructionistÕ and ÔselectionistÕ theory. For if growth is concerned, then the study of the strategies, which refer to multiple spatial and temporal cellular mechanisms of LTM can borrow not only con- *dimensions in the function of the tissue, were pro-cepts but also *methods and data from the study of posed for development and for learning alike (Hebb development. And as developmental processes follow 1949; Pringle 1951; Changeux and Danchin 1976; rules shared by different tissues, organisms and phyla Young 1979; Lo and Poo 1991; Edelman 1993; Marler (Wolpert et al 1998; Fraser and Harland 2000; Scott 1997; Quartz and Sejnowski 1997).

2000), the demarcation line between the mechanisms 2. The level of the *algorithms that implement the specific to LTM and those that occur in other develop-strategy Similar synaptic algorithms are postulated ing tissues that are irrelevant to learning, may be operate in experience-dependent modification in blurred. The implications of this will be further noted development and in adult learning. Foremost in current below. In the meantime, a few generalizations are note theories and *modelling are Hebbian algorithms, or worthy. Similarly to all other tissues (*ibid.*), the develop- their conceptual progenies, including some that restrict ment of the nervous system involves cell division, the plasticity only to Ôcritical periodsÕ (e.g. Bienenstock emergence of pattern, change in form, cell differentiation-1982; *metaplasticity).

tion, and growth. In the process, neurons migrate over 3. The level of the biological mechanisms that imple-dstances from their place of birth to their place of birth the algorithm there again, similar molecular and work, start to express specific gene products, including cellular mechanisms are discovered in development enzymes, *receptors, and *ion channels, form connec-and learning. They involve modulation of gene expres-sions with their target areas, and then establish specification by extracellular stimuli, culminating in tissue synaptic contacts. Even a brief account of each of these modelling (e.g. Corfas and Dudai 1991; Weisstaub families of processes and mechanisms far exceeds the 1995; Davi et al 1996; Martin and Kandel 1996; scope of this discussion (for guides to neurodevelop-McAllister et al 1999; Phan et al 1999; *CREB, *imme-ment, see Jacobson 1991; Goodman and Shatz 1993; Hatten 1999; for comments on the history of the code, *late response genes). Whether the mechanisms discipline, Cowan 1998). Suffice it to note that in prin- are only similar or indeed identical is another story, the ciple, two types of mechanisms work in concert in the conclusion of which is not yet known. For example, formation of functional circuits in brains activity inde- the similarity between experience-dependent synaptopendant and activity dependent. The former are guided by genetic instructions, and usually occur even before the neurons become functionally (Constantine-Paton and Cline 1998). Similarly, the role active. The latter depend on extracellular signals, such as hormones, growth factors, and ions. The interaction require a second thought (Verhaeghe 2000).

between genetics and experience is especially important during certain Ôcritical periodsÕ in development (e.g. number of real or apparent conceptual problems, Katz 1999; *birdsong, *imprinting, *nutrients). which transcend the discussion of the specific neuronal

It is useful to consider the relationship between experience-dependent modifications that take place in 1. The specialization paradox. Definitions 1 and 2 development and those that occur in learning, in terms above leave open the possibility that development may of *levels of organization and analysis.

1. The level of overall computational strategy. Stimuli that result in experience-dependent modifications may either ÔinstructÕ a system to change, or ÔselectÕ. For example, the ÔhardwareÕ version of Ôselection one or a few among multiple endogenous states. These models assume selective elimination of synapses. Yet ÔselectionistÕ strategy has ÔhardwareÕ and ÔsoftwareÕ versions. The ÔsoftwareÕ version proposes that experience selects and stabilizes certain morphological processes, and developmental processes eliminate configurations of the system. The ÔsoftwareÕ version degrees of freedom in the system, is there a paradox only assumes that experience selects and stabilizes? Only an apparent one. First, elimination of alter-certain Ôpre-representationsÕ, i.e. functional states of the system is itself added information. Second, elimination

of synapses does not necessarily undermine the potential to fulfil functional, not to mention representational complexity and capacity of a circuit, because this is also expected to be determined by change in the circuit. With powerful model systems functional synaptic capabilities that could be added in such as cultured *Aplysia* circuits, that could enable development (definition 3). Third, the hardware versionselective lesioning of individual synapses and neurites, of selectionist processes might occur in development—the evidence may soon be provided.

ment but only in some learning systems, e.g. the prepared. The persistence problem indeed LTM (Growth), learning ("birdsong," "imprinting"), and not in others. and given that circuits undergo substantial changes And fourth, synaptic remodelling and growth during with time (e.g. Purves et al 1986; Segal et al 2000): How adult learning may provide the brain with a continuous come memory endures in the circuit spite of the supply of substrates for further, ongoing development.turnover of its components? The solution to this Moreover, in some brain regions new neurons are added problem is discussed under "persistence."

in adulthood (e.g. Gould et al 1999a,b; Shors et al 2001; 4. What makes memory memory? If cellular mechanisms "birdsong," "hippocampus; but see some doubts concerning neurogenesis in the adult mammalian brain, in why not concentrate on development in "simple Rakic 2002). Nobody knows what these new neurons are systems, even in non-neuronal tissues and cell cultures doing there, but one possibility is that they compensate that are much easier to handle than brains, in order for reduced capacity induced by specialization. to understand the formation of memory? This is what

2. Therelevance issue When we do detect growth in some capable investigators try to do. But a caveat is circuits that learn, how do we know that this is at all appropriate. The simple system approach casts some related to memory ("criterion)? Growth and tissue light on "plasticity but not necessarily on "memory. remodelling that are triggered by a training situation The latter, we should remember, is a functional property that may fulfil functions other than learning, such as activity of circuits. Therefore, we should not expect to "homeostasis. At the time of writing, there is not even a decipher the computations and codes that are used, say, single case in which learning-related morphological in a cortical circuit, by analysing development in cell changes in circuits and synapses have been proven. Following the

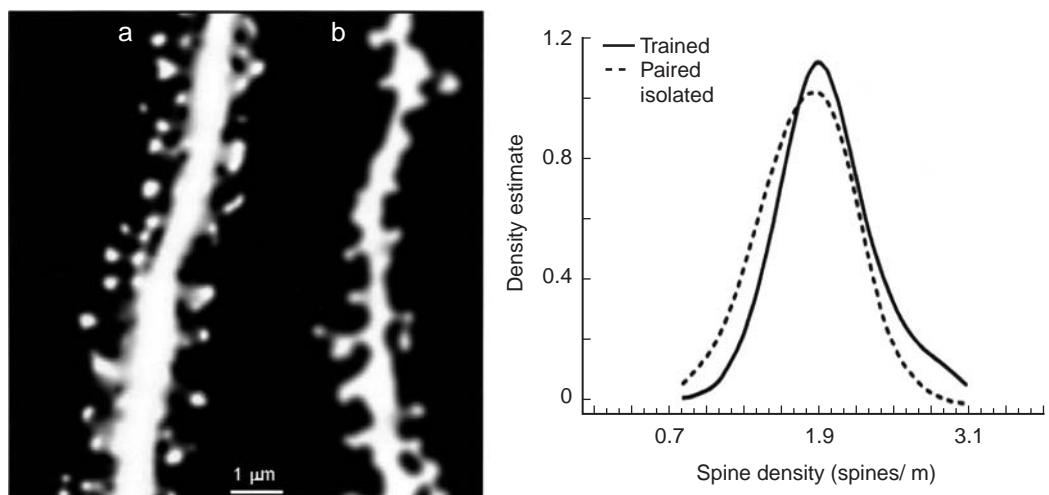


Fig. 25 Ongoing development and growth in the adult brain: The density of dendritic spines in the rat hippocampus is affected by experience. One group of rats was subjected to a complex, stimulating environment that enhanced their ability to learn their way in a maze. Another group was composed of individual rats caged in isolation in a quiet environment, yet another group of rats caged in pairs in a similar boring environment. The picture on the left depicts extremes of variability in the number of dendritic spines in hippocampal CA1 in trained (a) and isolated (b) rats. The graph on the right shows the overall increase in spine density in trained paired rats. Although the overall difference is small, it is significant and may reflect an important effect of experience on the localized growth contacts. Courtesy of Per Andersen; see also (1997) and Andersen and Soleng (1998).

same line of argumentation, even if we understand how itself, we should expect to encounter dimensions that neuronal circuits develop, we cannot hope to grasp their are difficult to grasp intuitively. These may involve contribution to memory and behaviour unless we quantities (e.g. the number of synapses in a human decipher the representations and computations per-brain), complexities (e.g. the spatiotemporal activity formed by these circuits in the subsecond range. This patterns of large *intracellular signalling networks or is clearly a time-scale (*dimension) very different from *cell assemblies), and qualities (e.g. *consciousness). that addressed in the study of development.

Selected associations: Consolidation~~Intermediate~~ early gene~~s~~ late response gene~~s~~ Persistence

Contemplating the dimensions of the research object at the outset of the investigation is always useful. It yields a rough estimate of what lies ahead, assists in focusing on the appropriate *levels of analysis and on the right *methodologies, and even provides a safeguard against certain types of *artefacts. The measures (definition 1) that are within the realm of the ÔmeseworldÕ are a straightforward business: we naturally tend to characterize an object in terms of size, location, or time. Other measures are invisible to the naive eye. These are Ôlatent dimensionsÕ, which could be real or merely useful hypothetical constructs. They may pop out even in the absence of rigorous statistical analysis, although their verification should involve statistics (Martin and Bateson 1993; Kerlinger and Lee 2000).

Alternatively, they become apparent only by factor analysis (Spearman 1904; Thurstone 1947; Kerlinger and Lee 2000). In factor analysis the correlations among variables are used to determine which variables vary of spaces with dimensions higher than the familiar four together and hence could share an underlying factor.

Such factors are candidate dimensions. For example,

ÔDimensionÕ stems from the Latin for Ôto measure outÕ. Definitions 1 and 2 are the ones most relevant to this discussion, which does not (yet?) involve treatment variables of space and time (definitions 3 and 4).

Brains are considered to have evolved in evolution analysis of the results of a battery of common intelligence tests unveils the presence of two major factors, of the universe. It is therefore likely, in spite of occasional sparks of unjustified hubris that claim otherwise, that the individual human brain perceives only limited dimensions of nature, in terms of both properties and with intuition.

magnitude. That segment of our physical ambience that is directly accessible to our senses and has shaped our intuition³ can be dubbed, based on its dimensions, as dimensions of the ÔmeseworldÕ. It refers to properties such as size, number, and location in a four-dimensional space; to mental, and emotion. When appropriate, for each dimension scales of millimetres to kilometres, milligrams to kilograms, seconds to years; and to complexities that are

suberved by processing a few chunks of information at a time. Whatever transcends the aforementioned properties, scales, or complexities, requires *culturally derived technical and conceptual tools for detection, qualification, quantification, and analysis (e.g. Nicolis and Prigogine 1989; Mainzer 1994; Wilson 1995).

Science literates do learn to accommodate in their mind notions of entities such as electrons and atoms, the speed of light, galaxies, and black holes; but whether such dimensions are always assimilated in intuition is open to debate. Similarly, in the analysis of the brain

Let us now illustrate some dimensions of memory. The sample below is highly selective. Some important dimensions are omitted, including level, location and taxonomy; *collective memories may extend over²⁴ This immediately implies that it is naive to expect to find a master solution to the mechanisms of memory. A Ôcognitive beatÕ is 10¹⁰ s. Whether a *stimulus triggers the formation of a memory or not is

determined within 10^{10} s (*attention, *perception, *phase). *Working memory lasts 10^1 s. Cellular consolidation of long-term memory takes place over 10^{10} s; system consolidation in the mammalian brain requires 10^{10} s and possibly even more (Dudai 1996). All this means that critical events in the biology of *acquisition should be addressed by biophysics (Dudai 1997). Practically, most of the current research on acquisition actually addresses events that take place long after initial critical decisions have been made, and some even forgotten. This is especially true for molecular studies, which deal with processes and mechanisms in the 10^{10} s range. These are hence expected to tap after-effects of initial encoding and registration, consolidation, and *homeostasis.

2. Size of the neural machine. The number of neurons expected to encode a relatively simple defensive reflex in *Aplysia is 10^{10} . The minimal number of cortical neurons needed to reliably encode and transmit physiologically meaningful information is estimated to be 10^6 (e.g. Shadlen and Newsome 1998). However, real-life engrams in the mammalian brain are expected to be distributed over much larger numbers of neurons, reaching even 10^{10} , depending on the complexity of the representation (upper estimates are based on *functional neuroimaging; for some estimates from cellular physiology, see Hurlbert and Derrington 1993).

3. Capacity. This is discussed separately (*capacity).
 4. Depth. Introspection suggests that we devote different amounts of mental resources to the acquisition of different types of information. This intuition is supported by systematic research, which shows that

the depth and extent of encoding varies among types of tasks and situations, and further, that this level of processing¹ of the acquired information has much to do with the robustness of retention and subsequent *retrievability (Craik and Lockhart 1972). For example, in verbal tasks, phonetic processing is considered shallower than semantic processing, and semantic encoding commonly results in better retrieval than phonetic encoding. The same applies to depth of processing in sensory perception and in mastering *skill. Depth² is a dimension of memory that has so far been influential in human memory research more than in animal research.

5. Types. The *zeitgeist portrays about a dozen types of memory systems in the mammalian brain (e.g. Milner et al 1998; *declarative memory, *taxonomy). All these systems are expected to have evolved

in response to specific needs and phylogenetic pressures. Although some basic molecular components are shared by multiple systems (*CREB, *immediate early genes, *ion channels, *receptors), the heterogeneity of types renders it again reasonable to conclude that there is no master solution to the mechanisms of memory.

6. Subjective dimensions. The effectiveness of a stimulus is a function of the interaction of the stimulus dimensions (*context included) with the *subject's state. The latter can be measured by subjective dimensions such as arousal, *attention, intention, awareness, familiarity, and expectancy (e.g. Boring 1935; Bermúdez et al 1998; *algorithm, *declarative memory, *learning, *surprise).

*Reductionists are possessed by the search for elementary dimensions. It is useful though to remember that emergent properties are also important dimensions; and, further, that the brain in fact accommodates all the perceived and inferred dimensions within it, and in that respect is omnipotent and dimensionless. This was crisply perceived by Dickinson (1896): ÔThe Brain's wider than the Sky/For I put them side by side/N/The one the other will contain/With one/Nand You/Nbeside/N/The Brain is deeper than the sea/N/For/Nhold them/NBlue to Blue/N/The one the other will absorb/N/As Sponges/NBuckets/Ndo/N/The Brain is just the weight of God/N/For/NHeft them/NPound for Pound/N/And they will differ/Nif they do/N/As Sylable from SoundNÔ.

Selected associations: Cell assembly, Reduction Stimulus-Synapse

¹Definitions 1 and 3 are different formulations of the same idea, so that in practice, the ÔmeasuresÕ in definition 1 are not necessarily independent. Broader, more sophisticated definitions of ÔdimensionÕ have been developed in the exact sciences, but they far exceed the scope of this discussion (Mandelbrot 1977; Greene 1999).

²This argument echoes the Panglossian paradigm, which trusts that natural selection is an optimizing agent (see *paradigm). It is prudent to take into account the possibility that brain and memory systems what they are not only because of adaptation but also because of accumulative structural and functional constraints. This caveat, however, is unlikely to nullify the subsequent assumption in the text concerning the limitations of our brain.

³Intuition³ refers to a fast, mostly innately predisposed system of knowledge about the world.

The potential distinction between the minimal number of neurons obligatory for representing an item and the actual number engaged in representing that item is another issue, the discussion of which exceeds the scope of the present discussion.

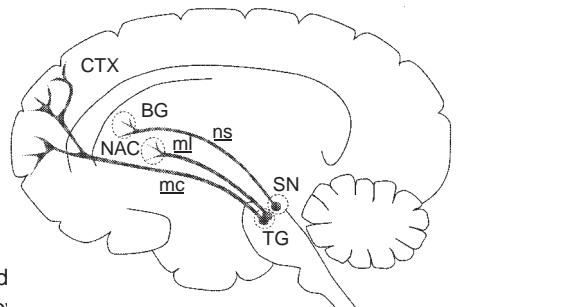
Dopamine

A biogenic amine that functions as a *neurotransmitter in the brain and as a regulator of physiological activity in peripheral tissues.

Dopamine (3,4-dihydroxyphenylethylamine) is the predominant catecholamine neurotransmitter in the mammalian brain. Catecholamines are so called because they are amines (compounds derived by replacing the hydrogen atoms in ammonia with organic groups) that contain the aromatic alcohol catechol. Other catecholamine neurotransmitters and hormones are adrenaline (epinephrine) and *noradrenaline (norepinephrine). The catecholamines in the body are synthesized from the amino acid tyrosine. In fact, till the 1950s, dopamine has been considered merely an intermediate metabolite in the pathway leading to the synthesis of noradrenaline and adrenaline. Only

later was it discovered that dopamine itself is a neuro-release and re-uptake, and its membrane *receptor transmitter (reviewed in Cooper et al 1996). In peripheral tissues dopamine regulates renal, cardiovascular, gastrointestinal, and other visceral functions. To the general public dopamine is known mainly because of its role in Parkinson's disease. This disease is caused by the degeneration of dopamine producing nerve cells in the brain. As dopamine does not penetrate the blood-brain barrier, it cannot be administered to the patient to replenish the brain with the missing chemical. Rather, the disease is treated with L-DOPA (L-dihydroxyphenylalanine), which penetrates the brain and is converted there to dopamine.

A convenient *taxonomy of the dopamine systems in the brain is based on the length of their efferent fibres. An hypothesis that has guided the field for many years now is the *dopamine hypothesis of reward. It systems include the tuberohypophyseal, incertohypothalamic, and medullary periventricular group. Long-range systems originate in dopamine neurons in the ventral tegmentum and substantia nigra and innervate the substantia nigra to the basal ganglia. They project to the substantia nigra via the midbrain tegmental area to some so-called *limbic structures, e.g. the nucleus accumbens (NAC). The mesocortical pathway (mc) projects from the ventral tegmental area to the *cerebral cortex, e.g. frontal cortex. (Adapted from Stahl 1996.)



An hypothesis that has guided the field for many years now is the *dopamine hypothesis of reward. It considers the mid-brain dopaminergic system as a common pathway for encoding the *reinforcing attributes of reward (Wise and Rompre 1989; Robbins and Everitt 1996; Nader et al 1997). The dopamine hypothesis of reward rests on multiple lines of evidence. Its roots could be traced to a *classic set of experiments, in which Olds and Milner (1954) demonstrated that rats self-stimulated certain centres in their brain via implanted electrodes. These reward centres include the mid-brain dopaminergic system. It was later shown that dopaminergic blockers inhibit self-stimulation as well as food-elicited reward (Robbins et al 1974), and addictive drugs, such as morphine, cocaine, amphetamine, and nicotine, increase the activity of mid-brain dopaminergic neurons (Ponti et al 1996; Nestler and Aghajanian 1996).

1997; Robbins and Everitt 1999; Berke and Hymanschizophrenia-linked defects in dopaminergic receptors, 2000). Furthermore, recording of neuronal activity and for specific dopaminergic drugs to ameliorate the from the brain of behaving animals has shown that disease (e.g. Okub et al 1997; Lidowet al 1998). The dopaminergic neurons respond preferentially to dopaminergic hypothesis, however, is only one of the rewarding stimuli (Schultz 1998).

ÖtheoriesÖ of schizophrenia (Willner 1997; Harrison

But do mid-brain dopaminergic neurons actually 1999). By the way, those who find it difficult to think and encode the reward, or do they encode something elselearn under a distracting loud noise, should note that which is required for the actualization of the neuronal this could be related as well to dopaminergic prefrontal and behavioural effect of the *reinforcer? Cellular malfunction: the music in a modest discotheque suffices analysis in the behaving *monkey, engaged in theto push the dopaminergic system in the prefrontal cor-*acquisition and the performance of a variety of *delay tex off balance (Arnsten and Goldman-Rakic 1998). tasks, has shown that dopamine neurons respond to Dopamine could have also played a part in shaping the salient stimuli whose detection is crucial for the one of the hallmarks of human behaviour, namely, learning, but do not themselves encode the reward.novelty seeking. It has been suggested by some authors During learning, the response of these neurons trans-(Benjamin et al 1996; Ebsteint al 1996), although fers from the primary reward to the conditioned, questioned by others (Gelernter et 1997), that reward-predicting stimuli. Moreover, the cellular individuals who persistently seek novelty, owe this response to the reward is highly characteristic: activapersonality trait to a certain genetically determined tion in response to rewarding events that are better thancomposition of subtypes of dopaminergic receptors. predicted, no response to events that are as predictedEven if at the end of the day the role of dopamine in and depression in response to events that are worsenovelty seeking will be proven true, we should not than predicted (Schultz 1998). It seems, hence, that theexpect to become daring adventurers just by swallowing dopamine neurons encode the prediction error of the dopaminergic drugs; as any other complex behavioural reward. Such prediction error drives learning in some trait (*neurogenetics), novelty seeking is probably formal *models (see the RescorlaDWagner model irdetermined by many genes.

*algorithm; *surprise; Schultz et al 1997). This is definitely an impressive example of cross-*level *reductive Selected associations: Algorithm, Attention, Neurotransmitter, Reduction, Reinforcer research, which binds learning theory, behavioural phenomena, brain neuroanatomy, and cellular and

molecular mechanisms. It provides learning theorists[†]The original observation was fortuitous; see *reinforcer. The se with biological tools to test their predictions, and neurobiologists with conceptual frameworks to accommorate their findings.

stimulation studies were replicated in many species, ranging from and chick, via goats, dogs, *monkeys, and dolphins, to humans (O 1969). Luckily, most humans do not normally have the opportunity self-administer electrical pulses to their own mid-brain dopaminer centres, but video games, which release striatal dopamine, co provide a safe substitute (Kempf 1998).

Intriguing and influential as it is, the dopamine prediction-error hypothesis is still only one type of interpretation of the data. An alternative interpretation proposes that the fast dopamine response is not a teaching signal but rather an *attentional switch (Redgrave et al 1999).

Much attention has been focused in recent years on the function of dopamine in the prefrontal cortex, including its role in *working memory (Goldman-

Drosophila melanogaster

Rakic 1995). The attentional-switch hypothesis of The common Öfruit flyÖ, which is extensively used dopamine action fits well the proposed dopaminergic in the study of genetics, developmental biology, role in working memory, in which attention must be and neurobiology. shifted quickly on and between the on-line and off-line *internal representations that are required to There are over 3000 different speciesDrosophilidae perform the ongoing memory task. Malfunction of (Greek for Ödew loversÖ), but none is as popular as the dopamine system, especially in the prefrontalDrosophila melanogaster, which became the pet organ-cortex, is postulated to contribute to cognitive patholo- ism of geneticists already a century agoDrosophila agelénogastergies in which attention is impaired, particularly Öblack bellyÖ in Greek, referring to the colour of the schizophrenia. This assumption, called the Ödopamine maleÖs bottom). The term Öfruit flyÖ is a misnomer, hypothesis of schizophreniaÖ, is guiding the search forbecauseDrosophila are actually after the yeast that

Drosophila melanogaster

flourishes on rotten fruit rather than after the fruit itself. *D. melanogaster* was one of the first organisms to be adapted and then bred purposely for scientific needs. Mutants are then screened for abnormal performance. It was introduced into the laboratory by Castle at Harvard in 1901. This was soon followed by Lutz, and geotaxis, via courtship, to sensory discrimination. Loeb, Morgan, and others (Kohler 1994). The major Even in a species that is readily amenable to genetic analysis, the neurogenetics of memory is clearly useless unless efficient, reproducible memory *assays are available.

What is it that has endowed *Drosophila* with such a successful career in science? Fruit flies are not only cute (at least in the eyes of drosophilists). They are also intelligent. Paradigms of *habituation, *sensitization, conveniently small, remarkably inexpensive, clean, harmless and *classical and *instrumental conditioning are now (except occasional allergies), and easy to cultivate. Their available, involving use-dependent modification of the generation time is only about 10 days at 25°C and the life cycle includes easily identifiable *phases (Ashburner 1989). Furthermore *Drosophila* displays a rich, hectic behavioural repertoire, including positive phototaxis (Dudai 1989; Rees and Spatz 1989; Liu et al. 1999).

(movement towards light), negative geotaxis (movement away from the centre of gravity), and gracious learning and memory rather specifically (Dudai 1988; Quinn 1985; Hall 1986; Dudai 1988; Corfas and Tully 1989). A number of single gene mutants affect courtship. All these attributes sufficed to convince professors at the turn of the twentieth century to use fruit flies at the turn of the twentieth century to use fruit flies in demonstrations of *development and behaviour. Pinto et al 1999; DeZazzo et al 2000). The modifier

But it is the amenability of *Drosophila* genetic analysis that has made the real difference. The diploids critical; whenever one deals with the effect of mutations on learning and memory, the issue of chromosomal number of *D. melanogaster* only four, including the sex chromosomes X and Y (XX is female XY male). The giant chromosomes in the larval salivary glands share molecular and cellular processes with other are real cytological gems. The small number of chromosome systems in the organism, no absolute specificity should be expected. Memory mutants of *Drosophila* display ability of wild types and spontaneous mutants, the short-term nonmemory defects (Dudai 1988; Corfas and generation time and ease of breeding—all these initiated Dudai 1990; Zhong et al 1992; Pržat 1998). The critical a meticulous, systematic analysis of *Drosophila* genetics. question is, however, whether the mutation still provides With time, the accumulation of knowledge, the large useful information on the phenomena, processes, and number of genetically mapped mutations, and the rich mechanisms of learning and memory. The answer in repertoire of experimental *methods, have all reinforced many cases is yes. Several mutations, including some the experimental advantages of *Drosophila*, and made it very popular in the study of genetics in multicellular organisms. Naturally, the genome of *Drosophila* was one of the first to be sequenced in the Genome project (Adams et al. 2000). independent and remarkable evidence in support of the role

The experimental advantages of *Drosophila* have also attracted animal psychologists and neurobiologists. Initially, polygene analysis was used to assess the contribution of genes to behaviour (e.g. Hirsch 1959). The field has advanced into a new phase with the use of single-gene mutations; the basic idea was to treat the flies as atoms of genetics and behaviour (Benzer 1967). In the pre-genetic engineering era, the mutants were generated at random, usually by feeding the flies with mutagenic chemicals (Ashburner 1989). Nowadays, mutations are induced by using virus-like transposable elements, neuronal circuits, and the individual neurons genetic elements that mutate the fly by jumping into its that subserve memory in the central nervous system

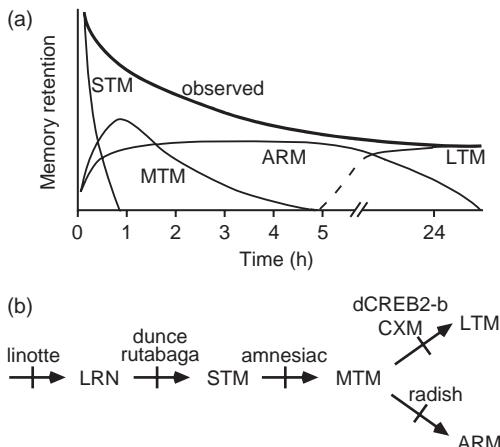


Fig. 27 Genetic dissection has unveiled multiple *phases in the *acquisition and the *consolidation of memory in the fruit fly. (a) Four functionally distinct phases are proposed to underlie the memory curve observed in normal flies trained to avoid a shock-associated odour: STM, short-term memory; MTM, middle-term memory; ARM, memory that is resistant to anaesthesia; LRN, learning; LTM, long-term memory. STM decays the fastest and LTM the slowest. (b) A scheme showing where in the pathway different mutants and pharmacological manipulations exert their primary disruptive effect. *linotte* is a mutant defective in a putative *protein kinase *linotinase*; *dunce* is a mutant defective in a form of the enzyme that degrades cAMP, adenyl cyclase-dependent phosphodiesterase; *rutabaga* is a mutant defective in the form of the enzyme that produces cAMP, adenyl cyclase (this form of the enzyme is sensitive to *calcium and may serve as a *coincidence detector of the *neurotransmitter and calcium *signals*); *radish* is a mutant defective in the production of a peptide that stimulates CAM synthesis; *dCREB2-b* is the product of which is yet unidentified; dCREB2-b, flies engineered to express an antagonist of the transcription factor *CREB; CXM, flies treated with the *protein synthesis inhibitor cycloheximide. The figure is adapted from Dubnau and Tully (1998).

molecular defects in the indicated mutants, see Duran et al. (1995); *linotte*, Byers et al. (1981); *dunce*, Duda et al. (1983), Livingstone et al. (1984); *rutabaga* and Waddell et al. (2000); *amnesiac* of *Drosophila* (Corfas and Dudai 1990; Davis 1993; Waddell et al. 2000; Zars et al. 2000; Dubnau et al. 2001). This search for the *engram is not too easy, for reasons including the fact that the brain and the thoracic ganglion of the fruit fly are small and compact. *Functional neuroimaging methods, similar to those already in use in the *honeybee, may facilitate the task.

Selected associations: CREB, cellular signal transduction cascade; neurogenetic Simple system

¹On the virtues of working with flies in general, see Dethier (1962).

²The accumulative body of knowledge, procedures, traditions, and rituals of the drosophilists provides an interesting example of the scientific subculture (Kohler 1994; Weiner 1999).

Engram

The physical record of a *memory; the memory trace.

The notion that *stimuli produce enduring physical changes in the brain, and that these changes are the basis for memory, has been with us since early times (e.g. see Plato's etched wax tablets of *methegetus* *metaphor). About 100 years ago, a German scholar, Richard Semon, termed the material record engraved by a stimulus in living tissue as the ÔengramÔ (Semon 1904). The etymological roots of the term are Greek, and it means Ôsomething converted into writingÔ. Semon had in mind a rather general theory of experience-dependent records in living organisms, which included not only neural but also *developmental and genetic memory in all types of tissue. In his book *The mneme, Semon suggested two mnemonic laws*. The first is the Ôlaw of egraphyÔ. It states that Ôall simultaneous excitations within an organism form a coherent simultaneous excitation complex which acts engraphically; that is, it leaves behind a connected engram-complex constituting a coherent unityÔ (ibid., p. 273). The second is the Ôlaw of ecphoryÔ according to Semon is the process that Ôawaken(s) the mnemonic trace or engram out of its latent state into one of the manifested activityÔ. The etymological roots of ÔecphoryÔ are also Greek, and it means Ôto be made knownÔ. The law of ecphory states that Ôpartial recurrence of the excitation complex, which left behind the engram complex, acts ecphorically on this spontaneous engram complex, whether the recurrence is in the form of an original or of a mnemonic excitationÔ (ibid., p. 274). Elements of Semon's writings are nowadays echoed in the discussions of *cell assemblies, *models of neural networks, and *retrieval. Unfortunately, Semon and his book were almost forgotten (Schacter 1982).

Most of the popularity of ÔengramÔ stems from a noted paper by Lashley (1950), entitled ÔIn search of the EngramÔ. Though seemingly an epitome of the cross-talk of scholarly ideas (Semon's chapter *The mneme* is entitled ÔThe Localisation of EngramsÔ), typically of Semon's fate, Lashley did not cite Semon even once in this paper. Lashley aimed at identifying Ôhabits of the conditioned reflex typeÔ in the brain. Following the path of Flourens, Franz, and others (Gomulicki 1953; Herrenstein and Boring 1965; Brazier 1988), Lashley used the *methodology of inference of function from dysfunction. He inflicted anatomical lesions on various parts of the *rat or *monkey brain, and tested the effect of the intervention on brightness discrimination and

Engram

*maze learning (Lashley 1929, 1950). After many years of research, Lashley came to the conclusion that effectors could not be considered as building blocks of high brain function. This notion of cortical area, except the relevant primary sensory areas, was influential in shaping later distributed models of learning and memory. He summarized brain and memory, for example, those of Lashley's studies in two principles: (a) the equipotentiality principle, Hebb (*algorithm, *cell assembly, *classic).

principle, which states that cortical areas are equipotent. What is the current status of the search for the principle of learning, and can generally substitute for each engram, a century after Semon and half a century after Lashley? The picture is not simple. At this stage, it could be useful to resort to the basic issues.

*performance is roughly proportional to the amount of tissue destroyed, rather than its position. Other conclusions were also drawn from the data, e.g. that the effect of a lesion is proportional in magnitude to the complexity of the task. ÔThis series of experiments, there must be some type of engram to ensure that the reduction in learning and memory be useful to resort to the basic issues.

1. The existence of the engram. Is there an engram? The question where the engram is should not be

concluded Lashley, Ôhas yielded a good bit of information about what and where the memory trace is not necessarily localized to those use-dependent changes in the circuit, is already

sometimes feel, in reviewing the evidence on the localization of the memory trace, that the necessary conclusion is that learning just is not possible. Nevertheless, certain types of memory as selective reactivation in spite of such evidence against it, learning does sometimes occur. (Lashley 1950).

of neuronal activity (*a priori, *cell assembly), use-

Lashley's conclusions about the engram were already criticized at the time of their publication (Hunter 1930). The main objections were, first, that the behavioural tasks were not well defined in terms of the sensory inputs and the behavioural strategies required for successful performance, and therefore a *subjective representation resides.

with partial brain damage could still succeed in the task by using the undamaged areas; second, the lesions were not delicate enough to differentiate the contribution of distinct functional divisions in the brain. Disappointed by the search for the engram, Lashley came to favour field theories of brain function, which regarded sensations as patterns of excitations being distributed throughout the cortical surface like waves in a liquid surface (Lashley 1950). This view was compatible with the Gestalt theories of the later part of his career, Lashley put this idea to experience that complex memories in humans will be highly mental test. He placed pieces of gold on the visual cortex of the monkey. The metal was expected to short-circuit the cortex and therefore disrupt visual perception. This did not happen (Lashley et al 1951). Similar conclusions were reached at about the same time by other investigators. Not surprisingly, Lashley himself remarked that he had destroyed all theories of behaviour despite the expected multiplicity of locations, and the in his ad-hoc experimental conclusions. Rather, it was in brain that the primate mediotemporal lobe subserves lesion techniques with behavioural analysis. On the declarative memory, the corticostriatal system conceptual side, he came to argue that dedicated memory, and the prefrontal cortex *working memory.

Candidate engrams have also been identified in classical contexts that of both resolution and *reduction: Where conditioning in mammals, in lower vertebrates (*bird- is it within that area? In a dedicated circuit? In identification), and in invertebrates (*Aplysia* *Drosophila). In identified neurons? In synapses? To what size of circuit do we most cases, the question of what are the precise functions hope to nail it down? What answer will finally satisfy tions of the identified regions in retaining the trace over our urge to localize things in the world? And if we keep time remains, however, unresolved. First, the fact that reducing the area, or the number of units in the area circumscribed brain region is necessary for a certain where will the transition be from an engram, to a type of memory does not entail that this region is sufficient fragment of that engram, or to a non-gram? client to encode the memory, even more so exclusive if These problems could apply to simple brains as well doing so (*criterion). Second, some areas in the candidate (Glanzman 1995).

date engram might be required for only some *phases. And as to term ÔengramÕ, many experimenters of memory but not for other phases. And third, the use it, others think that it carries the risk of spilling into engram may have ÔcoreÕ, responsible for the persistence of prose, and prefer the term ÔtraceÕ. Most authors, over time of the essential attributes of the item, and however, simply use ÔtraceÕ and ÔengramÕ interchange auxiliary components that either encode additional ably (e.g. Thompson and Kim 1996).

*dimensions of the item, or are recruited only in the encoding or the expression of the memory. All these issues resurface in the renewed attempts to identify engrams by means of *functional neuroimaging.

4. The transformation of the engram. In addition to the differential function of identified brain areas and pathways in a particular experimental protocol, the relative contribution of distinct areas and pathways to the engram could change dramatically when the *acquisition or retrieval parameters of the task are altered. This is the case even in relatively simple forms of learning, for example, in classical conditioning, when a shift is made from delay to trace conditioning, or from elemental to *contextual conditioning (Thompson and Kim 1996; Nader and LeDoux 1997; Desmettal 1998). This again calls for the depiction of engrams as multicomponent *systems, the individual components of which are recruited and expressed in a permutable known, and therefore, noting enigmas is often as useful manner depending on the specific task demands.

5. The level of the engram. Traditionally, the search for the engram refers to an anatomical expedition. But nowadays it is also cellular and molecular. Problems shortcoming, and most to both. Although many investigations similar to those concerning the neuroanatomical search may agree with much of the choice, some haunt the molecular and cellular search. Synapses and neurons modified by experience should carry some of their compiler. The reader is fully encouraged to type or another of a physical record of the experience expand or shrink the list unabashedly. But at least, it is (Dudai and Morris 2000). But the change could be a starting point.

minute, distributed, and alternate over time from one site to another. Again, in the molecular like in the circuit level, there might be a core engram and additional tiers of mechanisms that encode additional stimulus dimensions (Berman and Dudai 2001).

In conclusion, whatever the level of analysis, to expect the search for the engram in the mammalian brain to end up in the identification of a single locale is naive. And even if a candidate area is identified as important in maintaining the engram, the problem

Selected associations: Criterion, Memory, Metaphor, Persistence, Phrenology

¹

He was, however, well aware of Semon's writings (Lashley 1933).

²For what the Gestalt was, see *insight.

³This is another example of the classical sorites paradox, which explained under *insight; see also *reduction.

Enigma

An open problem, a mystery.

Science is driven by the unknown as much as by the known, and therefore, noting enigmas is often as useful as listing facts ("nos Greek for ÔableÕ). Enigma Ôto speak

- What are the neuronal codes of *internal representations? This is a central issue not only in memory research, but in neuroscience at large. Without knowing in detail how models of the world are encoded in the brain, there is little hope in providing answers to many of the questions that follow.
- What are the computational and physical changes that take place in internal representations in *acquisition and *consolidation of memory? Which of

Enigma

these changes are obligatory for long-term memory? Many alterations are detected in the brain after training, at the molecular, *synaptic, cellular, and *system *levels. Yet some of these alterations may not directly relate to experience-dependent modifications in internal representations (e.g. some could subserve *homeostasis). Are we currently pursuing the processes and mechanisms that are really relevant (*criterion)?

3. How are internal representations retained over time in spite of massive synaptic remodelling in the brain (*persistence)? Furthermore, there is some evidence for turnover of neurons in the mature brain (*bird-song, *hippocampus); if so, how is it that new cells integrate into existing circuits without disrupting old memories? Or do they?
4. How is complex information *retrieved from memory, frequently within a fraction of a second? And how much of retrieval is reconstruction, sometimes with doubtful faithfulness (*false memory)?
5. How much of our knowledge about the external world is due to selection by experience of pre-representations, generated by the endogenous activity of the brain? In other words, how much of our world models is encoded in our brain *a priori, and to what degree can we indeed master truly novel information and concepts?
6. Do all *percepts and thoughts leave a lingering trace in memory? If so, will we be able to tap into the remarkable pace of memory research, solutions to some latent information? Similarly, will we be able to restore *engrams once they become unretrievable? knowledge sooner than imagined. Other problems,
7. Will we be able to increase significantly the physiological *capacity and performance of our memory? be resolved formally but resist intuition (*dimension). Will it be done by pharmacology (*nootropics), by genetic engineering (*neurogenetics), or by bionics, and resolution of the analysis. For a molecular neuro-based on the integration of nano-chips with the biologist, the *developmental regulation of an ion central nervous system (Moravec 1988; Kuwanachannel et al 1995; Maheet al 1999; Wengt al 2001)? relevance of the fMRI (functional magnetic resonance
8. Will we ever be able to download memories directly imaging) signal for the *functional neuroimaging to and from the Web, in a non-invasive manner, expert. Hence, in addition to the aforementioned hence linking our brain to a gigantic, global Ômacro-enigmasÕ, many Ômicro-enigmasÕ are hidden in memory ÔsyncytiumÕ? This will surely provide the serious subdisciplines of memory research. Whether term *collective memory with a new meaning. If the they should be dubbed ÔenigmaÕ or simply Ôopen possibilities raised here, as well as in 7 above, even questionsÕ or Ôresearch objectivesÕ, is a matter of taste. materialize, what will be the biological, emotional, cognitive, and social price for the species and for the individual?
9. Will new types of memory systems evolve in our dimensions opens new vistas that unveil new enigmas. brain? A great variety of memory systems have already emerge in evolution, each time presumably even boring, may with time become a source of wonder to comply with the updated needs of the species. These systems include, among others, memory fotlight. As the English author G.K. Chesterton remarked

*skills, for space, for language, for facts, for events, for the self (*taxonomy). Some of these systems may have evolved at first in response to a certain selective pressure but later became adapted to new needs or even paved the way to new faculties and capabilities. Will new memory systems emerge to cope with the new technological environment, what will their capabilities be, and which new opportunities will they open for brain and behaviour?

10. And, finally: What is consciousness (*conscious awareness)? Similarly to enigma 1 above, this issue definitely transcends memory research, yet is intimately related to the function and mechanisms of *declarative, particularly *episodic memory, and to the role of *attention and memory in the *binding of our personality over time. Furthermore, to what degree are other species consciously aware of themselves and the world (*anthropomorphism)? Will we ever be able to really know what is it like to be a bat (Nagel 1974)? And will smart robots (Moravec 1988, Wengt al 2001) or neuro-silicon hybrids (Kuwanaet al 1995; Maheret al 1999) become conscious as we are? Will they have episodic, autobiographical memory, and what will it mean to them?

Scientific enigmas are there to be tackled (Duncan and Weston-Smith 1977; Doty 1998). Judging by the of the aforementioned riddles may become common knowledge sooner than imagined. Other problems, note also that what an enigma is, depends on the level of the analysis. For a molecular neuro-based on the integration of nano-chips with the biologist, the *developmental regulation of an ion channel is a pressing enigma, as is the physiological relevance of the fMRI (functional magnetic resonance

Before concluding, we should also remember that knowing that we do not yet know. Identifying new

almost a century ago (cited in Gratzer 1996): ÔIs ditchresearch on the different categories of human knowl-water dull? Naturalists with microscopes have told meedge. The new computer era opened new vistas for that it teems with quiet funÕ.

Selected associations: Classification,Culture,Dimension,Homo sapiens

Episodic memory

1. The *conscious mental reenactment of personally experienced past events.
2. The *recall or recognition of a unique event and the spatiotemporal *context in which it was experienced.
3. The *internal representations that are accessible to such mental reenactment or recall.
4. The brain *system that endows the *subject with the capacity to perform 1,2 above.

almost a century ago (cited in Gratzer 1996): ÔIs ditchresearch on the different categories of human knowl-water dull? Naturalists with microscopes have told meedge. The new computer era opened new vistas for understanding the storage and *retrieval of knowledge, which infiltrated human memory research. In the mid-1960s, Quillian proposed a method by which meaning could be stored optimally in a computer program, and his postulates were adapted by psychologists in their attempt to account for the storage of knowledge in real brains (Collins and Quillian 1969; Tulving and Donaldson 1972). This type of knowledge encoding was termed Ôsemantic memoryÕ (*declarative memory, *taxonomy). Tulving (1972, 1983) went on to distinguish semantic memory, which he dubbed Ômental thesaurusÕ, from another type of knowledge that humans have about the world, which is about temporally dated events, describable in terms of their perceptible attributes, and the spatiotemporal relations of these events to each other. This memory he termed ÔepisodicÕ. The term is now used, depending on the context of discussion, to denote a type of mental act or experience (definitions 1,2), a type of memory items (definition 3), or a type of memory system (definition 4)

Here are a few things to remember about episodic memory:

Episodic recollection is conscious time travel into the subjective past. This is considered by many as the most sophisticated faculty of memory, and the one most characteristic of humans. Further, a minority of authors even use the term ÔmemoryÕ and Ôepisodic memoryÕ as synonyms. These authors would usually concede that the *declarative memory of impersonal facts is also ÔmemoryÕ, but refuse to consider many other types of use-dependent change in behaviour, such as *classical conditioning, *habit and *skill, *bona fide* memory. This is evidently not the stand taken in this book (*memory).

The term ÔepisodeÕ is from the Greek, at, + eisodos, enteringpeisodionmeant a parenthetic narrative. Indeed an episodic memory item is only one scene in the individualÔs accumulative personal narrative. That there is memory which is episodic, as opposed to automatic responses, or to the recall of impersonal facts (*taxonomy), was discussed already by Greek philosophers if not earlier. A clear description of this distinct type of memory was given by Agusutine (400; *classic): ÔÉ I encounter myself and recall myself4. and what, and when, and where I did some did, and how I was affected when I did itÕ. The term Ôepisodic memoryÕ was, however, introduced into the scientific discourse much later, by Tulving (1972). This was on the background of intensive developments in cognitive

1. It is not only about whahowandwherbut also aboutwhen the ability to place unique experienced events on the temporal axis of personal history, be it distorted and poorly resolved, is characteristic of episodic memory.

It refers to unique experiences, hence each episodic item is the outcome of Ôsingle trialÕ learning (*acquisition). Recalled *real-life episodes, however, refer each to different time windows of experience. Further recollection effort may dissect amalgamated episodes into elementary events.

3. In humans, it involves autonoetic awareness, i.e., the conscious reflexive experience of private phenomena. Whether non-human species are also capable of experiencing such Ômental time travelÕ, and if so, what kind of awareness is involved, is an open question (see below). Definition 2 does not posit awareness and therefore fits particularly to be used in animal research; this definition, however, is considered by many authors to refer to Ôepisodic-likeÕ rather than to genuine episodic memory.

Whereas retrieval of memory is commonly oriented toward the present or the immediate future, i.e. application of knowledge for ongoing needs, retrieval of episodic memory is oriented toward the past, i.e. the past events are recognized as such (Tulving and Markowitsch 1998). The retrieved

- information, however, might then be harnessed for No consensus answer is available to this question. identifying and attaining future goals (Conway and The data that feed the debate stem from the study of Pleydell-Pearce 2000). brain lesions and from *functional neuroimaging.
5. The retrieval of episodes is expected to involve multiple steps, or components, which ultimately differ in the specificity of the information retrieved, such as the recollection of specific information about the target item (ÖwhatÖ) and about its source (ÖwhereÖ). In some types of *dementia, the deterioration of ÖwhenÖ, as well as the sequence in which the elements of the episode unrolled), and the recognition of the familiarity of each of these items (e.g., Yonelinas 2001 ; see also ÖrememberingÖ vs. ÖknowingÖ). Abnormal ageing is often associated with preferential impairment of episodic memory, e.g. Nilsson et al 1999; it is noteworthy that normal ageing is often associated with pre-recognition).
6. Many types of tests could be used to tap into episodic memory, including free recall, cued recall, evidence (reviewed in Mishkin et al 1997; see Tulving et al 1988 for a case of ÖsemanticÖ amnesia; also Zola-Morgan et al 1983 for some methodological caveats). Paired associates learning is but one example. In this due to hippocampal damage sustained very early in type of learning, the subject is presented in training life (Vargha-Khadem et al 1997). These patients were with a pair of stimuli, and then, in the test, pre- capable of developing normal language and social sented with one member of the pair and requested competence, and acquire new factual knowledge, in to retrieve the memory of the other. Word pairs are spite of displaying severe loss in episodic memory. commonly used in humans (e.g. Winocur and Based on these data, a suggestion was made that the Weiskrantz 1976; Shallice et al 1994), non-verbal *hippocampus and the subhippocampal cortici form stimuli in other species (e.g. Saunders and a hierarchically organized system for the registration Weiskrantz 1989; Sakai and Miyashita 1991; see also declarative knowledge. Episodic memory, so goes pp. 74Ö75). The task is sensitive to mediotemporal the idea, which depends on rich associations, is encoded damage (*amnesia), substantiating its declarative in the hippocampus itself, the top processing level in nature. Paired associates are considered ÖepisodicÖ hierarchy, whereas semantic memory, less dependent tests because, when the pairs used are unique, the on intricate associations, can be supported by recall unveils the memory formed in a single the subhippocampal cortici, lower on the hierarchy episode of experience. Yet, depending on the (Mishkin et al 1997, 1998). Alternative interpretations protocol used and particularly when the memory of the data, which do not support such a qualitative of ÖwhenÖ is not taxed, success on such task distinction between the semantic and the episodic might be construed as the outcome of the formation systems, were also raised (Squire and Zola 1998). of a semantic association, including sometimes Do animals have? If one posits autoetic awareness as a critical criterion for episodic memory, the issue of whether animals go on mental time travels Where is it in the brain? Being a declarative type of becomes complicated indeed and by some accounts memory, episodic memory is subserved by *cortical circuits, including dependence on the mediotemporal non-human species almost always set a more modest, lobe for acquisition and *consolidation, and on the yet still admirable, goal: to prove that the animal frontal lobe, among others, for retrieval (e.g., Fletcher has Öepisodic-likeÖ memory, which does not presuppose conscious awareness as a defining criterion. Lepage et al 2000; for more on functional differentiation in these areas by types of tasks and memory as a general strategy in memory research, is to look *phases, see *acquisition, *declarative memory, for the behavioural ecology of the species, and search *consolidation, *retrieval). A prominent question is for natural situations which could benefit from whether the brain circuits that subserve episodic memory differ from those that subserve semantic memory. Clayton et al (2001) list a number of potential candidate systems. One is brood

parasitism: brood parasitic birds such as the cuckoo^{possible} for us to identify the conscious awareness deposit eggs in the nests of other species and the young^{mental time travel, if it ever exists, in other species?} are later cared for by the host species. A success^{Can we ever come to know how is it like to be a bat brood parasite must remember where potential victims (Nagel 1974), particularly, a nostalgic bat? Some say have started their nests, and return to that place at that we will never be able to do this. But there might the right time to add the egg to those already laid in be another, though admittedly remote and less satisfy the nest. This could involve here what, and when factory solution. Suppose we identify in the human information of a single event. Another potential brain a characteristic functional tag of mental travel, candidate is a polygynous mating system, such as i.e.g. a distinct activity pattern unveiled by functional the meadow vole, in which a male mates with multiple neuroimaging of the behaving subject. This might be females that are distributed over a wide area and analogous, say, to the identification of candidate come into estrus at different times. Successful mating dream states by recording brain waves (e.g. Dave and in this case could greatly benefit from remembering Margoliash 2000). Suppose then that we identify this who, where, and when. These candidate systems unique functional tag in the brain of animals when they are somewhat difficult to investigate systematically in perform a task that involves episodic retrieval in the laboratory. But another type of suitable behaviour humans. We may then be able to say that there is a was found amenable to systematic, controlled analysis reasonable probability that the non-human subject food caching in the scrub jay (Clayton and Dickinson performs a mental time-travel. Not enough to firmly 1998; Clayton et al 2001). Scrub jays cache perishable conclude that this animal feels the same as we do when insects and seeds in multiple locations, and it may we recall our private past, but still, a hint that this might be adaptive for them to remember what has been indeed be the case.}

cashed where and when. Clayton et al (1998) have Selected associations: Amnesia, Conscious awareness trained scrub jays to appreciate that worms, which the Declarative memory, False memory, Recall birds like a lot, are perishable and therefore degrade over time. They then allowed the birds to recover the perishable worms, or non-perishable peanuts, which _____

the birds had previously cached in distinct sites.¹ This past is assumed by the subject to be veridical, but is not necessarily accurate. The birds searched preferentially for fresh worms, rarely accurately recalled (see *false memory). *Confabulations are hallucinations are excluded.

shortly after caching, but learned to prefer searching for² How many scenes are there all together is an interesting question the less-favorable (but still tasty) peanuts and avoid^{probably less than most of us would predict intuitively (*capacity)} searching for the worms after longer intervals in which Dudai 1997a).

these worms decayed. (Birds that did not have an³ *Autobiographical memory^Ö is often used interchangeably opportunity to learn that worms degrade over time, *Episodic memory^Ö. It might be preferable to distinguish between continued to search for the cached worms even long^{two. Whereas *Episodic^Ö refers to distinct individual episodes, *Autobiographical^Ö connotes the narrative formed from the combination of such episodes (see also Conway 2001).}

taken in the experiment to prevent odor cues of the degrading food.) This use-dependent modification in⁴ Autonoetic (*self-comprehending^Ö) awareness is regarded in the the food search strategy was taken to imply that the jays remembered not only what was deposited where, but also when it was deposited there^{Nhence fulfilling} the behavioural criteria for episodic-like memory (definition 2).

The story of the scrub jays shows that the demonstration of episodic-like memory in non-human species is possible, given the investigators are smart enough to match the right species with the right *assay (for an example of a different kind of approach, which attempts to identify primitives of episodic memory in the rat, see Fortin et al 2002). But is episodic-like memory a rudimentary form of what we humans experience as episodic memory? And will it ever be

⁵ *Source information^Ö is a term used in human memory research to refer to the time and place in which the target item was acquired; also *context.

⁶ The question can be posed at various *levels of analysis: is the functional system monolithic? Are the *algorithms the same? And is the hardware implementation identical? The question posed here refers to the hardware implementation at the circuit level but clearly reflects on the algorithmic and computational levels as well.

Experimental extinction

1. A decline in the frequency or intensity of a conditioned behaviour following the withdrawal of *reinforcement.
2. The experimental protocol used to obtain the aforementioned phenomenon.
3. A modification in the *internal representation of a conditioned association that leads to suppression of the conditioned response, due to behaviourally meaningful rearrangements in the relationship among previously associated *stimuli or stimuli and *reinforcers.

Pavlov noted that once one of his famous dogs (and there were many) had been conditioned to salivate to the sound of a metronome by associating the sound with food, the sound alone came to elicit salivation, as expected (*classical conditioning). However, when the metronome continued to be played without subsequent reward, with time salivation diminished. Pavlov termed this phenomenon Ôexperimental extinctionÕ (Pavlov 1927). Ever since, experimental extinction (which can easily be demonstrated in *instrumental conditioning as well) became one of the most fundamental problems in learning theory. A naive, *OckhamÕs razor type of explanation, might construe the situation as rather simple: the dog in the above example forms an association between sound and food, but when the sound is sounded without reinforcement, the association weakens and the dog ultimately *forgets. A simple explanation? Probably, but absolutely wrong. A selection of four types of observations will suffice to illustrate the case.

1. Spontaneous recovery After extinction has occurred, the conditioned response may recover with time because lack of reward creates ÔfrustrationÕ (note the without any additional training (Pavlov 1927). This *anthropomorphism), and as animals trained under immediately suggests that the original information partial reinforcement schedule got accustomed to frustration was preserved. Pavlov himself proposed that during extinction, they become more stubborn in extinction the conditioned reflex undergoes a training. The ÔSequential HypothesisÕ proposes that process of Ôinternal inhibitionÕ. To put his proposal in a broader context, we should note that he distinguishes two types of inhibitory processes, one in a central excitatory processes, commanding from the nonreinforced trials become extinguished reflexes, from central inhibitory processes, that act an appropriate nonreinforced reinforced alternation to negate the excitatory processes. Furthermore, he distinguishes two types of inhibitory processes, one in the brain, whereas the other in the periphery. The ÔExternalÕ inhibition arises when there is a clash with the excitatory processes in the brain, whereas the ÔinternalÕ inhibition arises when there is a clash with the inhibitory processes in the brain.

reflex itself becomes progressively inhibitory for the behaviour in question.

2. Reacquisition and saving Generally speaking, ÔsavingÕ is facilitation of relearning in retraining (in the Ôsaving methodÕ, retention is quantified by comparing learning and relearning scores; Ebbinghaus 1885). In many cases reacquisition of an extinguished behaviour takes fewer trials than the original training (although see Bouton 1993). Such cases imply that the brain saves more information about the original learning than it volunteers to give up at first.
3. Reinstatement After experimental extinction of conditioning, exposure to the unconditioned stimulus alone can partially restore the response to the conditioned stimulus (see *fear conditioning in Rescorla and Heth 1975). This again indicates that the conditioned association was not abolished.
4. Renewal Switching out of the extinction *context could result in re-emergence of the seemingly extinguished response (Bouton and Swartzentruber 1991).

Over the years, the phenomenology of experimental extinction has provided lots of excitement on the one hand, and insights on the other, to experimental psychologists and learning theorists. An additional notable example is the so-called Ôpartial reinforcement extinction effectÕ (PREE): behaviour that has been reinforced only intermittently extinguishes more slowly than behaviour that has been reinforced consistently (Humphreys 1939; Weinstock 1954; Amsel 1958; Wagner et al 1964; Rescorla 1999; Figure 28). This seems rather paradoxical, for why should less reinforcement lead to more memory? Several theories have been proposed to account for PREE. Among the most influential ones are the ÔFrustration HypothesisÕ (Amsel 1958) and the ÔSequential HypothesisÕ (Capaldi 1966).

The ÔFrustration HypothesisÕ argues that PREE works through partial reinforcement regimes, persisting stimulus traces from the nonreinforced trials become conditioned to the next reinforced response provided there is reinforcement. The ÔSequential HypothesisÕ proposes that during extinction, the memory of these associations maintains responding during extinction. It is thus seen that the ÔexternalÕ inhibition arises when there is a clash with the excitatory processes in the brain, whereas the ÔinternalÕ inhibition arises when there is a clash with the inhibitory processes in the brain. The ÔinternalÕ inhibition reflects on fundamental issues in learning theory, such as how associations are reinforced and *acquired, and how associations are retained, and *retrieved.

Indeed, there is no shortage of hypotheses of information processing, only limited facets of which why brains behave the way they do in experimental situations unveiled under a given experimental situation in the extinction. Many of these hypotheses refer to learning laboratory (for examples see *classical conditioning and memory processes that transcend issues of extinction *cue). Furthermore, Ôexperimental extinctionÕ tells (e.g. Bower and Hilgard 1981; Mackintosh 1983; us that when we relearn, we preserve the information Flaherty 1985; Bouton 1991). In the frame of the present about previous associations (e.g. Rescorla 1996); hence ent discussion, suffice it to note that experimental we constantly create mental *palimpsests.

extinction can be viewed as a dynamic learning process, ÔExperimental extinctionÕ offers additional take-in which *internal representations of target and *con- home messages. Being so widespread, it epitomizes the text stimuli are rearranged (definition 3). Experimental fact that some general principles and *algorithms are extinction is hence different from forgetting; it involves shared by many forms of learning. These learning a *phase of memory *consolidation for the new extinction ÔuniversalsÕ are expected to have selective advantage experience (Braud and Broussard 1973; Berman Consider, for example, PREE; nothing in life is sure, and Dudai 2001), and could itself be forgotten (Bouton therefore robust *performance under conditions of 1994). Seen this way, experimental extinction provides uncertainty makes sense. Experimental extinction also additional support to the *zeitgeist that classical and illustrates how a phenomenon that at first might appear instrumental conditioning are not at all solely about the merely of theoretical interest to a small group of contiguity or contingency of pairs of isolated stimuli; scientists, ultimately becomes important in *real-life. For rather these types of learning reflect intricate processes many years now there is much interest in experimental extinction in psychotherapy, in the treatment of post-traumatic stress syndrome and prevention of its relapse (Bouton and Swartzentruber 1991; Chareigl 1998).

The interest in brain mechanisms of extinction is on the rise as well (Falk et al 1992; LaBaet et al 1998; Berman et al 2000). One of the goals is to understand the neuronal mechanisms that differentiate learning the new (i.e. in acquisition of the *engram) from learning anew (i.e. in experimental extinction). This could tell us in due time how to prevent corruption of important learned information by subsequent experience (*false memory).

Selected associations: Associative learning Consolidation
Forgetting Persistence

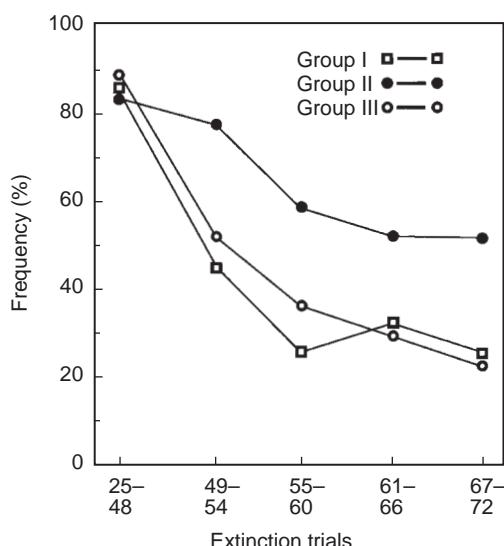


Fig. 28 An early example of the puzzling ÔPartial Reinforcement

Extinction EffectÕ (PREE): college students were divided into three groups and trained to blink their eyelid to a light because this light was followed by air puff to the cornea. Group I received in training 96 reinforced trials, group II 96 trials (only half of which were reinforced), and group III only 48 reinforced trials. All groups were then subjected to an experimental extinction protocol. The graph depicts the frequency of conditioned response vs. the extinction trial. The naive prediction is that group I will show the strongest acquisition and extinguish most slowly, whereas group II will show weaker acquisition. In reality, all groups showed similar acquisition, while group II was definitely the most resistant to extinction. For hypothetical explanations, see text. (From Humphreys 1939.)

¹As the clinic is mentioned, it would be only fair to note that the term ÔextinctionÕ carries also a different meaning in neuropsychology. It refers to the situation in which the simultaneous application of two identical tactile stimuli results in the report of only one of the stimuli, although each would have been reported if they were to be presented independently. This type of ÔextinctionÕ may indicate a lesion in somatosensory cortex. It is not ÔexperimentalÕ and has nothing to do with memory.

False memory

1. A retrieved *memory item that does not correspond to veridical experience but is believed to be so by the *subject.

2. The phenomena that refer to the report of such items by the subject.

False memory

ÔFootfalls echo in the memory/Down the passage which we did not take/Towards the door we never openedÔ often procedures typically involve the *recall or *recognition, more often than we tend to concede, mem-scenes (e.g., Bartlett 1932; Carmichael et al 1932; Eliot 1963): and facts mix well in poetry, but the charm could lead us to passages we never took in reality. Fantasy and Gazzaniga 1998; Tversky and Marsh 2000). A *classic study is that of Deese (1959) the test become nightmare if they do so in reality. Why does it material in this study was 36 lists of 12 words each. Each happen, when and how, are major questions in memory research. These questions have been approached target word, which itself was excluded from the list. For experimental psychology long ago (Bartlett 1932; example, for the target word ÔsleepÔ, the list was Ôbed, Carmichael et al 1932), almost forgotten (*zeitgeist), rest, awake, tired, dream, wake, snooze, blanket, doze, but regained much interest in recent years. Their slumber, snore, napÔ. The subjects were instructed to renewed discussion has already transcended the domain of science, invading courtrooms and newsrooms alike. of each list, recall orally the items from the list.

There is a great variety of phenomena that could be regarded as false memory. They range from delusion to extralist intrusions of words in the immediate recall. and *confabulations in diseased states to memory illusions. He found that many of the lists induced the subjects in normal individuals (Kopelman 1999; Kriat to produce the nonpresented target word as an intruder et al 2000). In the contemporary literature, however, sion on the test. ÔSleepÔ, mentioned above, had in his the term is commonly reserved to refer to the erroneous hands the largest probability of intruding into the memory, particularly *episodic memory, in normal relevant list; words like ÔroughÔ, ÔsoftÔ, ÔchairÔ, Ôsubjects. In the past decade, particular attention has been directed at the potential role of false memory in their associative list. This is hence a clear-cut case of recollection in adulthood of sexual abuse in childhood false memory: the subjects claimed to have heard the (Penfold 1996; Pope 1996; Winbolt 1996). It all started with a wave of reports on the recovery of such repressed memories in subjects undergoing psychotherapy. Theby Roediger and McDermott (1995). Word-intrusion apparent revival of trauma has culminated in litigations tests are highly recommended for convincing demonstrations against parents and caretakers. Soon after, however, filtration of false memory in the classroom as well as became apparent that in some cases (not all!), the memory public lectures.

ries of abuse could have been acquired by the patient in Why are some memories false? The question could the course of overenthusiastic therapy. In fact, a new diagbe posed in two versions: first, what are the brain nistic criterion has been suggested, termed Ôfalse memechanisms that generate false memories, and second, ory syndromeÔ, which refers to the situation in which awhy havenÔt some of our memory *systems been individual uncritically accepts suggestions of the theraperfected in evolution to yield a higher fidelity of pist and comes to believe illusory memories of abuse. Abutput. At the mechanistic *level, multiple possibilities this stage, therapists in lieu of parents became fashionable. could be entertained, which relate to distinct memtargets for legal suits. This has led to heated debates and *phases: perception, *acquisition, *consolidation, emotional flares in the psychotherapeutic community *persistence, and *retrieval. False memories might stem (ibid.), and, as expected, to juicy headlines in tabloids. from perceptual illusions (Roediger 1996), even from

Yet false memory in *real-life covers many phenom-dreams (Loftus 1996) and fantasies (Freud 1899). It is, ena that have nothing to do with claims of abuse. Ahowever, questionable whether these should be considpressing and more prevalent problem refers to the quesered as a source bbnal fidefalse memory, because tionable validity of courtroom testimony (Wells and from the point of view of the brain, the raw material Loftus 1984). Ordinary subjects are capable of adoptingfor memory was real. Distortions in the processing of and assimilating a fabricated autobiography, in the *percepts might be due to the amalgamation of the absence of any malicious intention (Loftus 1996). Laston-line experience with off-line experiences from but not least, false memories are not confined to indi-different times and *contexts, and to reconstruction viduals; when societies and nations adopt false *collecas well as repression of narratives by fitting them to tive memories, the resulting fantasies and emotionsemotive and cognitive schemata (Freud 1899; Bartlett could lead to global disasters. 1932; Carmichael et al 1932; Neisser 1967; Loftus 1984)

Situations that resemble real-life false memory can be simulated in *controlled laboratory settings. The Consolidation, processes that might take place after a

memory item is retrieved in a new context, Ôimplicitly (a priori) and endogenously generated representations could particularly provide an opportunity for new tions. In addition, the static ÔstorehouseÔ metaphors are information to modify the initial trace (Nader et al. passŽ; many biological memories are *biased, dynamic 2000; Sara 2000; Berman and Dudai 2001). The cues constructions of past occurrences what comes out available in retrieval could also cause subjects to select the ÔstorehouseÔ is not what was deposited there. rearrange and distort the retrieved information (Tulving Selected associations: Bias Real-life memory, 1983; Loftus 1996). The introduction of improved RetrievalZeitgeist neuropsychological assays of false memory, especially when combined with *functional neuroimaging, will surely cast additional light on the mechanisms ¹The fate of this signal paper in the years following its publication involved. It has already led to the identification of frontal areas that are recruited differentially in false vs. ²See in this context the ÔPanglossian paradigmÔ, in *paradigm. veridical recall (Schacter et al 1996c).

As to the phylogenetic considerations, several types which four conflicting versions of the same traumatic event a of possibilities should be kept in mind. One, that faulty offered by four narrators (Kurosawa 1950; Cook 1981). reproduction of information is an inherent constraint ⁴A caveat is appropriate here. This statement merely claims that of the biological hardware that embodies memory. In individual human being is an untrustable witness. It does not claim other words, the system is imperfect because it could that there are no facts outside there that could be identified and not be otherwise, unless we replace the hardware quantified by methods that control for bias in individual memory. That Second, the system still undergoes evolution, we are in ⁵What science attempts to do. For relevant debates, see Apple et al (1996); for the occasional misuse of science to support irrelevant claims such as the one this caveat tries to prevent, see Sokal better. Only that time here could mean zillions of years, Bricmont (1998). unless, again, we call bionics to the flag (*enigma). And third, which is related to the second, who says that accuracy is always a positive selective pressure in evolution?

It could be so for some types of memory systems, such as *skill, but not for others, such as episodic memory.

Fear conditioning

There are no doubt situations in which accurate recollection of episodes is but a burden; Plutarch (1D2C AD/1914a) was among those who recognized that become associated with fear.

ÔI dislikeÔ, he said, Ôa drinking-companion with a good memoryÔ. The possibility was raised that autobiographÔ Show me a man who is not a slave; one is a slave to lust.ical memory had evolved to bind our personality and another to greed, another to ambition, and all men are allow us to function better as distinct individuals in slaves to fearÔ (Seneca 63D65). Fear drives fundamental society; for this, autobiographical memory need not be responses to the world in individuals and societies alike neither large (Dudai 1997a) nor accurate (Conway/Durkheim 1895; Freud 1908). James (1890), influ-1996). Yet another possibility is that in moulding declar- enced by Darwin (1872), considered fear merely as an ative memory systems, evolution actually selects against instinct. He even thought that the need to exercise this accuracy of details, because excessive accuracy may instinct had diminished in evolution, and in a some-hamper *generalization and categorization (*mnemon- what naive burst of trust in the virtues of human kind, ics). The Rashomon phenomenon may hence be a price remarked: ÔThe progress from brute to man is charac-we pay for the cognitive success of our species. terized by nothing so much as by the decrease in fre-

There is much more to the discipline of false mem- quency of proper occasions for fearÔ (James 1890). Yet ory than the phenomenon itself. The rediscovery and already in its early days, experimental psychology enthusiastic analysis of false memory phenomena became interested in the ways in which fear is acquired the past few decades has catalysed a conceptual revolution in the field of memory research (Koriat et al 2000). fear as a Ôpassive defensive reflexÔ, and noted that mem This revolution is concerned with the shattering of the ory of a traumatic situation lingers for long and can concept of the brain as a faithful mirror of reality, block the expression of other acquired behaviours. and replacing it with the idea that *internal representa- Whereas Pavlov experimented on dogs, Watson, in a tions mix the filtered percepts of the world with chilling expression of pragmatic *behaviourism, did percepts acquired at other times, as well as with innate on human infants (Watson and Rayner 1920).

Fear conditioning

He frightened them with unexpected noises or sudden removal of physical support. One of his subjects, Albert B., 9 months old, initially afraid and unfearful (LeDoux 1996; Maren et al 1996; Rogan and LeDoux 1996; Amorapanthet al 2000). It has already come to fear a laboratory rat upon association with a sharp noise that caused the infant to jump violently, a response in particular in the mammalian brain. It fell, and cry. The ordeal led Albert, involuntarily, to also cast light the role of *amygdala in learning, into the scientific literature (Harris 1979) memory, modulation, and expression of emotional (Figure 29); nowadays, it would have probably led the behaviour. And almost as a fringe benefit, fear conditioning became the first system in which a *long-author into disgrace.

Fear is an emotion. Over the years, the concept of emotions as potentiation-like mechanism was shown to frequently considered as intimate feelings unfit for occur in learning in the behaving organism (Rogan mechanistic analysis. Most discussions of brain system (LeDoux 1997).

Ideas of emotion were rather vague and converged on the idea that emotions are subserved by the so-called biology, and pharmacology led to a model of Pavlovian limbic system. As in many other chapters in science, fear conditioning. According to this model, the CS and major breakthrough in understanding the neural substrates of emotion was provided by a *reductionist analysis of a *simple system. In this case, the *system was *classical (alias Pavlovian) fear conditioning, and involved in the expression of fear. After specifically its auditory version. A rat hears a tone (the training, the CS alone, upon reaching the amygdala, conditioned stimulus, CS) in conjunction with electric shock to the foot (the unconditioned stimulus, US). Although the circuit seems rather simple, several caveats are in place. First, The shock elicits a fear response (unconditioned although many laboratories agree that *acquisition and response). The tone then comes to elicit a fear response. Memory of fear conditioning occurs in the amygdala, in the absence of shock (conditioned response, CR). There are some who propose that the amygdala only The CR is manifested in multiple physiological responses, including increased blood pressure, secretions, and stress hormones, startle, and freezing. The latter is when fear learning becomes more complex, especially rapid and robust measure of fear (Blanchard 1969), although not necessarily the easiest to quantify. Pavlovian fear conditioning has proven to be a fruitful experimental system (Davis 1992; LeDoux 1997). In *real-life, the *context of the

case the hippocampus becomes involved (Maren et al 1998; but see McNish et al 1997). The *cerebral cortex is also expected to play a part. Yet, in approaching a complex system, one may be better off in adhering first to *Ockham's razor, and elemental Pavlovian fear conditioning offers an opportunity to do just that.

Fear conditioning unveils how the brain deals with the tension between speed and accuracy of response to danger. Analysis of even simple fear learning shows that the information about the CS reaches the amygdala via two different pathways (LeDoux 1996). A short one travels directly from the sensory thalamus to the amygdala and supplies information on general features of the stimulus but not on its detailed attributes. This short channel makes it possible for the organism to respond immediately. For a wandering rabbit, it is surely advisable to react as fast as possible to a fox-like-shadow and false positive, rather than contemplate the fine perceptual details of the predators' mouth from within. The other pathway runs from the thalamus to



Fig. 29 Little Albert undergoes fear conditioning to a rat, as detailed in Watson and Rayner (1920; courtesy of Ben Harris, see also Harris 1979). Conditioning paradigms did change dramatically over the past 80 years: nowadays, the rat is the one that is conditioned, while the human *subject only observes.

the cortex and from there to the amygdala. This slower route provides information about sensory attributes of the CS and can modulate the initial response. Functional neuroimaging studies of the assassination of President John F. Kennedy, 14 years earlier. The fact that this type of *recall involves what is true for the rat is true for Homo sapiens. The illumination of a specific scene explains the flashbulb amygdala is active when we acquire and express fear metaphor. Since then, recollections of additional (Adolphs et al 1995; LaBar et al 1998)¹, and subcortical, thalamo-amygdalar connections enable us to read (McCloskey et al 1988; Neisser and Harsch 1992), have to a fearful stimulus before we even get a chance to be used to analyse further the flashbulb memory think about it (Morris et al 1999).

Under certain circumstances fear conditioning situations could culminate in anxiety, neurosis and phobia. Fear and Anxiety share many features (Davis 1992) in which they were encountered, is clearly to the point where some authors used them interchangeably (e.g. Mowrer 1938). However, Fear and Anxiety are not the same. The first is a response to a settled. Among them: Are flashbulb memories faith-specific, identified event or situation; the second isful? And are the biological mechanisms that subserve abnormally heightened vigilance in anticipation of such memories unique?

An event or situation that are construed, either consciously or subconsciously, as threatening (Rachamimov, lucid, vivid, and detailed recollections. But already at 1998). In a neurotic state, the mere fact that the threat at the outset of the investigation of flashbulb memory it can be logically deemed unreal does not alleviate the. It became evident that these memories do not preserve all suffering. Our prefrontal cortex is normally capable of monitoring and assessing ongoing fearful and (1997). In addition, several studies have indicated that emotional situations (*Working memory of fear) the reported details are not necessarily accurate to and emotion; Davidson and Irwin 1999). This exerts begin with, and furthermore, could change with time some control over the response, and anticipates its (McCloskey et al 1988; Neisser and Harsch 1992). A consequences. However, when danger is subjectively appreciated as immediate and intense, *noradrenalin that flashbulb memories are unreliable, is that personal ergic and *dopaminergic neuromodulation disrupts consequentiality and emotional significance are not easy prefrontal cognitive functions (Arnsten 1998). Hence, to quantify and compare. Even though some signal public when life is in peril, evolution clearly relies more on life events are expected to generate flashbulb memories, instinct than on reason, but unfortunately, this is also in reality they do so in some subjects but not in others the case when the danger is only in the mental eyes (Conway 1995). The test protocol that is used to identify flashbulb memory could also itself influence the outcome, i.e., whether the recollection will be accurate or not (Koriat and Goldsmith 1996); *collective memory *cues and demand characteristic effects (*bias) may certainly colour the response. Such complications notwithstanding, it does appear that the fidelity of flashbulb memory, similarly to the fidelity of other *episodic recollections, must be treated with caution (*false memory).

Selected associations: Amygdala, ^{Ala}Priori, Classical conditioning, Consolidation, Limbic system

¹In a gender-dependent manner: in emotional situations, the right amygdala is preferentially activated in the male, the left amygdala in the female (Calhoun 2001).

Flashbulb memory

Memory for the circumstances in which one first learned of a *surprising, consequential, or emotionally arousing event.

Are flashbulb memories unique in their robustness and vividness? Some authors propose that this type of memory is not qualitatively different from other types of emotional memory (Christianson 1992; *fear conditioning). Others claim that flashbulb memories do comprise a distinct class of traces (Conway 1995). One type of suggestions is that the encoding of information during the *acquisition of the flashbulb memory is unique (Brown and Kulik 1977), in that it involves a

Flashbulb memory

particularly intense activation of specific brain circuits cases, but to obliteration of memory or repression of its (e.g. *limbic system; Livingston 1967). This leads to theretrieval in others (Loftus and Kaufman 1992).

ÔprintingÕ of a highly detailed and robust *internal representation of the association of the salient event with the *context. Other types of explanations propose that there is nothing special about the encoding of flashbulb memory, but that this type of memory is special only because the intense emotional valence of the original event causes the information to be assigned extra importance over time, or be *retrieved extensively, resulting in a more robust, although not necessarily more faithful, memory (Neisser and Harsch 1992).

Selected associations: Attention, Collective memory, Consolidation, Context, Surprise

Forgetting

1. The loss of learned information.

2. The inability to *retrieve learned information.

In recent years, brain research has unveiled clues to the biological mechanisms that encode the memory of intensely emotional and consequential events. These candidate mechanisms deal with two *levels of brain organization: the circuit level and the cellular level. The

circuit mechanisms are assumed to involve subcortical modulation of the *cerebral cortex, which causes certain sensory events to be *perceived as highly salient. Herman Ebbinghaus, the progenitor of quantitative psychology (Gorfein and Hoffman 1987), remarked that Ôall sorts of ideas, if left to themselves, are because of the concomitant activation (*coincidence) gradually forgottenÕ (Ebbinghaus 1885). Whether this detection) of neuromodulatory systems such as the statement is acceptable by laypersons and scientists *acetylcholine and the *noradrenaline systems (Naoraike, depends on what is meant by ÔforgottenÕ. If Ôforgot-

and Dudai 1996; McGaugh and Cahill 1997; Tang et al 1997) means Ôerased from memoryÕ, then many, including

(1997). This hypothesis is a neurobiological version of professional psychologists, tend to believe that every-

the Ôunique acquisitionÕ accounts mentioned above we learn is never erased (Loftus and Loftus 1980).

(Brown and Kulik 1977). The cellular explanations are In contrast, others, starting with Plato (caetetus 1991),

based on the assumption that the consolidation of trust that memory traces can indeed be obliterated long-term memory is triggered by a certain configura-

(Ôdrowned in the waters of LetheÕ, Galton 1879) is

tion of transcription factors (*CREB, *immediate early genes, *spaced training). This configuration acts as a switch that distinguishes an obliterated memory from a nonretrievable

molecular switch that induces a wave of activation one, the use of ÔretrievalÕ in the definition of ÔforgettingÕ or de-repression of gene expression at the modula(definition 2 above) is therefore a safer bet.

ted *synapses, culminating in the remodelling of the network connections and in the stabilization of the and *memory *systems (*taxony), but its magnitude (Bartsch et al 1995). The idea is that those tude and kinetics depend on the type of memory, on its momentary events that give rise to a flashbulb memory use, and on the conditions under which it is tapped induce the right configuration of the transcription fac- (Baddeley 1997). The variables involved are not tors very rapidlyÑin a few seconds or a few minutes straightforward. People display surprising forgetfulness instead of several hours. If this is true, it implies that the even for personal events that could be expected to rank kinetics of memory *consolidation is not fixed, but rather as important indeed to the *subject, ranging from depends on the conditions of training (Frey and Morris salient changes in personal status (Jencks 1979) to 1997; Dudai and Morris 2000). It also suggests that a routine dietary behaviour (Smith 1991). And when a robust long-term memory trace can be induced by frequently retrieved memory does seem ÔunforgettableÕ. Ôinstant consolidationÕ without necessarily going through it the original *engram that is reinforced with a labile short-term *phase. By the way, the notion that repeated use, or, alternatively, a changing engram that is long-term memory can be established in the absence of reconstructed and then *consolidated each time anew short-term memory is in line with evidence from other (*flashbulb memory, *real-life memory)? In most *systems (e.g. Emptage and Carew 1993).

memory *paradigms one is able to come up with

Whatever the mechanisms of flashbulb memory are, Ôforgetting curvesÕ (Ebbinghaus 1885), which show they should also explain why it is that intense emotional deterioration in *performance over time for almost experiences lead to remarkable memories in some material learned, except that in some cases the

time-scale is minutes or hours (e.g. nonsense syllables, *ibid*), whereas in others it is years to decades (e.g. a foreign language or autobiographical episodes; Linton 1978; Bahrick 1984). A useful method to quantify forgetting, or actually [1-forgetting], in the laboratory is to measure ÔsavingÕ. This is the decrease in the amount of training needed on retraining on the original task (hence measuring Ôthe saving of work in the case of relearningÕ; Ebbinghaus 1885). *Real-life approaches to forgetting focus on the determination of the loss in details and veridicality of the memory (definition 3; Koriat et al 2000; *false memory).

One could come up with multiple types of potential explanations for the various manifestations of forgetting. Four types of hypotheses concerning either true or apparent forgetting have specifically attracted the attention of experimentalists and theoreticians (Freud 1901, 1915; Pavlov 1927; McGeoch 1932; Underwood and Extrand 1966; Shiffrin and Atkinson 1969; Tulving 1983; Capaldi and Neath 1995).

1. Forgetting occurs because the biological substrate daily life (*prospective memory), the real nuisance that encodes the engram disintegrates or decays with time. This decay may involve the entire representation or, more likely, fragments of it, up to a point where degradation ceases to be Ôgraceful forgetfulnessÕ (Nietzsche, cited in Roth 1989). People who (*persistence) and becomes catastrophic.
 2. Forgetting occurs because the learned information is processed in a way that erases part(s) of the engram. This could be the consequence of either passive or active processes. ÔPassiveÕ means that with mere usage, the fidelity of the information deteriorates, and the representation gets noisy and ultimately meaninglessly. It could also facilitate the acquisition of new *skills, ÔActiveÕ means that information is actively being used to optimize storage, and last but not pruned over time, or ÔunlearnedÕ, to optimize storage, forgetting bad memories could smoothen the *capacity, retrieval, or performance (Hopfield et al 1983; McClelland et al 1995; *consolidation).
 3. A related possibility is that forgetting, or at least apparent forgetting (see below), occurs because other information alters the engram or interferes with its expression. The interference may be ÔproactiveÕ (of earlier learning on later learning), or whose water induced forgetfulness in those who drank it. ÔretroactiveÕ (of later learning on the recall of previously learned information; see examples in *classical conditioning). A notable case is *experimental extinction, in which an acquired *association is inhibited by repetitive post-training presentation of the unrewarded stimulus. The original information could still exist, and in experimental extinction of associative conditioning indeed it does, but it becomes ineffective in controlling behaviour. As noted above, the interaction may also occur in (2001).
- Although forgetting is frequently regarded as a nuisance, for example, when it involves tasks to be performed in
- Selected associations: Amnesia, Experimental extinction, Infantile amnesia, Retrieval
-
- Lethe was the mythological river in Hades, the Land of the Dead. In psychoanalysis, defence mechanisms are postulated unconscious mental operations that are aimed at the reduction of painful emotions, ideas, and drives (Vaillant 1992).

Ôre-consolidationÕ of the memory immediately after its retrieval. A special type of interference is promoted in psychoanalytic theory. This is ÔrepressionÕ, a defence mechanism that attempts to turn anxiety-provoking memories non-retrievable (Freud 1915; Laplanche and Pontalis 1973; *infantile amnesia, *palimpsest). Some authors will argue that interference mechanisms are not *fata fide* forgetting, because the original trace is not really obliterated; yet, as already noted, unless one deals with a straightforward case of experimental extinction, practically, it is usually difficult to determine whether a forgotten memory is abolished or only repressed.

Forgetting is due to the lack of appropriate retrieval cues or to the use of an inappropriate processing mode in retrieval (*transfer). This again is apparent forgetting; given the appropriate cues and processing, the memory will be actualized.

Although forgetting is frequently regarded as a nuisance, for example, when it involves tasks to be performed in daily life (*prospective memory), the real nuisance that encodes the engram might be not to forget at all. ÔThus even a happy life is possible without remembrance, as the beast shows; but a life in any true sense is absolutely impossible without forgetfulnessÕ (Nietzsche, cited in Roth 1989). People who suffer from ÔhyperamnesiaÕ, the antipode of *amnesia,

suffer from ÔhyperamnesiaÕ, the antipode of *amnesia, are miserable and would rather forget [two *classic cases Monsieur X of Guillons, cited in Roth (1989), and the This could be the consequence of either passive or active processes. ÔPassiveÕ means that with mere usage, increase the signal-to-noise ratio of our cognitive the fidelity of the information deteriorates, and the narratives, and *generalize about the world. Occasion-representation gets noisy and ultimately meaninglessly. It could also facilitate the acquisition of new *skills, ÔActiveÕ means that information is actively being used to optimize storage, and last but not pruned over time, or ÔunlearnedÕ, to optimize storage, forgetting bad memories could smoothen the roughness of life. We should not forget that.

Selected associations: Amnesia, Experimental extinction, Infantile amnesia, Retrieval

Lethe was the mythological river in Hades, the Land of the Dead. In psychoanalysis, defence mechanisms are postulated unconscious mental operations that are aimed at the reduction of painful emotions, ideas, and drives (Vaillant 1992).

³In psychoanalysis, defence mechanisms are postulated unconscious mental operations that are aimed at the reduction of painful emotions, ideas, and drives (Vaillant 1992).

An intriguing hypothesis is that ÔunlearningÕ, pruning, and reorganization of information occurs in dream sleep (Crick and Mitchison 1983; Sejnowski 1995). If this is the case, then we do not only forget dreams, we also dream to forget.

⁴For candidate repression processes in brain, see Anderson and Crump (2001).

Functional neuroimaging

The visualization of the functional organization of the brain by electromagnetic or optical methods.

The search for the *engram is a mapping expedition. It be noted at the outset, which reflect on the contribution requires *maps that chart both anatomy and function. of the functional neuroimaging methods to the analysis-Anatomyper seonly rarely tells us what specific brain sis of learning and memory in brain. First, these structures do. This is evident, by the way, from somemethods differ in their spatial and temporal resolution neuroanatomical terms that mean only a fruit or a sea(Figure 30). Second, they differ in the nature of the monster (e.g. *amygdala, *hippocampus). Surely if signal that they measure; some detect electrical activity early anatomists would have known something aboutdirectly, others only haemodynamic and metabolic what these structures do, they would have called themchanges secondary to electrical activity. And third, these by other names. Indeed, some idea on function couldmethods differ in the degree of invasiveness, which occasionally be obtained from tracing the connectionsmeans that some could be safely applied to behaving between various sites, e.g. a pathway from the olfactoryvolunteers, others to more daring volunteers, yet others bulb to the piriform cortex does suggest that the latterto immobilized laboratory animals only.

deals with olfaction, not vision. But the insight into function obtained this way is still limited. Anatomical tional neuroimaging method was electroencephalogram-brain mapping was born in antiquity (Galen 2nd century phy (EEG), which measures electrical potential AD; Thorndike 1923). It underwent a revolution in the differences among locations on or in the brain as a nineteenth century with the development of microscopy function of time and place. (The abbreviation ÔEEGÕ is and histology (Brazier 1988; history fans might also wishused both for the method and for the records that it to see DeFelipe and Jones 1988). The anatomical cartogenerates, ÔelectroencephalogramsÕ) The first to report raphy of the brain has reached new heights in the seonthat spontaneous electrical activity can be recorded half of the twentieth century. This was made possible byfrom the scalp of animals was Caton (1875). The effect the introduction of sophisticated tracing methods, of physiological conditions on these patterns of activity based on specific molecular probes such as lectinwas further investigated by his contemporaries (e.g. (proteins that bind sugars characteristic of specific cellsDanielovsky, see Brazier 1988). But it took several and cellular compartments), radioactive tracers, and decades before EEG had captivated the worldÕs attention enzymatic reactions (Brodal 1998; Cowan 1998).

Functional brain mapping has a long history as well:ing on his own son, and discovered a rhythmic the same Galen mentioned above was said to haveoscillation of electric potential with a frequency of already noted the effect of brain lesions on behaviourabout 8Ð12 Hz, associated with relaxed wakefulness. (Thorndike 1923). This approach had gained popular- Adrian and Matthews (1934) replicated BergerÕs finding among brain scientists in the nineteenth century; soings and localized the source of the ÔBerger rhythmÕ to was the study of the behavioural consequence of stimuthe occipital lobe. This was the first use of EEG in functionation of loci in the brain by electric currents (Brazier tional brain mapping.

1988; Finger 2000). Almost a century later, the intro- Scalp EEG is assumed to reflect mainly the summa-duction of the microelectrode has already permitted tion of graded post*synaptic potentials originating in the analysis of the response of single nerve cells in the *cerebral cortex. Detection of EEG sources deep in brain to specific sensory *stimuli. This has yielded thethe brain requires insertion of invasive electrodes. The first detailed functional brain maps (for a *classic contribution of cortical neurons to the EEG is itself a example, see Hubel and Wiesel 1977). However, thefunction of the endogenous states of the neuron and term Ôfunctional neuroimagingÕ nowadays does note activity of its input circuits (Lopes da Silva 1991). To commonly connote the construction of functional make the story even more complex, the electrical signal brain maps by meticulous analysis of the response obf scalp EEG is distorted by the intervening tissue and is single neurons, nor the inference of function from highly sensitive to the location of the recording elec-anatomical or metabolic lesions, but rather the visuali-trode. Not surprisingly, the task of the investigator zation of the function of large terrains of the brain by trying to identify and understand the source and phys-electromagnetic or optical methods.

Functional neuroimaging is based on electrophysiological methods; or tomographic methods(mos, a ÔcutÕ in Greek, so called because these methods involve construction of three-dimensional images from planar images, or ÔcutsÕ); or optical methods. The various methods will be explained below. Three points should

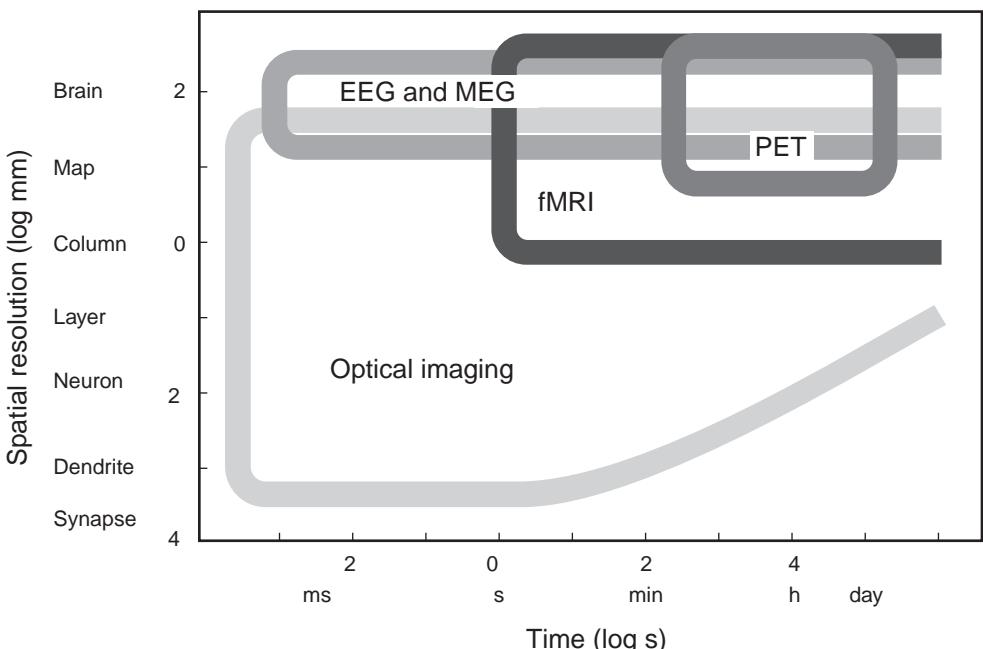


Fig. 30 Spatial resolution and temporal characteristics of various functional neuroimaging methods. *Time* refers to the time window during which experiments could be conducted. *Spatial resolution* is the imaging of intrinsic signals, or voltage-sensitive dyes, calcium-sensitive dyes, or optical probes; these methods differ in their spatial and temporal resolution but are combined in the diagram for simplicity. EEG, electroencephalography; MEG, magnetoencephalography; fMRI, functional magnetic resonance imaging; PET, positron emission tomography. PET time window is closed because it involves radionucleides that cannot be administered repeatedly over relatively long periods. Optical imaging is the most invasive of these methods yet provides the highest temporal and spatial resolution. EEG is the least invasive for reasons indicated in the text, PET and fMRI have contributed most to the search for the *engram, and fMRI is considered of the in the field of human memory research.

that of an expert attempting to diagnose the problems of a computer by holding a voltmeter up to it (Bodis-Wollner 1987). Keeping this in mind, still, a lot can be done. The ongoing activity recorded from the scalp of a freely moving subjects, including in healthy subject is at a frequency range of 1–30 Hz, with a few dominant state-dependent frequencies (the Berger rhythm (12–30 Hz); (0.5–4 Hz); and (4–7 Hz). EEG can also be used to detect event-related potentials (EP) or event-related potentials (ERPs), the latter being magnetoecephalography (MEG), offers some advantages, including a smaller sensitivity of the EP, as the latter is also used in cellular electrophysiology to denote the stimulus response of single neurons and localization of the source signal (Wiklund et al 1993). At the time of writing, MEG requires a cumbersome and expensive set-up, and the subject must remain immobilized throughout the measurement. In recent years negative wave (contingent negative variation, CNV) the use of many electrodes (10), the improvement of an imperative stimulus is preceded by a low frequency (Walter et al 1964); a rare stimulus in a sequence of frequent stimuli evokes a characteristic positive component (Sutton et al 1965, *surprise). The improvement in computational power, and the accumulating support from other disciplines such as cellular physiology, has boosted EEG as a functional mapping

method (Gevins et al 1999). Still, so far the major proven strength of EEG in research is in detecting and separating has contributed tremendously to neurocognitive mapping, by time and type, broad electrophysiological phenomena (Raichle 1983; Cherry and Phelps 1996). Selected nomenclatural correlates of fast cognitive processes examples of the localization of memory systems in the humans, e.g. in *attention, *acquisition, and *retrieval of mammalian brain by PET are provided in Buckner and memory (e.g. Kutas 1988; Johnson 1995; Patterson Tulving 1995; Buckner et al 1995; Fletcher et al 1997; 1995; Friedman et al 1996; Miltner et al 1999). Areas in Maguire et al 1997, 1998; Smith and Jonides 1997. For which EEG has been proven particularly useful are the example, PET has enabled remarkable insight into the analysis of *working memory, and the acquisition, brain systems that subserve spatial memory and its use retrieval, and the dependence of long-term retrieval on navigation in humans, in situations that simulate acquisition in *declarative tasks in humans; in all these real-life (Maguire et al 1997, 1998; *hippocampus). It cases the task typically involves verbal material.

has also provided a tremendous boost to the analysis of

2. Positron emission tomography (PET). This method can be used to measure certain aspects of cerebral metabolism, such as local blood flow, glucose utilization (*nutrient), or *receptor occupancy. PET is based on the use of isotopes that decay by the emission of

positrons (positive electrons). The emitted positron collides with an electron to produce two annihilation photons that travel 180° apart. Coincident detection of the two

annihilation photons permits the position of their source to be determined. In practice, a biologically relevant compound, labelled with the appropriate isotope, is injected intravenously or inhaled. The emitted radioactivity is monitored by an external ring scanner and used to compute

The isotopes used have a short half-life, in the range of minutes, so that large doses of radioactivity can be administered within acceptable safety limits. The short half-life necessitates access to an accelerator to produce

The tracers on site. For example, compounds containing oxygen into the blood as an exogenous contrast agent (Rosen et al 1989). But then a better method has been devised.

differences in regional cerebral blood flow. The underlying assumption is that such haemodynamic changes reflect alteration in neural activity; this notion can be traced back at least to James (1890) and Roy and Sherrington (1890; for a related pre-scientific idea, see Descartes 1649). Amino acids labelled

with H_2^{15}O are used to measure task-related receptor occupancy, and 2-deoxy- $\text{F}^{18}\text{-D}-\text{glucose}$ (^{18}F -2DG) to map glucose metabolism. The 2DG method was originally used for post-mortem imaging (Sokoloff et al 1977).

2DG is an analogue of glucose PET, is that the haemodynamic changes reflect regional that is taken up by the cells, but cannot be metabolized

like glucose, and is therefore trapped in an amount proportional to the level of glucose consumption. The assumption is that a high metabolic rate is indicative of increased neuronal activity. In the original method, resolution is in the range of a few seconds. The spatial

^{14}C -2DG was administered before the task, the signal is slower, and therefore, practically, the temporal increased neuronal activity. In the original method, resolution is in the range of a few seconds. The spatial

^{14}C -2DG was administered before the task, the signal is slower, and therefore, practically, the temporal increased neuronal activity. In the original method, resolution is in the range of a few seconds. The spatial

^{14}C -2DG was administered before the task, the signal is slower, and therefore, practically, the temporal increased neuronal activity. In the original method, resolution is in the range of a few seconds. The spatial

quantitative autoradiography of brain slices. In PET, of Advanced, high field fMRI methods, based on the course, the subject can live happily afterwards.

detection of early local changes in oxygen consumption

rather than the delayed, more diffused alterations in blood flow, could potentially improve the resolution (Kim et al 2000; on this issue see also Vanzetta and Grinvald 1999; Logothetis 2000). In behavioural experiments, to increase the signal-to-noise ratio, paradigms that use fMRI (or PET) commonly collect multiple images over extended time periods that contain successive trials of the same task (Öblock task paradigms). Such protocols do not supply information about responses that are time-locked to single trials and about trial-to-trial changes as opposed, for example, to EEG studies of ERPs (see above). In recent years, protocols have been developed that allow analysis of trial-to-trial responses in fMRI as well (Buckner et al 1996). This event-related fMRI is particularly useful in investigating brain response in situations in which different stimuli are mixed over time, and where the response is expected to vary from one stimulus to another.

fMRI is considered noninvasive, although the long-term safety for humans of the high magnetic fields that are already used on the *monkey must still be determined. The advantages of the high resolution and the assumed noninvasiveness clearly outweigh the fact that fMRI does not measure neuronal activity directly. At the same time, this situation emphasizes the need to understand in fine details the source, specificity, and physiological significance of the biological signal (Vanzetta and Grinvald 1999; Kist et al 2000; Logothetis et al 2001). The contribution of fMRI to the field of memory research is clearly on the ascending limb (Kelley et al 1998; in the original publication, the fMRI images are presented in pseudocolours).

(the question how can a single human being read a book) this literature certainly deserves a special functional neuroimaging study). Results cited in many entries in this book are either based on or supported by fMRI (e.g. *acquisition, *cerebral cortex, *hippocampus, *retrieval, *skill; for selected examples see Bushnell et al 1998; Fernandez et al 1998; Kelley et al 1998; LaBar et al. 1998; Poldrack et al 1998; Dolan and Fletcher 1999; Wagner et al 1999; Cabeza et al 2001; Figure 31).

4. Optical imaging Optical functional neuroimaging methods rely on the detection of intrinsic activity-dependent optical changes in neural tissue, or on the use of voltage-sensitive dyes, ion sensitive dyes and other extrinsic optical probes and tracers. Alterations in the intrinsic optical properties of nerve fibres were minimized. For the first time it was reported in the late 1940s (Hill and Keynes 1949) that the neuronal activity was described by Tasaki (1968). The voltage-sensitive-dye imaging methodology was subsequently improved and put to use by a number of groups (e.g. Cohen et al 1974, Grinvald et al 1981).

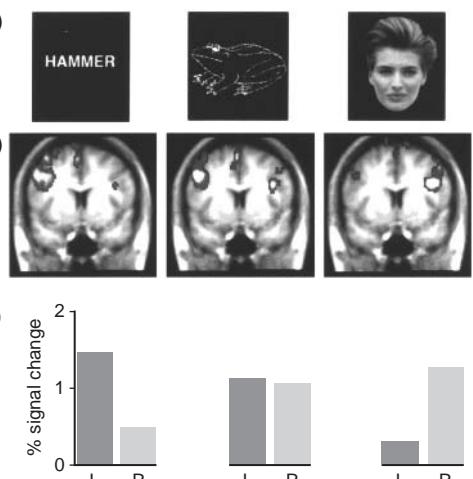


Fig. 31 An example of the use of fMRI to study brain substrates of memory.

Learning. Human subjects were subjected to fMRI scans while being presented with three types of visual stimuli (a: from left to right): word, object, and face. The instructions were to remember each item for a later memory test. The word-encoding task was expected to depend on verbal processing, the object on both verbal and nonverbal processing, and the face on nonverbal processing. Coronal sections (b) show dorsal frontal cortex activation. Peak activation was observed in the left frontal cortex for word encoding, the left and right dorsal frontal for object encoding, and the right dorsal frontal cortex for face encoding. (c) The per cent signal change in the left (L) and right (R) hemispheres. There is a clear hemispheric asymmetry in the verbal and nonverbal encoding situations. Adapted from Kelley et al (1998); in the original publication, the fMRI images are presented in pseudocolours.

Optical imaging of intrinsic signals relies on activity-dependent changes in light reflected from the imaged tissue. The intrinsic signals stem from activity-dependent alterations in local blood volume, oxygenation of haemoglobin, and light scattering caused by the local movement of water, ions, and released neurotransmitter(s) (Grinvald et al 1986; Malonek et al 1997; Vanzetta and Grinvald 1999). Optical imaging of intrinsic signals in its current state of the art is invasive, as it requires opening the skull. The optical changes can be visualized through intact dura or thinned bone, hence its invasiveness in experimental animals can be minimized. For the imaged tissue itself the process is nondestructive. The spatial resolution is high (Staining with voltage-sensitive dyes to measure range), whereas the temporal resolution depends on the rise time of the haemodynamic and metabolic changes.

Intrinsic imaging has been extensively employed to analyse the functional architecture of the mammalian brain, especially the visual system. The measurements

can be repeatedly performed on the same subject over long periods (in fact, many weeks). The latter property *criteria, some authors think that so far, the contribution is particularly advantageous in the study of the use and/or of functional neuroimaging to memory research is reuse of memory (*phase).

a bit overrated, whereas others think that this set of

The use of voltage sensitive dyes involves application methodologies has already passed the test of memory of dyes to the brain surface. This is invasive, and research in flying colours.

restricts the approach to animal studies. The advantage is a high temporal and spatial resolution (Shoham 1999). Among the optical imaging methods, this is the one that follows neuronal activity most faithfully, as it monitors real-time alterations in membrane potential.

An example of another optical imaging method that relies on extrinsic chromophores is *calcium imaging, i.e. using compounds that change their optical properties as a function of calcium concentration (e.g. Faber et al 1999).

The contribution of optical imaging methods to the neurobiology of memory has so far been limited. These methods, none the less, have a remarkable potential to contribute to the analysis of brain mechanisms of learning and memory in experimental animals. The use of optical imaging in the analysis of the olfactory perception and olfactory memory is only one example.

Calcium imaging has been used to detect experience-dependent alterations in odour *maps in the olfactory brain of the *classically conditioned *honeybee (Faber & O'Donnell 1999). Intrinsic imaging has been used to map stimulus or response from another. This is why it is convenient to treat these faculties together. Discrimination of the olfactory bulb as well (Rubin and Katz 1999).

Selected associations: Dimension, Engram, Homo sapiens, Phrenology

Generalization

1. Partial equivalence in the behavioural effect of different *stimuli or responses.

2. The acquired response to a class of stimuli on the basis of experience with exemplars of the class.

3. The occurrence of a learned response in circumstances that differ from those prevailing during *acquisition.

increases the repertoire of fine-tuned *perception and

All in all, functional neuroimaging is exciting, useful, and popular. Its potential for being even more so in the future is substantial. It has already provided us with remarkable data on the involvement of distinct brain areas and circuits in various phases and types of memory. But it is definitely not a magic bullet. The exploitation of its potential depends on proper adaptation of the specific technique to the right question and system, and in combining multiple synergistic methodologies in the experimental protocol. Selected examples include the use of molecular biology to image the dynamics of gene expression in the brain of laboratory animals (Service 1999), hence creating the opportunity to monitor correlates of consolidation in real time; the use of behavioural assays to image the substrates of memory illusions (Schacter 1996; Abeza et al 2001, *false memory); and the differential contribution of brain circuits to mathematical thinking (Dehaene et al 1999). Functional neuroimaging will be judged in the history of memory research not by the dazzling feats of the technology or by the aesthetics of pseudocoloured images, but rather by the ability to solve questions (e.g. Kosslyn 1999, *enigma).

*generalization is the functional counterpart of the ability to distinguish one stimulus from another. It is the ability to respond to them if this pays off behaviourally. The balance between discrimination and generalization is a function of the task and the situation. This balance in nature is nicely illustrated in the primitive brain of the rat, which can unexpectedly detect a snake-like shadow. The visual system, and in the thalamo-amygdala pathway transmits only some general features of the stimulus (that it is a long undulating object), but not detailed sensory attributes (revealing that it is only a loose black water pipe). This channel makes it possible for the organism to respond faster to the generalized gestalt of a snake, risking a false-positive response. The slightly slower

thalamocortico-amygadaloid route provides information about the detailed, discriminative sensory attributes of the stimulus (*cue), and prevents further costly physiological and behavioural reactions.

Generalization, discrimination, and their modulation by experience became fashionable research topic early in the history of psychology (Boring 1950 and Schoenfeld 1950). Since then, it is common practice to distinguish *Östimulus generalizationÖ* from *Öresponse generalizationÖ*. Stimulus generalization refers to situations in which a subject that had learned to respond to a particular stimulus comes to elicit the same response to other, similar stimuli. Response generalization refers to situations in which a subject that had learned to respond to a given stimulus comes to elicit other, similar responses to the same stimulus. A useful measure of stimulus generalization is the *Ögeneralization gradientÖ*, which depicts the range response to a conditioned stimulus (Figure 32). In some paradigms, the more difficult the task, the less the generalization, hence the steeper the generalization gradient (Ahissar and Hochstein 1997). A corresponding measure in discrimination is the *Öjust-noticeable-differenceÖ* (*ÖjndÖ*). This is the smallest change along a stimulus dimension that can still be discriminated. The relationship between the change in stimulus intensity that can just be discriminated (and the intensity of the stimulus λ) is approximated by *ÖWeberÖs lawÖ*: $\Delta\lambda/\lambda = \text{constant}$. The relation between the stimulus magnitude λ and the subjective sensation magnitude λ' is given by *ÖFechnerÖs lawÖ* ($\lambda' = k \log(\lambda)$ where k is a constant; Gescheider 1997).

Note that both opposed to nonsense objects, can markedly facilitate are not really *ÖlawsÖ* but merely generalizations, which discrimination learning (Jarvik 1953). Discrimination only approximate reality under limited conditions analysis is routinely used in psychophysics to study perceptual competence and use-dependent modification (*algorithm).

Discrimination is invaluable in the study of conditioning paradigms, in which the subject's ability to acquire and store new information is quantified by its ability to distinguish among stimuli and associate the appropriate stimulus with the unconditioned stimulus or *reinforcer (*classical conditioning, *instrumental conditioning). The use of discrimination protocols in probing the functional neuroanatomy of visual cortex considered as a rudimentary form of categorization, and its role in learning in the *monkey is but one example (e.g. Mishkin 1982). A similar use in dissecting the brain systems that process and learn chemical information, and in humans impair performance on even in the *rat is yet another example (e.g. Seltall 1996). An important variable in such experiments is the sensory attributes of the objects to be discriminated. Those attributes that support sensory differentiation are traditionally termed *ÖdiscriminandaÖ* (Tolman 1932). Appropriate discriminanda, e.g. of food items as according to their *level of analysis. Among the models

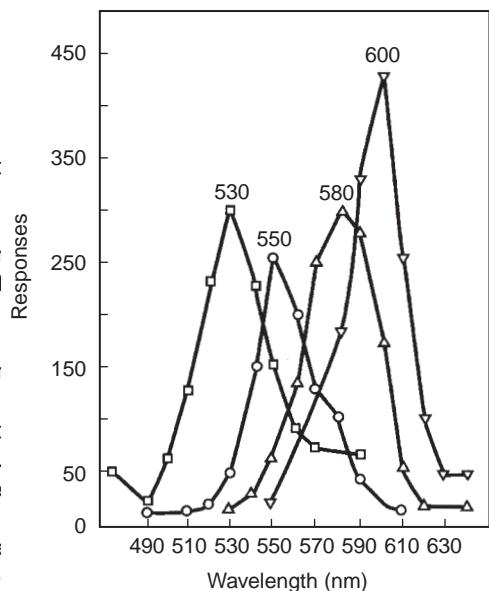


Fig. 32 Generalization gradients in the pigeon. Four groups of pigeons were trained to peck at an illuminated key to get food reinforcement. One group was trained to respond to illumination at 530 nm, another at 550 nm, still another at 580 nm, and the fourth at 600 nm. Generalization testing was carried out by presenting them with a series of random lights at different wavelengths and measuring their key pecking as a function of the wavelength. These curves depict the range of response for each group. The same gradients can, of course, be treated as discrimination curves. (Adapted from Guttmann and Kalish 1956.)

Generalization

that address computational and algorithmic levels, two nonactivated synapses (*context; for related findings prominent types are Ôfeature-basedÕ and Ôrule-basedÕ, see Martin et al 1997a). Nevertheless, at (Shanks and Darby 1998). Roughly speaking, feature represent, the possibility that the aforementioned observation-based models treat generalization as a bottom-up at the synaptic level contribute to generalization function of similarity in a feature-representation space, at the behavioural level should be treated only as whereas rule-based models envisage generalization as provocative speculation.

top-down process, based on abstract rules or categories
that are either innate (*a priori) or acquired. Models
that address the level of neuronal, ÔhardwareÕ imple-

mentation of generalization, date back to the early part
of the twentieth century. Pavlov proposed that the ^{1A} refreshing example of overgeneralization is cited by Bandura a
neuronal basis of generalization is a spread of excitation ^{Walters (1963)}. This is a letter from the advice column of a leading
from one specific brain region to another (Pavlov metropolitan newspaper. And so it goes:

1928). The idea was hence that the original stimulus Dear Abby:

was highly differentiated but the specificity lost due to My girl friend fixed me up with a blind date and I should have known
the rich interconnectivity of the brain. The same type of the minute he showed up in a bow tie that he couldn't be trusted
concept could be applied to response generalization fell for him like a rock. He got me to love him on purpose and then
This contrasts with a later hypothesis, that generaliza- to me and cheated on me. Every time I go with a man who wears
tion is the original state and differentiation develops bow tie, the same thing happens. I think girls should be warned about
with experience (Lashley and Wade 1946). It is likely men who wear them.
that in the brain both processes occur.

The circuit mechanisms of generalization are Dear Against:
expected to depend on the type of task. Whenever cognitive generalization is concerned, the *hippocampal^D Don't condemn all men who wear bow ties because of your experience. I know many a man behind a bow tie who can be trusted.
cortical axis immediately comes to mind (McClelland
and Goddard 1996). Which cellular and *synaptic
mechanisms subserve generalization in these circuits? Is
it at all subserved by distinct synaptic properties?

Glutamate

Recent observations on *long-term potentiation (LTP)
and synaptic specificity suggest candidate processes ^{an} amino acid that functions as the primary
mechanisms. LTP is considered as an input-specific excitatory *neurotransmitter in the vertebrate
mechanism that modifies only use-activated synapses central nervous system.

Engert and Bonhoeffer (1997) reported, however, that
this specificity is rather limited: in their preparation, L-glutamate is present in the mammalian brain at
synapses at a distance of up to ⁷ from the focus of remarkably high concentrations. For a while this
potentiation were also potentiated, regardless of the observation, coupled with the ability of glutamate to
activation history. This is a distance that can accommodate neurons all over the brain, cast doubt on its role
date many synapses. Although the contribution of such in neurotransmission; for how can such a Ônon-specificÕ
neighbouring synapses to the relevant *representation agent mediate specific information? The case for
is not yet known, this observation hints at a type of local glutamate as a neurotransmitter in the invertebrate
process that might contribute to generalization. In neuromuscular junction was easier to establish
another type of experiment, Frey and Morris (1997) (Usherwood 1994; *criterion). But with time it became
found that the persistence of potentiation over time clear that not only is glutamate a transmitter in mammals
depends not only on local events at the activated brain^{Nit} is the major excitatory transmitter,
synapse but also on prior activity of other synapses or and as such is critical for ongoing activity in the central
the same neuron. Weak tetanic stimulation, which ordin nervous system. Furthermore, it is now known to play a
narily leads to short-lived LTP only, resulted in long- key part in neuronal *plasticity and learning.

term LTP, provided repeated tetanization had already Glutamate belongs to the family of amino acid
been applied as long as 2D3 hours earlier at another neurotransmitters. The closely related amino acids
input to the same population of neurons. This may be L-aspartate and homocysteine possibly play a part in
construed as yet another mechanism in which a specific excitatory neurotransmission as well. Other amino
synaptic input expands its sphere of effectiveness acids that serve as neurotransmitters are the inhibitory

neurotransmitter -aminobutyric acid (GABA), and glycine, which serves as an inhibitory neurotransmitter and also as a modulator of glutamatergic transmission². (Cooper et al 1996). In neurons, glutamate is synthesized from glucose via the Krebs cycle and transamination of -oxoglutarate, and from glutamine (imported from glia cells), by glutaminase. Glutamate released from pre-synaptic vesicles interacts with several types and subtypes of glutamate receptors, depending on the neuronal circuit, synaptic target, and physiological context. Two major types of glutamate receptors are known: ionotropic and metabotropic. The ionotropic receptors are ligand-gated ionic channels, permeable to cations. There are at least three subtypes of ionotropic receptors, which differ in their ligand binding as well as in channel properties. These receptor subtypes are each named after the glutamate analogue that activates the receptor preferentially: amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptors, N-methyl-D-aspartate (NMDA) receptors, and kainate receptors (Seuberg 1993; Hollman and Heinemann 1994). The metabotropic receptors (mGlu) are coupled to intracellular signal-transduction cascades, which, again, exist in multiple subtypes (Hollman and Heinemann 1994; Riedel 1996). Additional proteins interact with glutamate in the brain, among them high-affinity glutamate transporters that swiftly terminate the glutamatergic synaptic signal (Auger and Attwell 2000). The glutamate transporters fulfil another function as well. Excess extracellular glutamate is neurotoxic and responsible for neurodegeneration under certain pathological conditions (Meldrum and Garthwaite 1990; Michaelis 1998). The transporters maintain extracellular glutamate levels below those that cause excitotoxic damage. In doing so they contribute to the compartmentalization of glutamate in the brain, without which our brain cells get excessively excited and die.

Glutamate, and multiple types of its neuronal receptors, have been implicated in multiple facets of cellular, developmental and behavioural plasticity in many learning and memory species, paradigms and brain regions (e.g. Metzger 1986; Bannermaet et al 1995; Aamodt et al 1996; Riedel 1996; Riedel et al 1999; Catalan et al 1997; Rosenblum et al 1997; Bortolotto et al 1999; Hayash et al 2000). Glutamate is also critical for long-term potentiation, the zeitgeist cellular model of learning in the mammalian brain. Three points concerning the role of glutamate in plasticity are noteworthy.

1. Glutamate is a prime candidate for a synaptically transmitted stimulus that triggers acquisition and retrieval

It possibly subserves cellular and circuit operations in other phases of learning and memory as well. Glutamate plays a part in coincidence detection at synapses that detect and encode associations. A prominent coincidence detector is the NMDA receptor, which associates glutamate, depolarization, and probably additional molecular stimuli, such as glycine. The NMDA receptor is assumed to be instrumental in implementing elementary types of synaptic algorithms of associative learning. The plasticity at glutamatergic synapses could be expressed not only in use-dependent alterations in the availability of glutamate in the synapse, but also in use-dependent availability of the glutamatergic receptors (Shet et al 1999). Further, these receptors interact with other proteins in the membrane, the cytoplasm and the nucleus. This is achieved via soluble second messengers, and also via mechanical links in a protein-protein network that extends from the membrane deep into the cytoplasm (Ottersen and Landsend 1997; Wyszynski 1997). The role of glutamate in plasticity must therefore be considered in the context the spatiotemporal state of the multi-dimensional system of the transmitter molecules, their receptor sites, and the intracellular macromolecular web that is regulated by the interaction of the transmitter with the receptor. The same argument for complexity holds for other transmitters as well (e.g. Shabot 2000), only that at this stage we know more about the complexity of the glutamatergic signalling network because of its universal role in transmission and plasticity. This complexity turns the life of the investigator more interesting (or miserable, depending on the personalities involved), but clearly adds dimensions to the processes and mechanisms that implement neuronal plasticity.

Being such a ubiquitous molecular mediator of behaviourally meaningful stimuli, glutamate is an appealing candidate for perturbation experiments, in which developmental and behavioural plasticity are blocked by applying receptor antagonists to the postulated site(s) of the engram (e.g. Morisset et al 1986; Bannermaet et al 1995; Reidel 1996; Rosenblum et al 1997). The glutamatergic synapse could also become the focus of mimicry experiments, in which the behavioural stimulus is simulated by molecular or cellular manipulations (*method). This type of approach is illustrated by studies of pregnancy blocking in the mouse (Kabal 1994). In the female mouse, post-mating exposure to pheromones of strange male, but not to those of the mate, blocks pregnancy. The mate is recognized because the female

forms olfactory memory of his pheromones during manifestation of the *plasticity of organic material, but mating (*flashbulb memory?). This memory is sub- also as driving force of the daily operation of individuals served by the accessory olfactory system, and involves *cultures: ÔÉ Habit a second nature! Habit is ten reduction of GABAergic inhibition by *noradrenaline times natureÉ Habit is É the enormous fly-wheel of released in mating. Infusion of agonists of one of the societyÉ it keeps the fisherman and the deck-hand at mGlu receptors, which in this system reduce GABAer-sea through the winter; it holds the miner in its dark-gic inhibition, into the femaleÓs accessory olfactory bulb**ness**, and nails the countryman to his log-cabinÉ during an exposure to a male pheromone, mimics theMany a reader nowadays will clearly disagree with effect of mating by establishing a memory for that JamesÓ social conservatism, but not with his appreciation of the role in our life of automatic or semi-pheromone without mating.

The strong evidence that glutamate is involved in automatic procedures, many of which are acquired via plasticity and learning marks the components of the repetitive *stimulus-response conditioning (Thorndike glutamate system as targets for candidate mnemonid911; *instrumental conditioning). Habits could be drugs. Indeed, compounds that bind to the AMPA sensorimotor, emotional, or cognitive, or all of the receptor-channel complex are already under clinical above elements combined in a single assembled routine. trial as memory boosters (*nootropics).

Selected associations: Acquisition, Long-term potentiation, Neurotransmitter, Receptor, Synapse

They could be highly useful and beneficial, as in vocational training, because they spare *attentional and cognitive resources, perfect performance, and prevent superfluous response; but the same brain circuits that bring all these benefits could also go astray and generate ~~possibly~~ disturbing habits (Long and Miltenberger 1998; Robbins and Everitt 1999; Leckman and Riddle 2000).

Being independent of conscious awareness, habit is by definition a non*declarative (implicit) type of memory (Hirsh 1974; Mishkin et al 1984; Squire and Zola 1996; *skill, *taxonomy). As opposed to *declarative memory, which is subserved by *cortico*limbic circuits, habits are subserved by corticostriatal circuits, i.e. reciprocal connections between the *cerebral cortex and the basal ganglia (Mishkin et al 1984; Salmon and Butters 1995; Knowlton et al 1996; Joest et al 1999). Two selected studies, one in the *rat, the other in *Homo sapiens*, will serve to illustrate the conserved role of the corticostriatal circuits in the formation and expression

Habit

1. A behavioural routine capable of being formed and *performed in the absence of *conscious awareness.
2. A behavioural routine as in 1, *acquired gradually via repetitive experience.

Definition 1 refers to ÔhabitÓ irrespective of whether it is habit in mammals. innate (*a priori), acquired, or induced by disease or drugs. Definition 2 restricts ÔhabitÓ to a type of *learned behaviour; it is a special case of definition 1, but is stated separately because this is what ÔhabitÓ commonly means in the contemporary learning literature. In the early learning literature, ÔhabitÓ was also occasionally used to denote a learned act in general, but this is now unacceptable. Habits comprise a substantial chunk of each trial to choose an arm. The performance is our behavioural repertoire, often to a larger degree than scored as the number of revisits (i.e. errors) to arms we tend to concede. Driving a car becomes a habit, but so is also eating junk food, or delivering the same semifirst eight choices. Success in this type of task demands nar for the ninth time. Nowhere is the dominance of the rat to identify, classify, and remember multiple habit in our lives better epitomized than in JamesÓ *classical principles of psychology (1890). Dubbing organisms as Ôbundles of habitsÓ (referring to the generic definition), James considered habits not only as an inescapable arm. In the training trials, the rat is conditioned by

confining it with food to either the ÔlightÕ or the ÔdarkÕ sunny or rainy, on the basis of four visual patterns, each arm. In the test, both arms are left unbaited, and linked to the weather conditions with a prefixed probability, unknown to the subject in advance. On each trial, amount of time spent in each arm is recorded. This typeability, unknown to the subject in advance. On each trial, of task taps into the ability of the rat to associate a stimulus-one, two, or three of these cues are presented side ulus (light) with a food reward. In the win-staytask, by side on the computer screen, and the response four randomly selected arms are baited with food and on each trial is *reinforced by visual and auditory lit. The rat is placed on to the centre platform of the feedback. This task involves gradual learning shaped maze. Immediately after the rat leaves a lit arm havingby repetitive stimulusÐresponseÐreinforcement loops eaten the bait, the arm is rebaited. When the rat over multiple trials, and does not require conscious retrieves the second pellet for any arm, the light is awareness of the information accumulated over trials; turned off and no further food is placed there. Overall, these task attributes are characteristic of habit learning. the rat is required to visit each of the four lit arms twice. The probabilistic classification task can hence be used to earning eight pellets within a trial. The trial is termi- tap into the ability to form a habit. The multiple-choice nated after a fixed time or after the eight food pelletsquestionnaireferred to declarative information about have been retrieved. Entries into unlit arms are scoredhe procedures and episodes of the habit task. as errors. This task involves learning an approach. Knowlton et al (1996) used the two tasks to test three response to a specific sensory cue (light), irrespective ofgroups of subjects: *amnesic patients with bilateral other environmental cuesand repeat the choices to hippocampal or diencephalic damage; non*demented each lit arm within a trial. This is construed to involve patients with ParkinsonÔs disease, which involves the formation of a stimulusÐresponse habit (Packardstriatal damage; and healthy matched *controls. The et al 1989; McDonald and White 1993). amnesic patients learned the habit as well as the

By using groups of rats with circumscribed brain controls, but failed on the declarative task. The parkin- lesions, McDonald and White (1993) found that dam- sonian patients, in contrast, performed well on the age to the *hippocampal formation impaired acquisi- declarative task, but could not learn the habit. The con- tition of the win-shifttask but not of the conditioned cue clusion: formation of habit depends on intact striatal preferencer the win-staytask; damage to the lateral circuits, but not on intact mediotemporal circuits, *amygdala impaired acquisition of the conditioned cuewhereas the opposite is true for the declarative task. preference task but not of the win-shiftor win-stay To the causal observer, the maze habit and the proba- tasks; and damage to the dorsal striatum impairedibilistic classification habit may look very different. But acquisition of thewin-stay tasbut not of thewin-shift they do share a lot in common. This is evident first, or the conditioned cue preferencetask. Hence, these from the analysis of the behavioural task, which in both authors showed, by inferring function from dysfunc- cases depends on the formation, via repetitive stimulusÐ tion (*method), that the formation of a stimulusÐ responseÐreinforcement cycles, of a stimulusÐresponse response habit depends on the striatum, and that theroutine; and second, from the identity of the brain neural system that subserves habit could be dissociatedcircuits that are essential for the behaviour in both from the neural systems that subserve explicit andcases. As the striatum subserves different types of affective memory. Additional evidence for the involve- habits, which involve different types of information, it ment of the striatum in the formation of the *internal is likely to execute generic computations, which are representations of habits was found in correlative required for the ÔsyntacticÕ assembly of pieces of action studies, in which neuronal activity was recorded from repertoires into routines (Graybiel 1998). The circuits the striatum of the behaving rat while engaged in mazthat encode the internal representations specific to the routines (Jog et al1999). habit are hence expected to involve additional brain

Whereas McDonald and White (1993) used a ÔtripartiteÕ approach, including modality-specific and association dissociationÕ approach (three tasks, three lesions)cortex. If this is the case, then use-dependent changes Knowlton et al (1996) used Ôdouble dissociationÕ ton striatal circuits will show larger *transfer than those identify the brain substrates of habit and dissociate itin other brain areas that encode information about from the brain substrates of declarative memory in a specific habit. This is why damage to the striatum humans! The two tasks used in this study wereprobabilistic classificatiand a multiple-choice question- leads to a ÔglobalÕ deterioration of habits. This relates task. In the probabilistic classificattask, the in particular internal representations, and those that *subject is requested to forecast the weather, whetheroccur in generic computations made over these

representations. But this is already a global issue, which itself new valuable information, which promotes adaptation to the milieu and prevents superfluous defensive reflexes. Kandel (1976) cites a fable by Aesop, which epitomizes this point: ÔA fox, who had never yet seen a turtle, when he fell in with him for the first time in the forest was so frightened that he was near dying with fear. On his meeting with him for the second time, he was still much alarmed but not to the same extent as the first. On seeing him for the third time, he was so increased in boldness that he went up to him and commenced a familiar conversation with him.Õ Be it a fox or a turtle, a spider (in which it was first described in the scientific literature; Peckham and Peckham 1887), a scientist or a molluscÑhabituation is part of the behavioural repertoire of all the cellular organisms analysed so far (Christoffersen 1997), including unicellular organisms and even cells in culture (McFadden and Koshland 1990). From the point of view of the neurosciences, however, there is some advantage in focusing on habituation in organisms that do contain a nervous system.

¹Not surprisingly, many authors considered the formation as well as the reversal of habits a key to the success of education at large, e.g. Rousseau (1762), Radstock (1886), and Rowe (1909).

²This task also exploits the innate tendency of the rat to shift its search for new locations. When given equal opportunity, the rat will prefer the *win-shift* over the *win-stay* strategy (Olton and Schlosberg 1978). This is hence an example of the interaction of an innate predisposition (**a priori*) with learning (for another example, see the delayed nonmatching to sample task in the *monkey; *delay task).

³Actually, because the rat is requested to enter the lit arm regardless of the identity and location of the arm, the use of cues other than the light, and of the relationship among cues, becomes counterproductive (McDonald and White 1993). This illustrates that the formation of the habit involves not only augmentation of a response, but also often painful suppression of irrelevant actions, and the survival of only those that count.

⁴For the logic and *algorithms of Ômultiple dissociationsÕ experiments, see *control.

⁵The habit in this laboratory task forms much faster than must habits in *real-life.

1. Stimulus specificity. Habituation to one stimulus does not usually generalize to other stimuli. This distinguishes habituation from response decrements due to adaptation, fatigue, or disease.
2. Intensity sensitivity. Commonly, the weaker the habituating stimulus, the more rapid or pronounced is habituation.

3. Rate sensitivity. The rate of formation, robustness and *persistence of habituation is a function of the time between the presentations of the stimulus (interstimulus interval, ISI). Habituation is faster when the ISI is short, and more persistent, once achieved, when the ISI is long; the dependence on ISI could, however, be rather tricky (e.g. Davis 1970).
4. Spontaneous recovery. withholding the habituating stimulus commonly results in time-dependent recovery of the response. Recovery is faster if the ISI in habituation training is kept short (see 3 above). Repeated cycles of habituation and spontaneous recovery result in progressively greater habituation.
5. Undershooting. Habituation may proceed below the naive response level.

Habituation

The gradual diminution of the response to a *stimulus following the repeated presentation of the same, or a similar, stimulus.

Habituation is commonly classified as a type of non-*associative learning (*taxony). This is because it is assumed to be governed solely by the parameters of the habituated, unconditioned stimulus, in the absence of associations with other stimuli. This assumption may be wrong. It is questionable whether any type of learning is indeed purely nonassociative. In habituation, associations are formed with the *context 4. (Wagner 1979; Marlin and Miller 1981; Rankin 2000), and possibly also with *palimpsests of the *internal representation, accumulated over the individualÕs history. Another common myth concerning habituation is that because it involves a diminution of response, no new information is acquired. On the contrary: that a certain stimulus can be safely ignored is

6. Dishabituation The presentation of another (usually noxious) stimulus results in the recovery of the habituated response.

organism. The major conclusion was that habituation is due to homosynaptic depression of the monosynaptic sensory-motoneuron connection that mediates the reflex (Fig. 5, page 16). The process involves *inactivation

Not all the above parameters are satisfied in every system that habituates. Dishabituation is considered *neurotransmitter molecules (Frost et al 1997). In the most critical *criterion, and is commonly employed long term, morphology is altered as well, and there is a to establish that habituation has indeed occurred. reduction in the frequency and size of the active zones Dishabituation resembles *sensitization, which is the in the synapse (Bailey and Chen 1983). All this portrays facilitation of a nonhabituated response; cellular, habituation as use-dependent modification confined to circuit, behavioural, and developmental studies have, the elementary, minimal reflex pathway. In real life, the however, indicated that habituation and sensitization habituated response is more likely to be subserved by differ in multiple parameters (Rankin and Carew 1988; heterosynaptic processes in polysynaptic pathways as Byrne and Kandel 1996; Hawkins et al 1998). Is dishabituation only a disruption or removal of habituation well (Hawkins et al 1998). Habituation has been (Dodge 1923), or is it an independent process superextrinsic to the minimal reflex pathways in another imposed on habituation (Grether 1938)? Habituation *simple system, the escape response of the crayfish and dishabituation could be shown to have different (Krasne and Teshiba 1995). As expected, multiple path-intrinsic time courses. This supports the idea that theyways are also involved in the habituation of more are independent processes that interact to yield the final complex behaviours, such as the orienting reflex in behavioural outcome (the dual-trace hypothesis of mammals (Kwolek et al 1990).

Groves and Thompson 1970). Multiple interpretations The cellular analysis of habituation could serve to and functional *models of habituation have been illustrate the problematics of *level shifts in a reductive proposed over the years (Coombs 1938; Sharpless and Jasper 1956; Sokolov 1963a,b; Glaser 1966; Konorski 1967; Wagner 1979; Staddon and Higa 1996). A useful go cellular, and started to record the response of classification distinguishes Œfeedback from Œfeedforward models (Staddon and Higa 1996). In Œfeed-forward models the response is inhibited by the *perception of the same or similar stimuli (Œrepetition suppression, or the immediate memory of the current stimulus. In Desimone 1996). Furthermore, if you present a novel, Œfeed-forward models the integrated longer-term surprising stimulus, the response will recover. Is this memory of past stimuli is fed forward to dampen the the cellular analogue of behavioural habituation? Well, immediate effect of the current stimulus. It is unlikely probably not. It may actually subserve *priming, which that any single type of model will generalize to all habituation systems, from the simplest to the complex. also be the cellular correlate of *recognition, resulting

The cellular bases of habituation have been pursued in an enhanced rather than a diminished behavioural in a number of experimental preparations. Noteworthy among these are the cat spinal reflexes (Spiegel 1966); the rat acoustic startle reflex (Davis 1970; Jorda and Leaton 1983; *fear conditioning); and the Aplysia defensive reflexes (Kandel 1976; Frost et al 1997; Hawkins et al 1998). The studies of short- and long-term forms of habituation in Aplysia epitomize a comprehensive reductionist research programme, in which the combination of reductive and simplifying steps (Dudai 1989; *reduction) resulted in the identification of circuit, *synaptic, and molecular correlates of habituation. Interestingly, although considered the simplest of all types of learning, the cellular and molecular analysis of habituation in Aplysia has so far yielded less elaborate mechanistic models than the analysis of sensitization or *classical conditioning in the same stimuli. Interstimulus interval = 1 min. (Adapted from Clark 1960.)

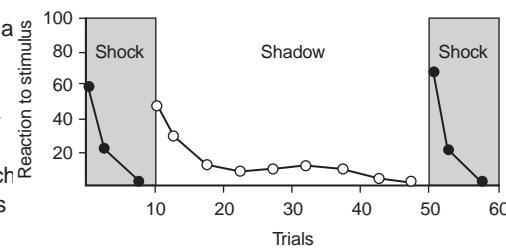


Fig. 33 Simple habituation: the *water* contracts in response to a mechanical *shock* (*filled circles*) or a moving *shadow* (*open circles*). The response habituates readily. Habituation to one type of stimulus is independent of habituation to the other type. This is different from the generalization of response decrement due to fatigue, which *generalizes over type

response. Hence habituation of cellular response may glory was hence rather shaky, and the fact that we do subserve a facilitatory behavioural response, and simonot talk nowadays about ÔBombycal *long-term poten-
larly, facilitation of the cellular response may end up in tiationÕ (LTP) or Ôhippopotamal place cellsÕ (see below)
a decremental behavioural response. The take-home message: the contribution of neuronal *plasticity to undercurrents of scientific etymology, or both. The behavioural plasticity does not necessarily honour seahorse won, and established itself quite firmly as a *OckhamÕs razor.

Selected associations: Context, Cue, Plasticity, Recognition, Sensitization

recurrent protagonist in the dreams or nightmares of brain scientists world-wide. Egyptian theology did leave a mark, nevertheless, in contemporary scientific literature: the hippocampus proper is still frequently referred to in neuroanatomy books and papers as ÔAmmonÕs hornÕ, and Cornua Amnis this source of the acronym ÔCAÕ used to denote hippocampal subfields (Figure 34) (de No 1934; for additional historical notes, Meyer 1971).

¹A process is called ÔhomosynapticÕ if it involves only the modulatory synapse, and ÔheterosynapticÕ if it involves modulatory interneurons. A pathway is ÔmonosynapticÕ if it involves only a single synaptic connection, and ÔpolysynapticÕ if it involves multiple synaptic connections.

²The relationship of habituation to some other types of us-
dependent modification in response is intricate. Priming is an example. Habituation could be regarded as a type of gradual negative priming. Indeed in an influential model of habituation, the decremental behavioural response is formulated in terms of variations in stimulus processing that depend on whether or not the representation of the stimulus, or its associations, has been primed (Wongfei 1979). Recognition is another example. Suppose in a recognition paradigm the subject stops responding because the stimulus is recognized as familiar. Is this habituation to the stimulus? Yet for habituation to occur, recognition of the stimulus is a must. In this example the ÔrecognitionÕ terminology will always be preferred in mammals when the mediotemporal lobe is involved.

Multiple terms are used in the hippocampal literature to refer to structures in the hippocampal region.

The Ôhippocampal formationÕ consists of the hippocampus proper, the dentate gyrus, and the subiculum. Occasionally, authors use the term ÔhippocampusÕ to refer to the hippocampus proper/the dentate gyrus.

The Ôhippocampal systemÕ includes in addition to the hippocampal formation the parahippocampal region, which contains the entorhinal, perirhinal, and parahippocampal cortices (Witter et al 1989). The issue is not merely nomenclature. When authors report that they have performed an Ôhippocampal lesionÕ, it is crucial to note what is it exactly that they lesioned. The hippocampal formation interconnects either directly or indirectly with multiple subcortical and cortical areas.

Without delving too much into neuroanatomy, it is useful to remember that the major cortical input to the hippocampus flows from the entorhinal cortex via the perforant path (abbreviated PP), and that major output to the cortex leaves via the subiculum. The intrinsic circuitry consisting of the successive projections from the entorhinal cortex to the dentate gyrus (via the PP), from the dentate gyrus to CA3 (via the mossy fibre pathway, MF), and from CA3 to CA1 (via the Schaffer

Hippocampus

A bilateral archi*cortical structure that extends as a ridge into the lateral ventricle, interconnects with multiple subcortical and cortical areas, and considered to play a critical part in certain types and *phases of memory.

In 1587 the Italian anatomist Arantius introduced the term ÔhippocampusÕ (seahorse) to describe Ôan elevation of white substanceÕ that rises at the base of the lateral ventricles (Lewis 1923). He wondered, however, whether Ôa white silk-wormÕ (byx) might provide a better description. Two centuries later, a spark of dubious imagination led to a new suggestion, ÔhippopotamusÕ. At about the same time, a structure in that same hippocampusÕ or ÔhippocampalÕ in their title, abstracts also came to be called ÔramÕs hornÕ.

The hippocampus is very popular in the neurosciences in general and in memory research in particular. In 2000, no less than 5640 papers included ÔhippocampusÕ or ÔhippocampalÕ in their title, abstract, or keywords. This means on the average more than 15 papers per day, about 0.6% of the total papers published in science throughout that period, double the popularity of the cerebellum and the *amygdala conform with a ramÕs head). The road of ÔhippocampusÕ opened, and an almost a fivefold increase over 1989

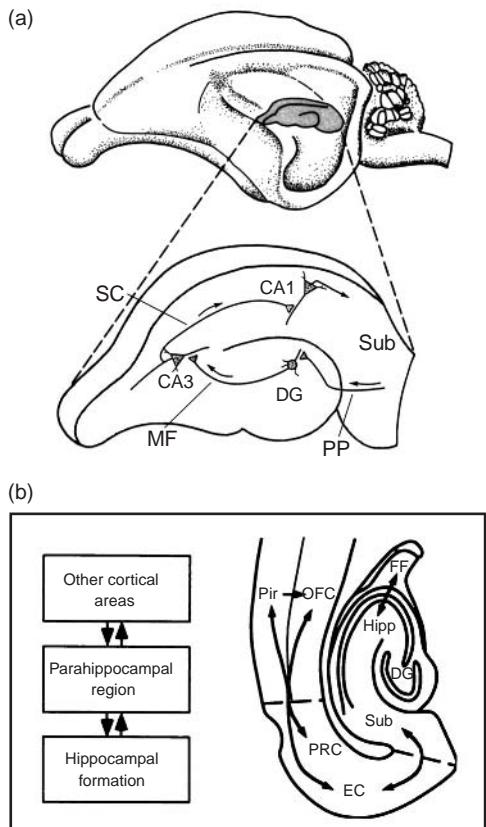


Fig. 34 The hippocampus, the hippocampal formation, and adjacent cortical areas. (a) A drawing of the rabbit hippocampus plus well as of an hippocampal slice. Only part of the pathways are indicated. CA1, CA3, pyramidal cell fields of the hippocampus; DG, dentate gyrus; MF, mossy fibre pathway; PP, perforant path; SC, Schaffer collaterals; Sub, subiculum. (Modified from Andersen 1971.) (b) Outline of a horizontal rat brain section (right) illustrating the flow of information (schematically depicted on the left) between the hippocampal formation, the parahippocampal region, and adjacent cortical areas. EC, entorhinal cortex; FF, fimbria-fornix (medial septal nucleus); Hipp, hippocampus; OFC, orbito-frontal cortex; Pir, piriform cortex; PRC, prepirhinal cortex; DG, dentate gyrus. Discussion of the role of the hippocampus in learning and memory must take into account not only the hippocampus or the hippocampal formation, but also the interconnected system with the adjacent cortex. The computations performed by the hippocampal system are not yet known. (Adapted from Eichenbaum et al 1996.)

(Science Citation Index 2001). Furthermore, about 25% of these 'hippocampal' papers explicitly mentioned learning or memory or LTP in their title or abstract or keywords. The majority of these papers, as well as many thousands before them, reach the conclusion that the hippocampus is important in event rather than fact memory (Vargha-Khadem et al 1997); again, this is still debated (Mishkin et al 1998; Squire and Zola 1998; Tulving and Markowitsch 1998; *taxonomy).

that the hippocampus is involved in learning and memory. But many of them fail to agree on what it does, and how and when it does it. The experimental evidence stems from multiple *methods and experimental *systems. Some data demonstrate correlation of hippocampal function with learning, others indicate an obligatory role (*criteria). Here is a brief illustration of the evidence.

1. Evidence from lesions in human pathology was noted already 100 years ago that damage to the medial temporal lobe, including the hippocampus, impairs memory (reviewed in Zola-Morgan et al 1986). This was substantiated in patient H.M., who underwent bilateral removal of pieces of the medial temporal polar cortex, most of the amygdaloid complex, the entorhinal cortex, and a substantial part of the hippocampal formation, and as a result became densely *amnestic (Fig. 2, p.11; Scoville and Milner 1957; Corlett 1997). But rather amazingly, confirmation of whether hippocampal damage is indeed sufficient to induce amnesia proved difficult (e.g. Aggleton and Shaw 1996; Aggleton and Brown 1999). Human amnesia is a consequence of an unfortunate pathology that is seldom restricted to a single region. Accumulative evidence from a number of cases in which hippocampal damage was a major feature was therefore needed to reach the conclusion that *recognition memory is subserved by the hippocampal formation (e.g. Zola-Morgan et al 1986; Kartsounis et al 1995; Reed and Squire 1997, 1998); however, lesions in additional temporal cortex

must be present to produce a severe memory loss (Reed and Squire 1998). A few points deserve special notice. First, the deficits are not confined to *declarative information (Chun and Phelps 1999). Second, the role of the hippocampus is important in long-term memory, but very remote memories, acquired before the damage had occurred, are spared (e.g. Teng and Squire 1999). This finding has led to the proposal that the hippocampus is required for a prolonged process of memory *consolidation, which in humans may require months or even years; once consolidated, memories become independent of hippocampal function (McClelland et al 1995; Aggleton and Fanselow 1998; see also Hatala 2001). This view, supported by animal studies (e.g. Winship 1990), does have opponents, who propose that the role of the hippocampus in some types of memory is not time limited (Moscovitch and Nadel

The major incentive for studying hippocampal throughout adult life (but see Rakic 2002). Training on lesions in the *monkeys to develop an animal *model learning tasks that depend on the hippocampus, but for amnesia (reviewed in Squire and Zola-Morgan not on those that do not, was reported to enhance adult 1991; Eichenbaum et al 1994; Murray and Mishkin neurogenesis (Gould et al 1999a). 1998). Many of the studies have focused on *delay tasks, 3. Evidence from *functional neuroimaging Despite mainly delayed-nonmatching-to-sample (DNMTS), some early failures to identify activation of the human which were considered sensitive to human amnesia hippocampus in *acquisition and *retrieval, many later Whereas early results have suggested that hippocampal functional neuroimaging studies of human subjects have lesions cause severe memory impairments, later studies delivered the goods (e.g. Lepage et al 1998; Schacter and unveiled complications. This was because the early Wagner 1999; Hassett et al 2001). An imaginative example lesions were not in fact confined to the hippocampus provided by studies of navigation in virtual reality, in and included adjacent cortical areas. It was later found which successful performance was associated with act- that lesions of the perirhinal and parahippocampal cortex that spared the hippocampus produced severe from London taxi drivers (Maguire et al 1997) to their memory impairment on recognition tasks, whereas clients (Maguire et al 1998). In these studies, the left hip- lesions restricted to the hippocampus yielded only hippocampus was found active in nonspatial aspects of the minor deficits if at all (e.g. Zola-Morgan et al 1989b; task. Other functional neuroimaging studies of human Murray and Mishkin 1998; *amygdala). To complicate subjects have used a variety of sensory and verbal tasks, life even further, it was also noted that versions of and have identified hippocampal involvement in a num- DNMTS as administered to monkeys may not be sensitive of declarative functions (e.g. Lepage et al 1998; Dolan tive to recognition memory impairment in humans and Fletcher 1999; Schacter and Wagner 1999; Eldridge after all, because the extensive training of the monkey). Still, in some reports, the focus of activity in on that task involves acquisition of hippocampal- learning and memory tasks was identified in parahip- independent rules that facilitate *performance hippocampal regions rather than the hippocampus proper (Aggleton and Shaw 1996; Reed and Squire 1997). But (e.g. Brewe et al 1998). Some neuroimaging studies also all in all, the data from the monkey lesion studies suggest differential involvement of anterior vs. posterior hippocampus contributes to somerior hippocampus (as well as other mediotemporal lobe aspects of recognition and inter*stimulus-association structures) in acquisition (encoding) vs. retrieval, memory. It also plays a part in encoding spatial information although the nature of the postulated functional segrega- tion remains unclear (e.g. Dolan and Fletcher 1999).

Hippocampal lesions in other mammals such as in rodents and in the rabbit, impair performance on tasks involving spatial memory, *contextual memory, *work- memory, and a variety of stimulus*stimulus and stimulus*action associations (e.g. Olton and Feustland Dostrovsky 1971; O'Keefe and Conway 1978). 1981; Winocur 1990; Bunsey and Eichenbaum 1996; Clark and Squire 1998; Maren et al 1998; Moser and Moser 1998a,b; Steckler et al 1998b; Corbit and Balleine 2000). On some tasks, lesions of dorsal hippocampus were found to be more damaging than those support the hypothesis that the hippocampus forms in the ventral hippocampus (Hock and Bunsey 1998; and maintains spatial *maps, or, more generally, *cognitive maps). In recent years, in addition to the *classical anatomical lesions, several other types (apart from Tolman 1948; on its history, see Best and of lesions have been used. These include transient phakomatoses (White 1999). Over the years, place cells and their role in macological lesions, i.e. inhibition of targeted enzymes (encoding experience-dependent spatial maps have and receptors in the hippocampus (e.g. Riedel 1999); *neurogenetic lesions, i.e. mutations in identified genes (e.g. Tsien et al 1996a,b) and artificial satiation of hippocampal cellular *plasticity mechanisms (Krentz et al 1998; O'Keefe 1999). Electrodes mounted into rats hippocampal place cells even made it into

2. Evidence from neurogenesis There is evidence that neurons continue to be produced in the hippocampus suffice it to say that in both laboratory and *real-life

situations, location in allocentric space could be a major dimension in world models encoded in the hippocampus (O'Keefe 1999). Physical space is not, however, the sole representational parameter of hippocampal units. Although place cells became quite popular from the outset (*episodic memory), or of sets of other representations set of their identification, they were never claimed to catalogue by yet unknown attributes. This latter view exploit the response repertoire of hippocampal neurons considers the hippocampus as some sort of a mental (e.g. Ranck 1973). More recent studies have demonstrated that the activity of many hippocampal neurons is related to perceptual and behavioural events as well as their interactions, regardless of the location of where these events occurred (Woolf et al 1999).

With all this wealth of data, interpretations, and functions of the hippocampus in a catchy phrase, even related to perceptual and behavioural events as well as their interactions, regardless of the location of where these events occurred (Woolf et al 1999).

b. *LTP. All the pathways in the trisynaptic circuit, the PP, MF, and SC (Figure 34), sustain LTP (Bliss and Collingridge 1993), a *synaptic plasticity mechanism that is assumed to subserve learning. If we indeed assume that LTP contributes to learning, then the hippocampus is surely equipped with the right cellular machinery.

5. Evidence from biochemistry and molecular biology

A number of studies have reported changes in hippocampal enzymes, growth factors, neurotransmitters, and gene expression, that were correlated with learning and memory (e.g. Sunayashiki-Kusuzaki et al 1993; Meyer et al 1996; Cavallaro et al 1997; Atkins et al 1998; Hallet et al 2000).

So what is the role of hippocampus in learning and memory? Despite thousands of man-years, smart paradigm, fascinating data, stimulating models (e.g. Treves and Rolls 1994), and the apparent neuroanatomical simplicity that has always attracted anatomists and physiologists, the truth is that we do not yet know for sure what the hippocampus does. One way of looking at the issue is within the framework of the expectation

that there should be differentiation in *engrams along the following lines: some parts of the trace should reside in brain regions that deal with modality-, task- or content-specific information (e.g. spatial maps in the hippocampus) (Gaffan 1998; see also *cerebral cortex).

The term was coined by Cannon: "The Other parts could depend on regions that subserve coordinated physiological processes which maintain many types of engrams by performing global operations. (Hirsh 1974, 1980; Teyler and DiScenna 1986; Wallensteiret al 1998; Holland and Bouton 1999). Judged by its connectivity to other brain areas, the hippocampus does fit to execute global operations. These could be of two types, which possibly overlap but which is relatively constant" (Cannon First, 1932). Antecedents of the concept of homeostasis can be traced back to ancient Greece (Adolph 1961). In the elsewhere. Examples are temporary binding of multi-representations to promote the formation of new physiological regulatory mechanisms has led to the ones, oral-hocevaluation of the contextual importance of on-line input or of retrieved information.

Homeostasis

The maintenance of steady state(s) by a system in the face of change. A special designation for these states is homeostasis. The word does not imply something set and immobile, a condition which may vary, but which is relatively constant (Cannon 1932). Antecedents of the concept of homeostasis can be traced back to ancient Greece (Adolph 1961). In the nineteenth century, the identification of a variety of physiological regulatory mechanisms has led to the notion that the body maintains a stable internal environment, for example stable temperature, blood

Homeostasis

pressure, or sugar level, in spite of changing conditions of its *performance is rather rigid. In such cases, (Cannon 1932; Adolph 1961; Brazier 1988). Most use-dependent modifications in the operation of local notable was Claude Bernard's conclusion: 'all the nodes in the system, e.g. *synapses, may represent the vital mechanisms' have only one object, that of pre-operation of the regulatory mechanisms that restore serving constant the conditions of life in the internal proper operational conditions, keep the system stable, environment' (1878, translated and cited in Cannon and at most perform some fine tuning. Thus, although 1929; Olmsted 1938). This idea that a stable internal local change is observed, its role might prevent milieu is characteristic of, and essential for, life became lasting overall alteration in the performance of the a tenet of biology (Jones 1973; Houk 1980). It is also system rather than promote it.

central to discussions of adaptive control in artificial One way of construing neuronal *plasticity in systems (Wiener 1961). Unfortunately, that biological learning and development is to regard it as a process systems are inherently homeostatic is not always prophetic involves a lasting modification in the set point of erly remembered by students of the nervous system; to the homeostatic system (definition 2 in *plasticity; also frequently authors disregard the possibility that the Bienenstock et al 1982; Bear 1995; *metaplasticity). In goal of a neuronal change might not be to bring about as such case, the use-dependent neuronal modifications long-lasting alteration in the system, but rather, on the detected by the experimenter might indeed constitute contrary, to prevent it.

Brain scientists are bound to encounter homeostasis, and face the delicate interplay between stability and change, in many branches of the neuroscience only a homeostatic, restorative process in the circuit, ranging from the study of membrane properties, which does not culminate in a lasting representational via neurodevelopment, up to widespread autonomic change. The distinction between these two types of regulation, drives, motivation, emotion, cognition, change is important but not easy. For it to be made, and behaviour (for selected discussions, see Blessing 1997; McEwen 1997; Risold et al 1997; Zhou et al 1997; Davis and Goodman 1998; Fanselow 1998) molecular, cellular, or morphological modification Mattson 1998; Damasio 1999). All the aforementioned indeed subserves a lasting change in the internal representations of homeostasis are relevant to learning. What makes life even more complicated, is Here we will focus briefly on one aspect of homeostasis that in complex systems, modification of individual only, which is not yet sufficiently elaborated in the components is not necessarily informative as far as current literature. This is the potential relevance of alteration in the properties of the system as a whole homeostasis to candidate cellular mechanisms of learning concerned. This means that, although some local changes in *receptor availability or *neurotransmitter models.

For our purpose, suffice it to reiterate that in order to release, are plausible candidates for subserving fulfil their basic roles in *perceiving the world and sentential change in the circuit. They may not do so, reacting to it, nervous systems must maintain relative after all.

stability that ensures sustainment of input-output The distinction between the role of candidate synapse-relationships (again control) within a desired limitic plasticity mechanisms, such as unveiled in *LTP, in This is done under conditions in which the system is homeostatic control as opposed to lasting representation. Open, i.e. exchanges materials and energy with the environment, change, is thus one of the current challenges of world, and the world itself is in an ever-lasting flux. the cellular biology of learning.

Homeostatic mechanisms that secure emission of a given range of behavioural response to a given range of stimuli include various types of feedback and forward regulation (Jones 1973; Houk 1980). Such mechanisms usually involve comparison of output with a reference signal, or set point, which represents the desired value of the output. In some innate or reflexive behaviours, which had been moulded in evolution to allow fast reaction and survival (*a priori), the set point by which the system judges the aptness

Selected associations: Persistence, Plasticity, System

One could come up with the remark that even if the circuit is altered, the ultimate goal of this memory is to retain the steady state of the organism as such in its milieu. In other words, the goal of learning is to maintain homeostasis. This reflects the importance defining the *level of discussion.

Homo sapiens sapiens

Human, the only extant species of the primate family Hominidae.

Humans are a very popular species in memory research (100). Over the years, far more memory experiments have been published on humans than on *monkeys, or on allods for quantifying memory were first documented invertebrate species combined. Only rodents still keep only a bit more than a century ago (Ebbinghaus 1885). an edge in popularity in labs that specialize in the neu-Darwinism, combined with practical considerations of memory, but this could change, with the widespread availability of *functional neuroimaging. And yet, human beings almost always identify themselves with the side of the experimenter, even in situations in which they themselves suffer the fate of the experimental *subject, be it involuntarily in evolution or disease, or voluntarily in the lab. This raises some additional doubts on whether *Homo* (from Œarth in Latin, a reminder of old myths) is indeed always *sapiens* (from Œto be wise to taste in Latin, another reminder of a biblical story).

There used to be additional *Homo* (Wood and Collard 1999). At least with one of these Neanderthalensis, we shared this planet for a while. It is questionable whether we remember the experience, a sort of *infan-samnesia, although it is still possible that some reminiscences do linger in the obscure legends of our *collective memory. It is generally assumed that *sapiens* emerged 1.210⁵ years ago, probably in Africa, and made the first massive out-of-Africa exodus 0.61 1.10⁵ years ago (Quintana-Murci et al 1999)! Assuming 20 years per generation, it means that the distance between us and the first true human may be only 5000 generations, not an astronomic number (try to imagine several thousand individuals holding hands; this is it). What was the brain power of the lost hominids species? And which cognitive capabilities, memory included, enabled us to win over the Neanderthal, or at least to linger longer? Attempts to unearth the answers combine prehistoric archaeology with anatomy, molecular biology, and common sense (Wilkins and Wakefield 1995; Wood 1996; Wood and Collard 1999; Yamei et al 2000). Our current ideas on the memory *capacity of our ancestors are mostly speculations. The scientific community will no doubt be delighted if one day a method is devised to determine the problem-solving ability or *working memory *capacity in early hominids (cloning from hominid DNA could yield big surprises, but is unlikely to occur). However, at this point in time, the only clues to human memory emerge from what we get from experiments on living humans.

The study of memory in general had probably started with human subjects. First it involved sporadic observations intermingled with philosophical speculations and pedagogical generalizations (e.g. Sorabji 1972). These were followed by systematic introspection, in both its pre-scientific (Quintillian 1st; Augustine 400) and scientific versions (e.g. Wundt in Germany, Titchener in the USA, Boring 1950). Objective *methods for quantifying memory were first documented in 1885. An edge in popularity in labs that specialize in the neu-Darwinism, combined with practical considerations of memory, but this could change, with the widespread availability of *functional neuroimaging. tolerated on humans, have provided the background for the study of memory in experimental animals (e.g. Boakes 1984). But even when animals became preferred subjects in the study of learning, a prevalent notion was that they are primarily convenient models for understanding humans and the general intelligence of mind: "Most of the formal underlying laws of intelligence can still be studied in rats more easily than in men (rats) do not go on binges the night before one has planned the experiment they avoid politics, economics and papers on psychology" (Tolman 1945; *rat, *simple system).

Let us list briefly the pros and cons of conducting memory research on human subjects. First, here is a short list of selected pros:

1. Only humans have a human brain. Whatever we find about the *engram in experimental animals, even in tasks in which these animals excel (e.g. *maze), or in animal models of human pathology (e.g. *amnesia), must still be adapted to and verified in the human brain.
2. The highest forms of learning, involving language, reasoning, and imagery, as well as intricate emotional experiences and the memory of the self (Conway and Pleydell-Pearce 2000), can only be studied in humans. Attempts to identify rudiments of these capabilities in non-human species are far from yielding satisfactory alternatives to human subjects (*anthropomorphism, *declarative memory, *episodic memory, *monkey, *Ockham's razor).
3. Humans (usually, admittedly not always) can follow instructions quickly and efficiently (the reader is cordially invited to take a breath and imagine, eyes closed, what is it like to be a lonely, frightened, perplexed *mouse in its first encounter with a bizarre problem box).
4. Only humans can report their experience verbally, in detail and in response to specific questions.

5. Human volunteers take care of themselves. No need over the years, a large variety of similar tasks have been for animal rooms, costly maintenance, even not used in the investigation of both human and animal quality-time according to NIH guidance. Unless memory. On the one hand, sheep were trained to recognize they are a real nuisance, human subjects come and recognize faces (Kendrick and Baldwin 1987), horses can go as requested, and the experimenter can simply convince them to read prose (Pfungst 1911, they cheated), and forget about them in between experiments. monkeys to master math (Kawai and Matsuzawa 2000).

And now here is a selection of cons, for a balance: On the other, human subjects were expected to salivate like Pavlovian dogs (Lashley 1916), run in mazes like

1. Invasive methods are out of question. This is probably rats (Woodsworth and Schlosberg 1954), and fearably the critical disadvantage of working with unexpected noises like rabbits (Watson and Rayner 1920). We clearly cannot test a hypothesis, or 1920). In general, in memory research it is best to replicate an amnestic pathology (e.g. Scoville choose a task that fits the species and permits it to and Milner 1957), by inducing brain lesion to disclose its full potential. As is the case with other humans. We also create new artificial worlds to which our memory systems must rapidly adapt. Virtual reality (e.g. Jones 1930). Intentional *neurogenetic manipulations are also a no-go.
- names in evolution. To our favour it should be added
2. In some protocols, overenthusiastic human subjects that we are unique in trying to overcome by technology are particularly prone to demand characteristics. The limitations of our innate, *a priori capabilities, and other sorts of *biases that could undermine the and improve our memory (*mnemonics, *nootropics). validity of the results. This, however, may not be We also create new artificial worlds to which our memory unique to humans (*Clever Hans).
- systems must rapidly adapt. Virtual reality (e.g. Jones 1930). Intentional *neurogenetic manipulations are also a no-go.
3. You do not have to be a scientist to discover Maguire et al 1998) is but an example. The Web is that humans are not easy to work with. In another. Such new environments impose great most places it is difficult to get a sufficient number of human subjects for lengthy experiments, and the *plasticity of cognitive *skills. They also tend to shy away from though, or boring, tasks. They may start the experiment and then disappear. Animals have no choice, although even monkeys revolt from time to time. Animals also do

not request payment for their participation in an experiment and surely will not request a raise. Also, animals are not required to sign a letter of consent, and will not sue the experimenter even if they become confident that their neurosis is due to their experience as subjects in a demanding experiment. It is not surprising, therefore,

¹Estimates of the structure and timetable of hominid lineages are characterized by substantial uncertainties and large standard deviations. The discovery of even a single new type of skeleton, or of a site with hominid artefacts, could shift these estimates remarkably. See, for example, Leakey (2001); also Humans on the move, *Science* 291: 1721–1753 (2001).

to discover occasionally that the acronyms of (TMS, see *amnesia) are explored but their future as acceptable subjects in human psychophysics or neuroimaging papers are those of the names of the authors

themselves.

Homunculus

1. A diminutive human being.
2. In the theory of mind, an intelligent supervisor in the brain that reads information and commands action.

Homunculi (Latin, diminutive of *homo, man) have a rich history in science and philosophy, but not all homunculi were created equal. As a term in biology, homunculus is a close relative of *animalculus* (Latin, inner mental structures). The function of the inner animal. The latter was a generic term used by the early microscopists of the seventeenth century to refer to the explained in turn, so Skinner (1971), *Explanation* microorganisms discovered under the magnifying lens stops with him. But he also added: *Science does no*

for behaviourism. On the one hand, homunculi could relieve psychology from the need to explain inner mental processes; on the other, themselves they were postulated to be the explanation which will not be able to dehumanize man; it de-homunculizes him. Guided by a combination of naive observations and wishful thinking, animalculi were occasionally depicted as miniature editions of full-sized animals. Probably the most famous one was invented by the Dutch microscopist Nicolaas Hartsoeker. While harbouring an intelligent executive agent, that is more-or-less in the image of its host, is dubbed *the homunculus lus*: a curled-up tiny human being enclosed inside a fallacy (Kenny 1971). Some authors argue that depicting spermatozoon like a passenger on an aeroplane diversion does not necessarily imply adaptation for a crash. Hartsoeker actually wrote that what he drew was not what he saw but what one might hope to see, yet with a hierarchy of progressively sillier homunculi: this remark was rapidly forgotten, whereas the Homunculi are bogeymen only if they duplicate entire homunculus was noticed.). The mythical homunculi the talents they are rung to explain... If one can get a in sperms are currently of interest primarily to historians of biology. In this discussion we will deal with minded, blind homunculi to produce the intelligent another species of homunculus, created in philosophy behavior of the whole, this is progress (Dennett 1978; to account for the operation of the mind. Basically, so see also Minsky 1985). Note, however, that if the goes this version of the homunculus story, there is a lit-homunculus multiplied extensively and made really little man inside our head, that sees, hears, smells and is stupid, one disposes of the homunculus rather than of tastes, feels, contemplates and plans, pulls pulleys the fallacy.

presses levers, and makes us think what we think and do. Most neuroscientists are familiar with another, more what we do. Admittedly, such an homunculus does have tangible use of the term *Homunculus*, in neuropsychology. How nice would it be to be able to roanatomy and neurology. Resting on the shoulders of explain the *enigmas of the brain by *reducing them to the great European neuroanatomists of the nineteenth a search for a little fellow that hides somewhere there century, several teams of investigators have mapped the and is responsible for it all. The problem is that the representation of body surface in the brain (Marshall solution simply postpones the difficulty, is clearly too et al 1941; Penfield and Rasmussen 1950). They came *anthropomorphic, and any smart homunculus would up with the finding that somatic sensations arising have rejected it.

from the body surface map on to specific areas of the

Rephrasing Eliot on cats (Eliot 1939), the naming of primary somatosensory cortex, although the *map is homunculi is a difficult matter. In psychology they distorted: different surfaces of the body occupy areas become variants of *central executives* (see *working memory). In physiology they resurface disguised as *sensory grandmother cells*, *command neurons*, and more (*homunculus*). An analogous *motor homunculus* exists below). In philosophy, homunculi have been discussed in the primary motor cortex. Despite the graphic representation of bodily figures on cortical areas in neurology books, the use of the term *Homunculus* in this (Descartes 1649) is a version of the homunculus with context does not imply that a supervisor resides in those

areas, even if some newcomers to brain research might overcome some very basic intuitions in order to drive erroneously suppose that it does. him, or her, out.

From the point of view of memory research, the concept of ÔhomunculusÕ is pertinent to two critical albeit related issues: the encoding of *internal representations, and the localization of the *engram.

For if there were homunculi, one possibility would have been that learning involves changes in the way they read and govern. There are two extreme views on the nature of representational codes in the brain.

One is that complex representations are realized in single neurons (Ôunitary codeÕ, e.g. Barlow 1972). Such units are dubbed ÔgrandmotherÕ, ÔgnosticÕ, or ÔpontificalÕ cells or units (Konorski 1967; Baust et al 1988)!

A related concept exists for motor programmes: the **Honeybee**

Ôcommand neuronÕ, a neuron responsible for a certain behaviour and critical in generating it (Wiersma and Ikeda 1964; Kupfermann and Weiss 1978; Edwars 1999). Now, single units that encode complex representational organs of pollen and nectar collection and of

tations do carry a connotation of ÔhomunculiÕ: if honey production.

there are cells that encode the grandmother, why not

cells that encode complete autobiographical narratives? Humankind has displayed keen interest in bees and yet others that read the whole brain, encode, since the dawn of history. There is no evidence that and navigate our consciousness? The opposing view is the opposite was ever true. Cave paintings dating considers internal representations as distributed over 10 000 years ago already depict bold honey harvesters many neurons, while none of the individual units driving away the stinging bees with smoke (Menzel and encodes a significant part of the representation Mercer 1987). A few millennia later, when the Almighty (Ôpopulation codeÕ, *cell assembly). In between these the Israelites from slavery to freedom, he promised views one may envisage neuronal populations of a good and large land, a land flowing with milk and various sizes, the members of which respond to com-honey (Exodus 3:8). To this day, cultivation of the plex stimuli and possibly even represent meaningful common honeybee (*Apis mellifera*). (Rutner 1988), chunks of complex representations, e.g. cells that are a significant source of income to some, and a hobby respond to hands or faces (Gross et al 1992; Desimone 1991). Such cells are detected in circuits in multiple locations in the brain (Desimone 1991; ↑ *Scalaidhe et al 1997). Similarly, even Ôcommand neuronsÕ in sim years more than half a million copies (Root 1972). ple systems are commonly described as groups of cells. Bees are endowed with a remarkable behavioural (Kupfermann and Weiss 1978). Internal representa-repertoire that is manifested in both solitary adventures tions seem thus distributed, even though the critical and social life. It is subserved by acute visual, odour, number of units that encode a meaningful chunk of the taste and tactile perceptions and discriminations, a representation might be small (e.g. Young and Yamanouchi 1992; Shadley et al 1996; *cell assembly). At least in the flight, dance ÔlanguageÕ, and more (e.g. von Frisch 1967 mammalian brain, the search for the engram should Menzel and Mercer 1987; Getz and Page 1991; Seeley therefore focus on distributed neuronal populations, 1995; Menzel et al 1996; Giurfa and Menzel 1997; not on a single cell in a fixed address or on an elusive Sirinivasar et al 2000; Esch et al 2001). There is a long *plastic homunculus.

The main virtue of the ÔhomunculusÕ is that as how much of bee behaviour is innate and how much concept it forces us to think about how the brain acquired throughout life (e.g. Lindauer 1967; Gould understands and controls itself. All this notwithstanding 1984), but clearly, under certain circumstances, bees are standing, it is tempting to assume that the homunculus is proficient learners (Bittermaier et al 1983; Lehrer 1993; per se still popular, more than we tend to concede, Hammer and Menzel 1995; Brown et al 1998; Erber even in the mind of serious neuroscientists. We must et al 1998). They manage to do all their tricks with a

Selected associations: Anthropomorphism, Reduction, Subject

¹The important element in the concept is the convergence on a single processor. Gnostic units, for example, were not depicted necessarily distributed over many cells (Konorski 1967).

tiny brain (1 mm^3 , not strikingly larger than a single giant neuron in **Aplysia*) that contains less than a million nerve cells. Despite the brain's compactness, area shown to play a part in learning in other insects as well (*Drosophila). The US pathway begins with the compartmentalized sensory and associative centres; chemoreceptors that sense the sucrose. They send connecting pathways and certain individual neurons information to central motor neurons that control the can be identified and manipulated. Bees are hence proboscis, and to interneurons that innervate a number amenable not only to ethological and behavioural analysis, but also to neuroanatomical, neuropharmacological, and cellular investigation.

named VUMmx1, was shown to correlate with the US

Yet those are not the cognitive or neuronal virtues and, furthermore, to be capable of substituting for it of the bee that have carried it to these pages. Clearly (Hammer 1993; see Ômimicry under *criterion, many species do outperform the bee in behavioural method). The reward function of food can be substituted by microinjection of the *neurotransmitter complexity and brain power. The bee is of interest heretuted by microinjection of the *neurotransmitter because it is the subject of a systematic, multi-level programme, that has successfully managed to link the phenomenology of ecological patterns of activation of cAMP-dependent *protein behaviour to the mechanistics of circuits and molecules. Furthermore, this programme attempts to explain concretely *real-life learning in terms of projections of US-related interneurons in the brain alterations in identifiable *internal representations. This critical step in bridging behaviour and brain is still the CS and US in this system (*coincidence detection), a rather uncommon enterprise in the neurobiology of learning and memory.

The multiplicity of association loci is in accord with data from cellular and circuit analysis of classical condi-

Bees can be tested for memory as freely-behaving in other organisms (e.g. *Aplysia*). It is plausible populations, freely-flying individuals, or restrained to assume that the multiple sites of association in PER individuals. The latter situation offers advantages for conditioning in the bee's brain are not functionally mechanistic studies. The most popular paradigm is equivalent.

olfactory *classical conditioning (Bitterman et al 1983; Hammer and Menzel 1995). A bee extends its proboscis recently proceeded to target experience-dependent (the insect's version of a tongue) when chemoreceptors changes in the coherent activity of neuronal population on the proboscis or antennae are stimulated by foodations that are expected to encode internal representations e.g. a sucrose solution. This is called the Ôproboscis' of odours and their hedonic valence. *Functional extension reflex (PER). In the context of classical neuroimaging of neuronal *calcium currents unveiled ditioning, the sucrose is the unconditioned stimulus specific odour-induced spatiotemporal activity *maps (US) and the PER the unconditioned response (UR). in the antennal lobes (Joerges et al 1997), that were The response can be conditioned by pairing an odour, specifically modified in associative learning (Faber et al which initially is practically neutral with respect to the 1999). Further research is needed to determine the PER, with sucrose. Pursuing the terminology of classi-causal relevance of these alterations in circuit activity cal conditioning, the odour is the conditioned stimulus to representational change (this caveat applies as (CS), and with conditioning comes to evoke the PER well to the use-dependent morphological alterations (the conditioned response, CR). Such learning is usedhat were detected in the olfactory glomeruli; Sign in foraging, hence is couched in a language familiar to 1997). But already at this stage, the tiny brain of the the bee. This is probably the reason why this learning is one of the first places in which the discussion of fast and robust.

Both the CS and the US pathways of the modifiable pathways, *synapses, and molecules, but also putative reflex have been mapped in the bee's brain. The population-encoded internal representations are real pathway starts with the olfactory chemoreceptors, must for understanding the neurobiology of memory. which project to the antennal lobes, the functional The bee thus appears to navigate us in the right analogue of the mammalian olfactory bulb. In the direction.

lobes, the information is processed by approximately

5000 interneurons and 1000 projection neurons. The Selected associations: Associative learning, Classical co-projection neurons reach other parts of the brain, ditioning, Simple system

Immediate early genes

Genes whose products are induced rapidly and transiently in response to extracellular *stimulation.

The term immediate early gene (IEG) was borrowed from virology. During the infectious cycle, the viral genome is expressed in an orderly programme, which involves immediate early, delayed early, and late genes. Another example: a growth factor, brain derived neurotrophic factor, known to be involved in synaptic plasticity in brain, is expressed in the hippocampus simplex products of IEGs are detectable at 1 h of infection, of delayed early genes at 3 h, and of late response genes at 6–7 h (Weinheimer and McKnight 1987). Each phase in the cascade is required for the initiation of the next phase. An analogous picture was later unveiled (Impey et al 1996; Yin and Tully 1996). This is construed in the response of mammalian cells to extracellular stimuli (Nathans et al 1988; Lanahan et al 1992). The modification of cellular IEGs is detected within minutes of the extracellular stimulation, and commonly lasts only for a short time (e.g. tens of minutes; 1986; Dudai 1989; Milner et al 1998; Sheng and Greenberg 1990).

Some IEGs encode transcription factors (TFs). These are intracellular proteins that control the expression of genes and hence the differentiation, function, and plasticity of the cell. Many TFs are known. A few common encounters in the neurobiological literature are c-Fos, c-Jun, Zif/268, and members of the CREB/ATF family (Sheng and Greenberg 1990; Hill and Treisman 1995; Herdegen 1998).

The genes for certain TFs, such as CREB, are always expressed in the cell to some degree or another. The analysis of the role of gene expression in plasticity is currently an industrious interface between developmental neurobiology on the one hand and the molecular neurobiology on the other; the two disciplines of the neuroscience use the same methodology and terminology (Martin and Kandel 1996; but to put the similarity in proportion, see Constance-Paton and Kline 1998).

TFs commonly involves phosphorylation by protein kinases, such as the cyclic adenosine monophosphate-dependent kinases, or the mitogen-activated protein kinase (Hunter and Karin 1992; Xieal 1996). TFs are hence components as well as targets of intracellular signalling pathways. They are capable of coupling the activation of TFs to cellular signal transduction pathways, to long-term alterations in the structure and function of the cell. These long-term effects could be mediated by the song in the hummingbird. Similarly, Fos and other

modulation of the expression of late response genes (Hill and Treisman 1995).

Not all IEGs, however, encode TFs. Many encode membrane and cytoskeletal elements, regulatory proteins, enzymes, and secreted proteins. For example, the extracellular protease (an enzyme that degrades proteins), tissue plasminogen activator, is induced by

experience as an IEG in the hippocampus (Qian 1993). Its role in this case is probably to clean the extracellular space in order to permit tissue remodeling. Another example: a growth factor, brain derived neurotrophic factor, known to be involved in synaptic plasticity in brain, is expressed in the hippocampus simplex products of IEGs are detectable at 1 h of infection, of delayed early genes at 3 h, and of late response genes at 6–7 h (Weinheimer and McKnight 1987). Each phase in the cascade is required for the initiation of the next phase. An analogous picture was later unveiled (Impey et al 1996; Yin and Tully 1996). This is construed in the response of mammalian cells to extracellular stimuli (Nathans et al 1988; Lanahan et al 1992). The modification of cellular IEGs is detected within minutes of the extracellular stimulation, and commonly lasts only for a short time (e.g. tens of minutes; 1986; Dudai 1989; Milner et al 1998; Sheng and Greenberg 1990).

The idea is that, whereas weak training results in only transient post-translational modifications in the neurons, training that involves consolidation of long-term memory as a growth process that endows the memory with immunity to molecular turnover (Goeler et al 1986; Dudai 1989; Milner et al 1998; development, *protein synthesis). The focus of research in developmental neurobiology (Cur-

The genes for certain TFs, such as CREB, are always expressed in the cell to some degree or another. The analysis of the role of gene expression in plasticity is currently an industrious interface between developmental neurobiology on the one hand and the molecular neurobiology on the other; the two disciplines of the neuroscience use the same methodology and terminology (Martin and Kandel 1996; but to put the similarity in proportion, see Constance-Paton and Kline 1998).

The sensitivity to behavioural and physiological manipulations render the induction of IEGs as well as the activation of TFs useful metabolic markers of neuronal activity, which could identify functional circuits in the brain. This is the molecular equivalent of functional neuroimaging. For example, by monitoring the short-term events, encoded in the state of the intra-behaviourally driven expression of the IEGs, forebrain nuclei that subserve the production of bird-song in the hummingbird. Similarly, Fos and other

IEGs have been used to map the circuits of *condi-protein DNA-binding domain that centres on a *DREB* and tioned taste aversion in the rat (Swank and Bernstein 1994; Lamprecht and Dudai 1995). Given the appropri- associated protein¹. Guessing the origin of the name of a transcri- ate IEGs, the *method could also be adapted to supply information on the dynamics of circuit recruitment in a task. This was done using *Arc*, an IEG that encodes a cytoskeletal-associated protein. The mRNA of *Arc* is delivered within minutes of its production from the nucleus into the cytoplasm and ultimately into the dendrites. Guzowsk^{et al} (1999) have exploited this property to infer the history of activity of individual neurons in the rat hippocampus at two close time points, as a function of exposure to a novel or familiar environment. As predicted by physiological evidence and by *models of spatial *maps in the hippocampus, *Arc* was induced in a single subset of hippocampal neurons upon sequential visits of the rat to the same environment, but in two overlapping neuronal subsets upon sequential visits to two different environments.

In spite of the impressive evidence on the involvement of IEGs in learning and memory, the question is its social preferences to an object or to a class of yet unsettled whether their role is permissive, or causal objects.

or both. The waves of gene expression that are observed

after training could induce alterations in the *internal representations in the circuit, yet could also fulfil to be an epitome of free choice of a mature human *homeostatic functions unrelated to the representa-being. Well, we may be wrong. Members of many tional change. Further, IEGs are universal devices; they are induced in all tissues in response to a great variety of preferences to a specific class of objects. This acquired stimuli. In neurons, they are also induced in response to bias comes to restrict the choice of the mate much later stimuli that do not result in a memory. We must there- on. It is called Ôsexual imprintingÕ. In other words, there fore identify those contributions of IEGs that are always traces of oneÕs parents in oneÕs spouse. Th specific to learning and memory, and elucidate their basic phylogenetic function of sexual imprinting is con- particular contribution in each case. Whether specific, sidered to ensure that in due time, individuals do not permissive, or obligatory²IEGs are definitely useful waste their energy in courting the wrong species. Most (*criterion) in providing cellular explanations for some readers of both the scientific and the general intriguing behavioural phenomena of learning and literature are much more aware of another type of memory. For noteworthy examples, see *flashbulb imprinting, filial imprinting, in which a juvenile of the memory and *spaced training.

Selected associations: Consolidation, CREB, Late response genes, Protein synthesis

Imprinting

The process in which an individual learns, during

a sensitive period usually early in life, to restrict its social preferences to an object or to a class of yet unsettled whether their role is permissive, or causal objects. The waves of gene expression that are observed after training could induce alterations in the *internal representations in the circuit, yet could also fulfil to be an epitome of free choice of a mature human *homeostatic functions unrelated to the representa-being. Well, we may be wrong. Members of many tional change. Further, IEGs are universal devices; they are induced in all tissues in response to a great variety of preferences to a specific class of objects. This acquired stimuli. In neurons, they are also induced in response to bias comes to restrict the choice of the mate much later stimuli that do not result in a memory. We must there- on. It is called Ôsexual imprintingÕ. In other words, there fore identify those contributions of IEGs that are always traces of oneÕs parents in oneÕs spouse. Th specific to learning and memory, and elucidate their basic phylogenetic function of sexual imprinting is con- particular contribution in each case. Whether specific, sidered to ensure that in due time, individuals do not permissive, or obligatory²IEGs are definitely useful waste their energy in courting the wrong species. Most (*criterion) in providing cellular explanations for some readers of both the scientific and the general intriguing behavioural phenomena of learning and literature are much more aware of another type of memory. For noteworthy examples, see *flashbulb imprinting, filial imprinting, in which a juvenile of the memory and *spaced training. The species forms attachment to the mother immediately after hatching. Here the idea is to provide the newborn with much needed food and care.

Different types of imprinting, even in the same species, are established in different time windows and last for different times (Hess 1959; Bateson 1966; Immelmann 1972; Vidal 1980; Leon 1992; Hudson 1999; ten Cate and Vos 1999). Multiple sensory modalities are involved, depending on the species, the object to be imprinted, and the occasion. Indeed, the world of imprinting is astonishingly rich: imprinting navigates Salmons across oceans and rivers to their natal habitat (Dittman and Quinn 1996), socializes dogs with *junwas* isolated from the avian sarcoma virus (Pfaffenberger and Scott 1959), and can turn a *Zinc_finger binding protein clone number 205* finger denotes a laboratory mouse into a Mozart fan (doesnt work with

¹For more on transcription factors, see *CREB.

²The names of transcription factors, and hence many IEGs, are acronyms that reflect the activity of the molecule, its structure, or the idiosyncratic preferences of the person who first described it. Here is the meaning of names that are mentioned in the text: *Öink* (Biskis-DJinkins *mussteigenic* *gacoma* *virus*), with the Öo standing for Öcellular, to distinguish it from the viral gene, which preceded by Öju-nanaÖ, Japanese for Önumber 17Ö, because it is isolated from the avian sarcoma virus (Dittman and Quinn 1996), stands for humans (Pfaffenberger and Scott 1959), and can turn a *Zinc_finger binding protein clone number 205* finger denotes a laboratory mouse into a Mozart fan (doesnt work with

Schoenberg; Crosset al 1967). Although usually characteristic of the young, learning to restrict social bonding is established by olfactory imprinting (IMHV), lesions in which impair the learning process in parturition. Imprinting also plays a part in the mother–infant bonding in humans (Kennell al 1979), and here, again, olfactory cues are important.

The molecular and cellular mechanisms unveiled might expect to find out that a nursing mother who switches too many fragrances cultivates a neurotic chick are similar to those identified in other types of neurotic.

*acquisition and *consolidation. They involve, among

Filial imprinting is especially striking in precocial birds and was the subject of systematic observation already during the early days of experimental psychology (Spalding 1873). A few hours after hatching, the chick approaches and follows a conspicuous moving object, which may or may not be the mother. In nature it usually is; in the laboratory it may actually be an earnest scientist (Lorenz 1937). After hatching an becoming able to look around, a greyleg gosling utters its lost piping, to which its mother answers with a rhythmic cackle. To this the gosling responds by greeting. The mutually releasing sequence of piping-cackle-greeting is predictable with a high degree of probability... The program timing the period of sensitivity of that irreversible learning process for this particular moment is obviously adaptive. The built-in mechanism conveys to the gosling information which, if verbalized, would say: "When you first feel lonely utter your lost piping, then look for somebody who moves and says "gang, gang, gang" and never, n forget who that is, because it is your mother" (Lorenz 1981). This imprinting process involves at least two distinct, interactive components. One is the innate (*a priori) predisposition to approach *stimuli that have the characteristics of the natural mother. The other is the learning to approach a stimulus to which the chick is exposed during the sensitive period—which may be the natural mother, Lorenz, or an artificial stimulus in the lab.

The approach behaviour of the domestic chick, although not as long-lasting as the one in Lorenz's, combined with the visual ones. The chick is imprinted on a combination of visual and auditory *cues, which are *bound synergistically (Smith and Bird 1963; Bolhuis 1999). Candidate forebrain substrates of both visual and acoustic imprinting have been identified (Maier and Wainwright 1972; Horn 1985).

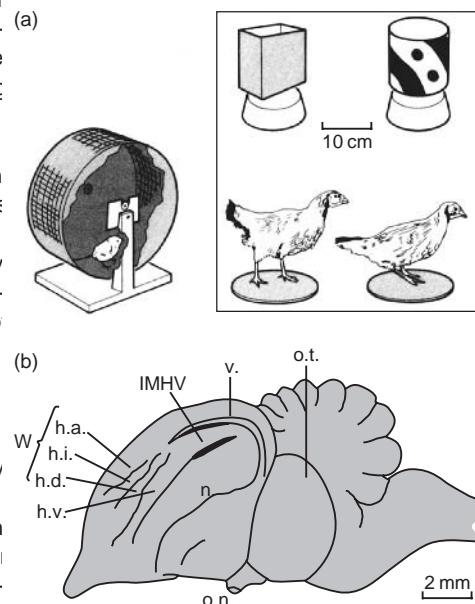


Fig. 35 (a) Apparatus and stimuli used in the study of filial imprinting in the domestic chick. Imprinting is quantified by measuring the approach toward the imprinted object. The chick is placed in a training wheel, which is here drawn with one of its opaque sides exposed. As the wheel rotates on its axle, the distance to the object remains constant. The rate of rotation is

others, *glutamatergic-D-methyl-D-aspartate *receptors, different conceptual frameworks (biological, cognitive, other *neurotransmitter systems, *protein kinases, psychosocial), and some of them refer to different *immediate early genes, cell adhesion molecules, and phases of memory (*acquisition, *consolidation, morphological synaptic *plasticity (Horn and McCabe retention, *retrieval).

1990; Sheet al 1993; Solomoniet al 1998; Ambalava-

nare et al 1999; Bock and Braun 1999). One class of explanations suggests that the problem lies already at the acquisition phase: early personal

Imprinting could be considered a subclass of memories that are not retained to begin with, because the Ôprepared learningÕ processes, in which brain maturing systems that are required for autobiographical, tion (*development) is modified by sensory experience*episodic memory simply do not mature before the age during a sensitive period. This sensitive period is con-of 3D4 years (Nadel and Zola-Morgan 1984; Nelson strained, among others, by the growth potential of 1998; *declarative memory). A related suggestion the neuronal circuits and by hormonal states. Other implicates both acquisition and retention and rests on examples are visual (Wiesel 1982; Crair. 1998) and cognitive rather than neurological arguments. It claims auditory (Knudsen 1998) sensory learning early in life, that the infantÕs mind cannot form the appropriate and the learning of *birdsong. Such learning could leave in the young brain dormant *engrams, which, organizing new information in a sensible manner. The given the appropriate conditions and cues, are capable generic term for such abstract mental structures is of being reactivated after many years in the adultÕs schemata (Bartlett 1932; Piaget 1969; Cohen 1996). In (Knudsen 1998).

Selected associations: A Priori, Acquisition, Birdsong, Development

the absence of mature schemata, so goes the argument, autobiographical experiences cannot be stored in an effective, retrievable form. A version of this argument considers the intense episodes of infantile memory inconsistent with the categories of the adult schemata, incapable of being assimilated into the adult memory (Schachtel 1947; see also FreudÕs suppression hypothesis below). Similar suggestions invoke the lack in infancy of linguistic competence, which is assumed to be required in encoding autobiographical episodes (Nelson 1992); immaturity of a ÔmeÓ system, postulated to be necessary for integration of episodic information into the internal personal narrative (Howe and Courage 1997); or, similarly, immaturity of a Ôself-memory systemÓ, postulated to hold the autobiographical memory base together with the current goals of the self (Conway and Pleydell-

Infantile amnesia

The lack of *recall of autobiographical memories dating to infancy.

The observation that infancy is not remembered was Pearce 2000).

noted with interest by students of the mind, and probably by others as well, throughout the ages (Augustine 300; Rousseau 1798; Freud 1901). The experimental famous argument is that early memories are formed data confirm folk psychology: adults do not remember but later suppressed to become non-retrievable, autobiographical episodes that had occurred prior to the age of about 3 or 4 years, and report that their inner more, those early memories that are recalled are actual personal narratives begin to make sense (if they do) only about the age of 6 or 7 years (Dudycha and Freud 1901). No experimental evidence has been Dudycha 1941; Wetzler and Sweeney 1986; Nelson reported so far to support this psychoanalytical 1992; Eacott and Crawley 1998). Claims for the rediscovery in adulthood of the memories of early infancy should be treated with great caution, as they could reflect *false memory.

Deficiencies in retrieval comprise another class of explanations for infantile amnesia. Here the most famous argument is that early memories are formed screens, which hide the real, difficult experience do) only about the age of 6 or 7 years (Dudycha and Freud 1901). No experimental evidence has been reported so far to support this psychoanalytical framework of the interaction of the individual with

Why do individual life histories begin with a period of oblivion? Over the years, several types of explanation for infantile amnesia have been proposed. They involve search for the roots of infantile amnesia within the psychosocial explanations, which

society. Autobiographical episodes, so it is suggested (Rovee-Collier 1997), or that their brain is incapable of becoming encoded properly only after the infant becomes aware of the social function of autobiographical memory (it does; Jusczyk and Aohne 1997). Even fetuses are aware of the social function of autobiographical memory (Saffran et al 1996; Jusczyk and Aohne 1997). Even fetuses may have learning and memory capabilities that parents are not aware of. The development of a life history that can be shared with others (Hepper 1996). In estimating the mental capacity of infants, it took a lot of grant.

Many of the aforementioned explanations are not money to reach the conclusion reached by every normal parent: these babies outperform us in many ways. Such as frontal cortex and cortico-limbic circuits, may be yet unable to subserve the cognitive and the psycho-physiological rationales for chosocial faculties of categorization, Öinner language¹, preventing adults from remembering their adventures in the crib? It might be related to a mix of biological self-comprehension, or social understanding. All this in the crib? It might be related to a mix of biological constraints and selective pressures. First, evolution did not imply that very young infants do not have the ability to acquire read-hoc declarative knowledge (they not come up (yet?) with the ability to construct instantly a perfect brain; it takes years to *develop). Second, slow brain maturation may have an advantage in coping with a changing environment, as it reduces the chance of fast and robust encoding of erroneous outcomes of certain types of learning in early infancy. Third, autobiographical memory could lack significant phylogenetic advantage early in life (and see *capacity). All the above combined, it probably pays better to dedicate first the brain power of the newborn to the acquisition of critical, basic *skills, rather than to the long-term declarative memory of the pains and the joys of the first months of life.

Selected associations: Amnesia, Development, Episodic memory, Persistence, Real-life memory

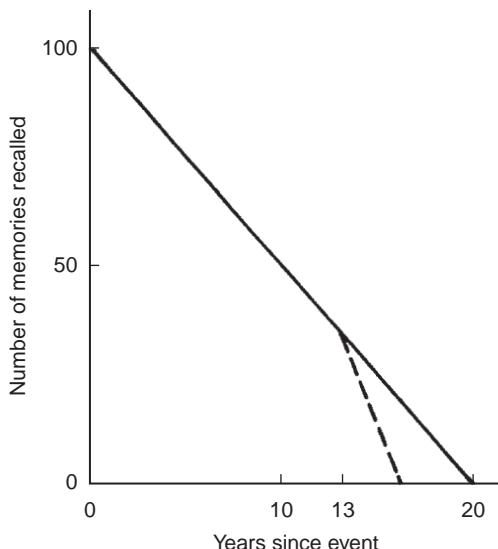


Fig. 36 Although the existence of infantile amnesia is supported by introspection, personal accounts, and anecdotal evidence, its objective verification under *controlled conditions is not trivial.

Three major types of variables are involved in such experiments: the age at learning, the age at retrieval, and the length of the retention interval. The ideal experiment should control the age at retrieval, vary the age of

learning, and, most importantly, define the expected normal forgetting over the retention interval. Infantile amnesia will then become apparent as accelerated forgetting below a certain early age at learning. The

graph depicts the hypothetical distribution of memories across the lifetime of a 20-year-old human *subject. The solid line represents an ideal function of normal forgetting, while the inflected broken line represents the accelerated forgetting that one should observe in infantile amnesia. Based on the analysis of the data in the scientific literature,

Wetzler and Sweeney (1986) confirmed that indeed, phenomena that approximate the hypothetical curve are observed in reality, and that there is accelerated forgetting for memories acquired below the age of

5. (Adopted from Wetzler and Sweeney 1986.)

Insight

1. The sudden realization of a solution to a problem.

2. An abrupt improvement in the *performance on a task.

Some types of learning, such as the acquisition of *skill, progress gradually, through numerous repetitions. This is termed Öincremental learningÖ, or Örote learningÖ (Hebb 1949). In contrast, other types of learning, both

in real-life and in laboratory setting, occur abruptly, following a step function. Two examples are *flashbulb memory and *conditioned taste aversion. There is, however, a type of abrupt learning that differs from

these examples. It cannot be described as fast acquisition of information about an on-line event. Rather, the *subject is presented with a problem, which it finds difficult to solve. After a typical period of either fruitless overt attempts or behavioural silence, suddenly, a solution comes to mind. We all are familiar with these situations. There is even a special term that conveys the subjective flavour: the ÔAHA! experienceÕ (Kaplan and Simon 1990; Sternberg and Davidson 1995). When we watch animals under situations that seem to involve sudden realization of a solution to a problem, we tend to *anthropomorphize and conclude that they also have their ÔinsightÕ, uttering ÔAHA!Õ in doglish chimpanzeesh.

Some cases of alleged insight are anecdotal. It is told that the chemist Kekule suddenly saw in reverie the structure of the benzene ring, although doubts were raised whether the story is true (Gruber 1995). The most famous of all ÔAHA!Õ experiences is that of Archimedes, who allegedly jumped naked from his bath shouting ÔEurekaÕ (Greek *ηύρεκα* Ôfound itÕ). After suddenly realizing a *method to determine the amount of alloy mixed with the gold in the crown of the king of Syracuse. Again, the story is surely refreshing, but already Galileo considered it implausible.). As science cannot rely on anecdotes, various protocols were developed to demonstrate insight under controlled conditions. The following are two *classic cords. The subjects were asked to tie together the two examples. Kohler (1917, 1925) reported a number of hanging strings. However, the distance between the ÔinsightfulÕ or ÔintelligentÕ experience-dependent behaviours was too large. After a while, the subjects suddenly realized that they can tie the pliers to one of the placed a chimpanzee behind an array of vertical bars, swing it like a pendulum, and catch it in its and a heavy stone with a cord tied around it on the up-swing while holding the other string. Reports of other side (Figure 37). Food was attached to the cord ÔinsightÕ are not confined to anthropoids. Over the halfway between the anchoring stone and the bars. These years, cases of apparent ÔinsightÕ were described as prealthough some also disputed, in cats in problem boxes vanted the chimp from reaching the food. The only way to get the reward was to shift the cord between the bars until it formed a straight angle with the array of bars. Just pulling the cord was of no avail. Suddenly the chimp realized that she can take the cord in one hand, pass it around the bar to the other hand and hence move it, step by step, from one inter-bar spacing to another, till it formed the required angle (b). (Adapted from Kohler 1917)

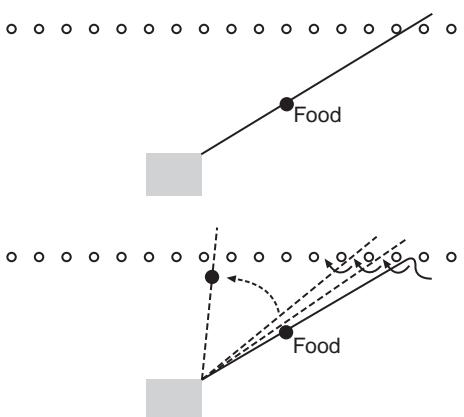


Fig. 37 A *classic insight experiment. Kohler (1917) placed a chimpanzee behind an array of vertical bars, and a heavy stone with a cord tied around it on the other side. Fruit was attached to the cord halfway between the stone and the bars, and the cord was inserted through the bars in an angle that prevented the *subject from reaching the reward (a). The only way to get it was to shift the cord between the bars until it formed a straight angle with the array of bars. Just pulling

suddenly realizing a *method to determine the amount of alloy mixed with the gold in the crown of the king of Syracuse. Again, the story is surely refreshing, but already Galileo considered it implausible.). As

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The chimpanzee tried at first to pull the cord, but in vein. and peck a hanging banana (Epstein 1984). In all

Suddenly she somehow realized that she can take the cord in one hand, pass it around the bar to the other hand and hence move it from one inter-bar spacing to another, step by step, till it formed the required angle, culminating in happy end. Individual chimps differed in the kinetics of their response, but most reached the right solution.

Reports of ÔinsightÕ made *behaviourists sad and in the Gestaltists happy. The mere idea that learning involves internal reorganization in the brain in the absence of

Other classic ÔinsightÕ experiments were carried out by Maier (1931) on humans. A typical one is Ôthe penorthodox behaviouristic tenet that only public behaviour is the subject matter of psychology and that

dulum experimentÕ. Subjects were introduced into a room that had two strings hanging from the ceiling, and internal processes should be ignored. Attempts have been made either to play down, or to

explain ÔinsightÕ by rather complex chaining of stimulus~~s~~conditions, performance on these skill-like tasks shows response contingencies (Keller and Schoenfeld 1950). Sudden improvement, resembling insight, either on the Bower and Hilgard 1981). In contrast, the Gestalt particular task, or on the ability to solve the type of trusted that the nature of *perceptual and mental part~~s~~tasks (*learning set). It was suggested that this abrupt is determined by the whole, and that enquiry into the improvement on Ôlow-levelÕ learning depends on incre-mind should consider global organization and proceedings in Ôhigh-levelÕ knowledge (Rebilal 1997). top-down (Kohler 1925; Koffka 1935; Hochberg 1998). Although this conclusion could prove to be *paradigm-The idea that mental structures are restructured to specific, it does cast doubts on the generality of type-achieve a new meaning in the *context of previous distinction between rote learning and insight. knowledge was exactly in line with what they were. The attempt to separate abrupt from gradual learn-preaching for. With time, ÔinsightÕ became a focus~~s~~ brings to mind the so-called ÔSorites paradox' (of interest in cognitive psychology in relation to Greek for ÔheapÕ; Williamson 1994). It is attributed to information processing and problem solving (e.g. Eubulides of Miletus, a contemporary of Aristotle, and Weisberg and Alba 1981; Kaplan and Simon 1990). It goes like this: does one grain of wheat make a heap? Ohlsson 1994a,b; Sternberg and Davidson 1995) Do two grains? Three? Ten thousands? Where is the Several *models have been proposed for insight/transition point? For those remote from agriculture, the behaviours. They involve elements such as reshuffling~~bald man~~ version may evoke more empathy: Is a man and recategorization of building blocks of prior with one hair on his head bald? With two? Three? If the problem-related knowledge, the sudden identification addition of any single hair is not critical, one is led to of *cues, the use of multiple heuristic solutions and the admit that a man with 10 000 hairs is bald. The bound-identification of invariants in such solutions. Amongaries of the terms ÔheapÕ, ÔbaldÕ, ÔincrementalÕ, or Ôa~~a~~ these elements, the need for prior problem-related learning~~learning~~ are therefore vague. Attempts to distinguish knowledge stands out in species far away on the phylon~~insight~~ from incremental learning resemble attempts to genetic scale (e.g. Epstein 1984); again, it appears consider Ô*flashbulb memoryÕ as inherently different that in order to learn something, we must already know from other episodic memories. Naturally, we are a lot (*a priori). However, as noted by Kaplan and Simon impressed by the extreme cases. But in real life, a (1990), knowledge is a two-edged sword, as inflexible spectrum should be expected of time-scales, interactive knowledge may guide the search for the solution astray.levels of processing, and complexity of *internal representation.

A major question concerning insight is whether it is a sensations. Insight may involve latent increments in special type of learning, differing in its computational knowledge, and rote learning may involve Ômicro-in-strategy, the *algorithms and their biological imple-sightsÕ. Sharp *taxonomies may exist only in the eye of mentation from rote learning. For example, is insight our cognition.

restricted to higher processing *levels because it seems Selected associations: Acquisition, Binding, Delay task, to affect ÔglobalÕ cognitive structures? And are there any Learning specific circuit properties that play a part in insight

only? Hebb (1949), for example, who considered insight as the most advanced form of adult learning, did¹ For more on the Gestalt school of psychology see *binding.

not think that its basic mechanisms differ from those of rote learning. So far, one of the difficulties in comparing insight to incremental learning was the traditional use

of different types of behavioural paradigms~~s~~problem solving in the study of insight, skill acquisition in the study of incremental learning. The use of certain *perceptual learning tasks, involving visual detection and discrimination, could provide a solution, because these tasks tap into elements of both skill learning and insight (Ahissar and Hochstein 1997; Rubial 1997).

In these tasks, if the task is made easy, learning *general-ment is made contingent upon *performanceizes over *dimensions of the stimuli, matching the properties of high-level visual areas, whereas when the task is made difficult, learning shows little *transfer if at In *classical conditioning the subject learns relations all, typical of low-level perceptual skill. Under certain among *stimuli; in instrumental conditioning (also

Instrumental conditioning

1. Types of *associative learning in which the probability or intensity of behaviour changes as a result of its consequences.

2. Types of training protocols in which *reinforcement is made contingent upon *performance of the proper behaviour.

Ôinstrumental learningÕ) it learns the impact of its actions on the world. The scientific interest in this type of learning can be traced to Bain (1859), who, impressed by his experience in the Scottish Highlands, noted Ôassociation of movement with the effects produced on outward thingsÕ in animals trying to leap over obstacles: ÔÉ spontaneous impulses of locomotion lead to opening; in some experiments Thorndike manipulated them to make attempts. Any attempt causing a hurt is his cats to lick themselves in order to get out. Note, desisted from; after a number of trials and failures, however, that, whereas in classical conditioning the proper adjustment is come to, and finally cemented. Experimenter controls (ideally) all the experimental parameters, in instrumental conditioning there is a more democratic division of labour: the subject decides how and when to reinforce it.'

In the introduction of the systematic study of instrumental conditioning into the laboratory.

In a typical experiment, Thorndike placed a hungry cat into a puzzle box, a small crate hammered together from wooden slats (no fat grants those days)ng *paradigms is also known by other names: (Figure 38). A piece of fish was placed visibly outside the box. The box had systems of pulleys, strings, and catches arranged that pulling a loop, or pressing a lever, allowed a dog to a door to fall open, and the cat to jump out and devour food.

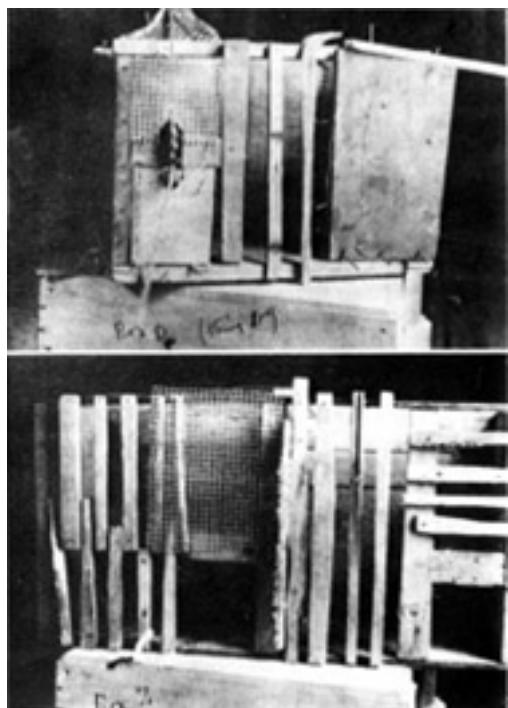


Fig. 38 Two of the puzzle boxes used by Thorndike in his studies of instrumental conditioning. For more on Thorndike's puzzle boxes, see Thorndike (1911); Chance (1999). (Courtesy of Yale University Library.)

Instrumental conditioning is so termed because the

individual's behaviour is instrumental in the materialization of the reinforcement. This family of conditioners together from wooden slats (no fat grants those days)ng *paradigms is also known by other names: (Figure 38). A piece of fish was placed visibly outside the box. The box had systems of pulleys, strings, and catches arranged that pulling a loop, or pressing a lever, allowed a dog to a door to fall open, and the cat to jump out and devour food.

Thorndikeian conditioning type R for response, Skinner 1938) trial-and-error conditioning operant conditioning (operant because the spontaneous behavioural response operates on the environment, and is in turn affected by the environmental effects (Skinner, 1938); and Skinnerian conditioning after Skinner, whose problem boxes, descendants of Thorndike's puzzle boxes, came to epitomize the social and educational philosophy that all behaviour is malleable by operant conditioning (Ôoperant behaviourismÕ; Skinner 1948).

*taxonomy of instrumental conditioning lists no less than 16 different subtypes, differing in the relationship of the behaviour (or its omission) to the outcome (or its prevention), and in the presence or absence of an antecedent signalling stimulus (Woods 1974). Among the most popular subtypes: signalled reward conditioning, in which a signal signifies that the reward will follow if the behaviour is executed (a ÔgoÕ situation); signalled omission reward conditioning, which is similar to the above only that the behaviour has to be withheld (a Ôno-goÕ situation); active avoidance conditioning, in which following a signal, punishment is avoided provided the response is made; and passive avoidance conditioning, in which punishment is avoided if the response is withheld.

What is it that gets associated in instrumental conditioning? The theory of instrumental conditioning, similar to that of classical conditioning, has developed remarkably since the introduction of the paradigm. Thorndike himself extracted from his experimental findings a ÔlawÕ (*algorithm) that he called Ôthe law of

Instrumental conditioning

effect. This influential theory appears in several forms (two-process theories; Rescorla and Solomon 1967), Thorndike's writings. Here is the formulation at the (c) response-reinforcer, or action-outcome association behavioural and *system levels: Of several responses made to the same situation, those which are accompanied by satisfaction to the animal will, other things being equal, be more firmly connected than those which are accompanied by discomfort to the animal will, other things being equal, have their connections with that (*criterion) for the behaviour. It is likely, therefore, that situation weakened, so that, when it recurs, will be in instrumental conditioning, *internal representations less likely to recur. The greater the satisfaction or discomfort they are used with indifferent or pleasurable results, the greater the strengthening or weakening, with associative weights that depend on the task, of the bond (Thorndike 1911). And here is the formula: a priori knowledge of the subject. Just as

at the circuit, cellular or *synaptic levels: an example to illustrate that instrumental conditioning connections between neurones are strengthened every time they are used with indifferent or pleasurable results, consider the following experiment (Colwill and Rescorla 1985): rats were trained on two different discomfort. This law includes the action of two factors, instrumental responses, lever pressing and chain frequency and pleasurable result. It might be stated that pulling, each associated with a different reinforcer, a compound form as follows: (1) The line of least resistance is, other things being equal, that resulting in pairing of one of the reinforcers with a malaise-greatest satisfaction to the animal, and (2) the line of least resistance is, other things being equal, that oftenest reducing injection of LiCl (*conditioned taste aversion, resistance is, other things being equal, that oftenest CTA), to decrease the hedonic value of that reinforcer versed by the nerve impulse may call (1) the law of effect and (2) the Law of Habit (Thorndike 1907; conditioning, *cue). When the rats were again given italics in the original)⁴. Two points deserve particular attention. One, the law of effect is an adaptation of the reinforcers, each rat preferred to make the specific Darwinian selectionism (*a priori, *stimulus). Second, instrumental response that had not been devalued by Thorndike's attitude was rather modern: he explicitly CTA. This suggests that the rats encoded the reinforcer treated learning as multilevel phenomena and processes identity and ADO contingency as part of the knowledge and well appreciated that whatever is observed about the instrumental learning situation, and that this behavioural level, is manifested at the neuronal level as knowledge was susceptible to post-training experience, well, and vice versa.

The picture that emerges is hence of instrumental

The law of effect continues to drive research to this conditioning leading to the *acquisition of specific day in both the behavioural and the brain sciences (e.g. knowledge bases, rather different from the picture Ahissaret al 1992). It does not, however, have the depicted by the early minimalist SDR theories. This is power to explain all the processes that occur in instrumental conditioning. Further, from the aforementioned processes and their interaction must take into account discussion it becomes evident that in spite of the different three types of elements that play a part in every instrumentality in the training protocols and the particular types mental conditioning situation: the response whose probability or intensity is modified, the reinforcer that is contingent upon this response, and the stimulus in the presence of which this contingency takes place. Three Mackintosh 1983⁵.

types of associative configurations have dominated the theoretical discussion of the interaction of response, reinforcement, algorithms, and biological hardware (*level) of reinforcer, and stimulus in instrumental conditioning. The incentive to understand the computational the-instrumental conditioning is high. Much of what we (Colwill and Rescorla 1986): (a) stimulus-response learn in our lifetime is by trial and error. Furthermore, association (OSDR theories; e.g. Guthrie 1952; *association together with *observational learning, instrumental learning). (b) Pavlovian S-D reinforcement association is contemplated as the method of choice occurring in parallel with the SDR association to train the smart robots that will share this planet with

us in the future (e.g. Saksida et al 1997), and we had better find the way to teach them efficiently and, what is even more important, the right things only. The neurobiology of instrumental conditioning is, however, still fragmentary. At the system level, brain circuits have been identified that perform selected types of computations in instrumental conditioning. Special interest is dedicated in recent years to those circuits that encode the reinforcement and the ADO associations. These include *cortico*limbic-Dstriatal-Dpallidal circuits (Robbins and Everitt 1997), with specific structures assumed to play distinct roles such as anticipation of reward, computing the deviation of the actual from the expected outcome, control of response and its adaptive correction, and possibly also representation of ADO causality (Schultz et al 1997; Trembley and Schultz 1999; Balleine and Dickinson 2000; Baxter 2000; Corbit and Balleine 2000; Corbit et al 2001; see also *dopamine, *habit, *reinforcer). As to the cellular, synaptic, and molecular mechanisms of instrumental conditioning their study could benefit from the use of *simple systems and, although the analysis of trial-and-error learning in simple systems is so far less developed than that of classical conditioning, some promising preparations are already available (Cook and Carew 1989; Chen and Wolpaw 1995; Nargeot et al 1997). We might expect the molecular mechanisms of instrumental conditioning to be similar to those of classical conditioning and many other forms of learning; the characteristic instrumental contingencies are probably encoded at the circuit level.

Selected associations: Associative learning, Classical conditioning, Maze, Reinforcer, Skill

¹Excluding, of course, consequences that eliminate the opportunity to perform this behaviour again.

²Operant conditioning is sometimes distinguished from instrumental conditioning in that the latter involves distinct responses within a structured task, whereas the former refers in addition to repeated emission of spontaneous behaviour that results in obtaining the goal. This distinction, however, is not systematically honoured in the literature and will not be further elaborated here.

³Operant behaviourism aspired to explain all types of behaviour, including human language (Skinner 1957). This was belligerently contested by linguists and cognitive psychologists alike (Chomsky 1959). By the way, Skinner's methods found their way even into top secret war projects: during the Second World War he was engaged in an attempt to train pigeons to guide missiles by operating problems in the warhead (Skinner 1960).

⁴On precedents of Thorndike's law, and on its place in the history of the behavioural sciences, see Cason (1932) and Wilcock (1969); see also *reinforcer. The empirical *generalization that

consequences of the response is an important determiner of whether this response will be learned, is called 'the empirical law of effect' and can be used independently of Thorndike's theoretical assumptions (*reinforcer).

The relevance of classical- to instrumental conditioning has multiple facets and all should be taken into account in the interpretation of the data. One is the postulated processes shared by these two types of learning. A very different facet is the possibility that conditioning that is considered instrumental is actually Pavlovian. Consider, for example, a pigeon trained to peck an illuminated disk in a Skinner box to obtain food. The classical interpretation is that food delivery is contingent upon pecking, i.e. an operant conditioning situation. However, if the experimenter simply illuminated the disk before each food delivery, irrespective of the pigeons' behaviour, the pigeons pecked at the light as if there were an instrumental contingency. This is a consummatory response, and the contingency was probably between a conditioned stimulus (illuminated disk) and an unconditioned stimulus (food). Hence, in this case, Skinner's famous pigeons were disguised Pavlovian dogs.

Internal representation

1. A *map of event space in neuronal coding space.

2. A neuronally encoded structured version of the world which could potentially guide behaviour.

'Representation' and 'internal representation' are used in multiple senses in philosophy, linguistics, and the cognitive sciences. The meaning of 'internal representation' as used here deserves, therefore, careful clarification, especially as it is ardently *reductionistic. Generally speaking, 'representation' is the expression of things in one language transformed into another. 'Language' is

any set of symbols with rules for putting them together (Mar 1982). We are not engaged here, however, in the formal treatment of representations at large, but rather in the application of the concept to memory research.

In the context of brain sciences, 'representation' means encoding of things in the world, such as objects, events, and processes, in neuronal language(s). This encoding is done in a way that enables the nervous system to manipulate the representations, modify and transform them, while maintaining: (a) parsing, which is the distinctiveness of things represented, and (b) structural relationships between the things represented. Both are needed for useful interaction with the world.

'Representations' have a long and rich history in the philosophy of mind, referring to some kind or another

of Ômental imagesÕ, or elements of an inner Ôprivate representationsÕ (definition 2). Representation is hence languageÕ or a Ôlanguage of the mindÕ. Some aspects of inherent and fundamental function of nervous this usage can be traced back to ÔphantasiaÕ, which systems. Therefore, internal representations are meant ÔappearanceÕ or ÔperceptionÕ in Greek philexpected to vary tremendously in their complexity. phies (Irwin 1991; Long 1991; Annas 1992). A limited Some are very simple, for example, a neuronal yet highly varied selection of notable examples includes circuit subserving withdrawal in response to pain treatments by British *associationism (Hobbes 1651; (e.g. *Aplysia encodes a representation of Ôno painÕ or Warren 1921), Kant (Kant 1781; Caygill 1995), Bergson various intensities of pain, and the appropriate motor (1908), Wittgenstein (McGinn 1997), and more recent response programmeOther internal representations philosophers and cognitive theorists (Stich and are far more complex, and many, for example represent Warfield 1994; Markman and Dietrich 2000). In mod- tations of propositional attitudes, are highly complex. ern discourse, it is useful to distinguish between twoHowever, regardless of their complexity, all internal *levels of treatment of ÔrepresentationÕ. One is cognitive representations as considered here: (a) are encoded in mental, ÔsemanticÕ, or ÔsymbolicÕ. ÔMental representations are in one way or another in neuronal systems; (b) deter- tionsÕ in this sense are theoretical postulates invoked to fine the behavioural output to an input; and (c) when account for Ôpropositional attitudesÕ. The latter are altered, may modify the potential to react rather than regarded as Ômental sentencesÕ characterized by a immediate action or reaction to an input (Dudai 1989, cific content, being about something in the world 1992; *learning, *memory).

(ÔintentionalÕ), and conditions that can satisfy the In computational neurosciences, a further distinction proposition. For example, believing that being angry is sometimes being made, between ÔrepresentationsÕ and at y, or desiring z are all Ôpropositional attitudesÕ. The Ôinternal representationsÕ. This stems from *models of other level of analysis in which ÔrepresentationsÕ are associative networks. The simplest associative network is rently used is the computational or implementational composed of two layers, input and output. A set of input level, which some philosophers of the mind refer to as patterns arriving at the input layer is mapped directly ÔsubsymbolicÕ; here representations are activated via to a set of output patters at an output layer. Under tors in neuronal coding space (e.g. Cooper 1973); these conditions, the *system is said to lack Ôinternal rep- Churchland and Sejnowski 1992; definition 1). The rel- resentationsÕ, because the coding provided by the exten- evance of ÔsymbolicÕ representations to ÔsubsymbolicÕ world suffices to generate the output. In contrast, ones is a matter of heated debates (e.g. Fodor and when the number of layers increase and intermediate, Pylyshyn 1988). Phylogenetic considerations as well as hiddenÕ layers are added, the representation is said to be *OckhamÕs razor lead to the assumption that ÔsubsymbolicÕ internalÕ (Rumelhart 1986). However, this distinc- bolicÕ and ÔsymbolicÕ representations are the micro- and does not hold water when real nervous systems are the macrolevels of the same brain and mental facultyconsidered. In even the simplest nervous systems, sen- This is clearly a case in which interlevel translation visory information is recoded and manipulated in neu- Ôcorrespondence rulesÕ is badly needed (*reductionism). language, be it at the level of cells or circuits For our purpose, we should also note that often, even (*percept). Therefore, any representation of information computational neuroscientists who manipulate Ôsubby the nervous system should be considered ÔinternalÕ. symbolicÕ representations do hope to explain complex Ôinternal representationÕ is thus a generic term, refer- mental states at the end of the day.

The stand taken here is strictly reductive. The tenet is nervous systems. Indeed, with evolution, it became that nervous systems, even the most primitive of them manifested in many forms and realized in a variety of all, had evolved to encode knowledge about the worldcodes. But as an umbrella term, it is highly valuable. At ÔknowledgeÕ is used in the most elementary sense artlessconceptual level, it focuses our attention on the devoid of *anthropomorphic connotations of aware- ness and *consciousness. It refers to structured bodies to search for representational codes and look for the of information possessed by the organism about themost important changes, i.e. the representational ones, world, and capable of setting the organismÕs reaction to systems that learn. Admittedly, we are still short of the world. ÔWorldÕ means both the external milieu and even a mini-dictionary that translates neuronal activity the external states of the organism, and the organismfrom representational code into behavioural change. means, specifically, the nervous system. These neuBut that day will soon come. And from that day on, the ronally encoded structured versions of the world that philosopher shall dwell with the neurobiologist, and the could potentially guide behaviour are the Ôinternalmutual interest in ÔrepresentationsÕ will no doubt lead

them once-in-a-while to dare and attend each other. They distribute and markedly amplify the message. They are termed Ôsecond messengersÕ, as opposed to the Ôfirst messengersÕ which are the extracellular stimuli (Sutherland et al 1965). About 20 families of intracellular signal transduction cascades have been identified so far. For a tiny selection, to be used merely as an appetizer or an entry point to the intricate world of intracellular signalling cascades, see Cantley (1991), Berridge (1993), Hunter (1995), and Seger and Klein (1995). Furthermore, in real life signalling pathways are intimately interwoven into complex networks (Figure 39) (Weng et al 1999), to the point where their taxonomy looks like a heroic feat.

Selected associations: Attention, Binding, Learning, Map, Memory

¹In the intact organism, even in this simple case, the representation encoded in the reflex circuit is in fact but one element in a structured body of information encoded by the nervous system

²For a limited selection of expeditions for the neuronal Rosetta stone that might yield this interlevel translation: see Alkon (1988), Shadler et al (1996), Daer et al (1998), Kitazawa et al (1998), Stanley et al (1999), Miyashita and Hayashi (2000), and Zhang and Barash (2000); see also *Aplysia hippocampus*, and *honeybee.

Intracellular signal transduction cascade

Any of the specialized molecular pathways in the cell that decode extracellular signals and convert the information into cellular response.

Intracellular signal transduction cascades (Latin for Ôto transferÕ), also termed Ôsignalling pathwaysÕ, are intracellular molecular pathways that decode and transduce specific information conveyed to the cell by distinct extracellular *stimuli, such as hormones, cAMP (Sunaharæt et al 1996; Tesmeet et al 1999). Depending on the specific type of G-protein, the level of signal transduction cascades are activated by sensors of cAMP in the cell increases or decreases in response to stimuli in specialized sensory receptor cells, but they will not be further discussed here.) Intracellular signal transduction cascades span multiple cellular compartments, from the cell membrane via the cytoplasm to the nucleus. They are ubiquitous in all species and tissues, and involved in all aspects of cellular life, from proliferation, via *homeostasis and *plasticity, to death.

The information in intracellular signal transduction cascades flows from transmembrane *receptor(s) to cascades. Some of the modified proteins are other systems of interacting enzymes and regulatory pro-enzymes, others are signalling and regulatory molecules, which are linked to each other by adaptor molecules, still others are transcription factors, which scaffold proteins to provide the right signal channelling.

(Koch et al 1991; Niethammer et al 1996; Whitmarsh et al 1998). Specific nodes in these cascades are linked, which the cAMP cascade can itself sustain information via smaller diffusible substances such as cGMP, adenosine-3',5'-monophosphate (cAMP), calcium, storage device and potentially contributing to the inositol triphosphate, or eicosanoids (a family of lipid *persistence of experience-dependent modifications molecules), whose level is modulated following the neuronal circuits. One involves the experience-stimulus-receptor interaction. These substances-dependent degradation of the regulatory subunit of

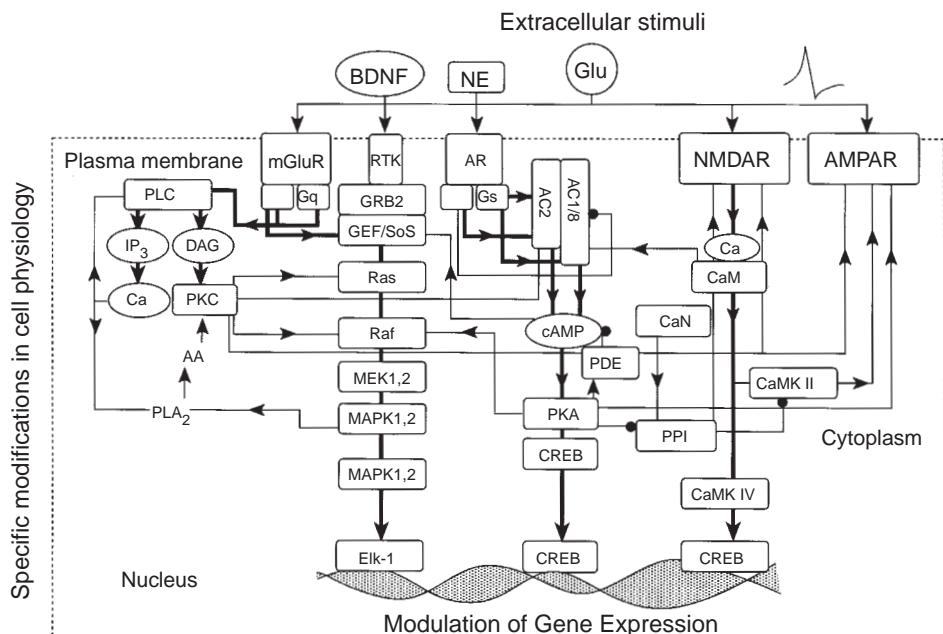


Fig. 39 Intracellular signal transduction cascades convey extracellular information from the cell membrane to the cytoplasm and interact to form complex signalling networks, whose spatiotemporal pattern of activity at any given points in time controls cell memory. This highly simplified scheme depicts the information flow and the interactions of only a few cascades. See [Wang et al. 1999](#).

PKA, which results in an increase in the availability of overlyingly rich (for only a few selected examples, the free, active catalytic subunits. This mechanism has been specifically implicated in memory in conditioning *Aplysia* (Chainet et al 1999). The other mechanism involves modulation of gene expression (few generalizations: *immediate early genes). A most prominent substrate of PKA in this case is *CREB, which in many systems is instrumental in switching on the long-term phase of neuronal plasticity (*Aplysia* *long-term potentiation). CREB itself is a substrate for multiple signalling pathways. cAMP also regulates certain proteins in a PKA-independent manner (Kawasaki et al 1998). All in all, stimulus-induced modulation of the cAMP cascade results in multiple molecular modifications, some of which involve existing proteins, others the synthesis of new ones.

Research on the role of intracellular signal transduction cascades in plasticity, learning, and memory is

Intracellular signal transduction cascades encode at the cellular level facets of the representations of neurons and neuronal circuits. In the not-yet-available *reductive theories of memory, values representing spatiotemporal patterns of activity of signalling pathways will probably be terms in the $\hat{O}laws$ that bind representational events at the different levels of operation of the brain (see also 3 below). We do not yet know, however, which parameters of signalling pathways are critical for computations and representations by neurons and neuronal circuits. Such parameters may not necessarily be the

mere level of a second messenger, or the activity of a key enzyme in the cascade (e.g. Barkai and Leibler 1997).

- The spatial and temporal complexity of intracellular signal transduction cascades contributes to the representational and computational repertoire of neurons and hence probably also of neuronal circuits.

The combinatorial interaction between cascades increases the intracellular complexity while providing additional options for signalling specificity (e.g.

Madhani and Fink 1998; Crabtree 1999; Wetglin 1999). All this also implies that the idea that reduction culminates in simplification is a myth. As every cellular biologist knows, the more we understand the inner working of a cell, the more we complicate life.

- Intracellular signal transduction cascades couple multiple temporal domains in the nervous system: they respond to transient biophysical events, occurring at the millisecond range, by inducing biochemical change that last much longer (Dudai 1997). They are therefore expected to be instrumental in subserving the transformation of "percepts" into "engrams".

¹For what transcription factors are, see *CREB, *immediate early genes

- Intracellular signal transduction cascades provide change that releases the ligand on the other side of the membrane (Reith 1997; Amara 1998). In some cases the

learning machines (Dudai 1994) coincide with the opening of ion channels. Ion channels are classified on the basis of their ion selectivity and the cellular signal that opens or closes them (Hille 1992; Rudy and Iverson 1992).

- Intracellular signal transduction cascades implement transitions from short- to long-term plasticity in the process of memory consolidation. They are therefore candidate "consolidation devices" in biological learning machines.

Each of these types is further classified on the basis of information over time by becoming "persistently" active long after the activating stimulus had dissipated. They are therefore candidate "information storage devices" in biological learning machines, the basis of gating distinguishes between "voltage-gated" least in the context of short-term memory.

(K⁺), "calcium (Ca²⁺), and chloride (Cl⁻) channels.

"second messenger"-, and "agonist-gated channels" are regulated by membrane

Bearing all the above in mind, we should still note that, although every neurotransmitter or hormone is expected to modulate the activity of some intracellular signal transduction cascades in its neuronal target, it does not necessarily follow that the ensuing cellular alterations are necessarily relevant to learning. Whether they do or not depends on whether the neuronal modifications culminate in a family. With the advances in molecular biology and the identification of hundreds of genes that encode channel proteins, additional taxonomies are now possible, which take into account previously unknown evolutionary tenance and plasticity, but only sometimes to memory.

"receptor-gated channels" by second messengers such as cyclic nucleotides (or G-proteins)

"ligand-gated channels" by "neurotransmitters" (see Jan and Jan 1992).

"voltage-gated channels" are considered as members of the same superfamily. With the advances in molecular biology and the identification of hundreds of genes that encode channel proteins, additional taxonomies are now possible, which take into account previously unknown evolutionary kinship (e.g. Jan and Jan 1992).

Ion channel

A protein containing a regulated, selective pore, which mediates the flow of particular ions down their electrochemical gradient from one side of a biological membrane to the other.

Channels belong to families of proteins that translocate substances across biological membranes. These families include channels, pumps, and transporters ring at the millisecond range, by inducing biochemical change that last much longer (Dudai 1997) down their electrochemical gradient. They are fundamental to all types of excitable cells. Pumps drive ions instrumental in subserving the transformation of against their electrochemical gradient. Transporters bind specific ligands and undergo a conformational

change that releases the ligand on the other side of the membrane (Reith 1997; Amara 1998). In some cases the distinction between a channel and a transporter is therefore candidate "associative devices" in biological learning machines (Dudai 1994).

Ion channels are classified on the basis of their ion selectivity and the cellular signal that opens or closes them (Hille 1992; Rudy and Iverson 1992).

"second messenger"-, and "agonist-gated channels" are regulated by membrane

(K⁺), "calcium (Ca²⁺), and chloride (Cl⁻) channels.

"voltage-gated" least in the context of short-term memory.

"receptor-gated channels" by second messengers such as cyclic nucleotides (or G-proteins)

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Ion channel

The history of research on ion channels is an intriguing and memory, which narrows the field a bit, chapter in biophysics and neurobiology, now spanning but still not enough to do minimal justice to its richness over a century (reviewed in Hille 1992; Armstrong 1998). It is useful to consider the role of channels in learning and memory in the context of the operation of Hille 1992). It then evolved through a set of metho- hypothetical cellular learning machines. Such biological and conceptual breakthroughs to yield robust, cal machines are expected to include several types of quantitative models of excitability (e.g. Hodgkin and molecular devices that embody acquisition, association, and Huxley 1952). In recent years, a combination of cellular, storage, and readout of information (Dudai 1993). physiology and molecular biology started to unveil the cellular acquisition devices are receptors capable of detailed structure-function relationship of individual responding to incoming stimuli. Cellular conjunction channels and their interaction with other cellular components. One of the hallmarks of the field is an attempt to comprehend the computations, temporal dynamics, and use-dependent modification of multiple types of devices are macromolecules whose activity in retrieval channels in neuronal compartments (e.g. Koester and expresses the experience-dependent alteration in Sakmann 1998). The molecular and cellular biology of cellular activity. Several of the above roles can be ion channels is no doubt one of the most booming sub-realized in a single molecule.

disciplines of neuroscience. At the time of writing, 5000 papers a year are published on voltage-gated channels, although they can also subserve association alone. Our interest here lies in the role of channels in information, retention, and retrieval of information. The

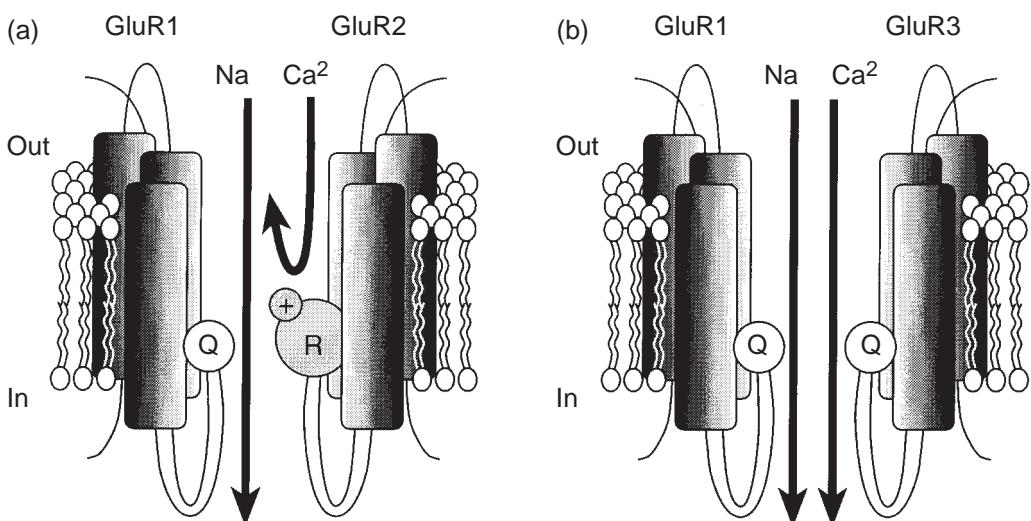


Fig. 40 An example of an agonist-gated (alias ligand-gated) ion channel. This is a highly simplified schematic of the AMPA-type glutamate receptor, which mediates fast excitatory transmission in vertebrates and is considered to subserve neuronal plasticity, e.g. LTP, and possibly memory. For example, it is proposed that AMPA receptor channels increase upon use-dependent facilitation of central synapses (e.g. 1998). It is also a target for experimental memory-enhancing drugs (nootropics). Glutamate binds to a site on the extracellular domain (not indicated in the drawing), and activates the channel itself. It is a central aqueous pore engulfed by multiple types of subunits (GluR) that transverse the neuronal membrane. The pore allows sodium (Na^+) influx, potassium efflux (not shown), and, depending on the composition of the subunits that form the channel (Ca^{2+}) influx. (a) The activated channel allows calcium influx as well. Q is the amino acid glutamine, R is arginine, which is positively charged and can block calcium entry. Some naturally occurring poisons, e.g. certain spider toxins, are calcium permeable. Out and In refer to the outer and inner faces of the neuronal membrane, respectively. (Adapted from Pellegrini-Giampietro et al. 1998)

N-methyl-D-aspartate receptor channel (NMDAR) is also play a part in storage and retrieval of long-term but one example. This macromolecular complex is memory is still unclear (*late response genes). composed of two types of subunits, NR1 and NR2. The roles of NMDAR in NMDA-dependent LTP and NR2 subunit contains the recognition site for the of K channels in learning in Aplysia only selected *neurotransmitter *glutamate, and NR1, for glycine examples (for additional proven or postulated roles of (Anson et al 1998)! The channel is basically the inner channels in neuronal and behavioural *plasticity, see pore formed by the aggregation of four subunits (e.g. Changeux et al 1998; Blackwell and Alkon 1999; Rosenmund et al 1998), always containing NR1 and at MacDermott et al 1999). Computations performed by least one of multiple NR2 subtypes. It is a channel batteries of channels will surely occupy prominent that is blocked by magnesium ions under resting conditions in future *algorithms of biological learning, tions. Binding of glutamate activates the receptor but and in *models that interrelate events at the molecular, does not remove the magnesium block. To release the cellular, circuit, and behaviour levels (Dudai 1997b; latter, the membrane must become depolarized. The *reduction). And, finally, on the more pragmatic side: NMDA receptor channel is hence a coincident detector, ion channels also provide promising targets for cogni-gated by both agonist and voltage (e.g. Seutin et al 1995). It is assumed to play a decisive part in acquisition of certain forms of *long-term potentiation and learn-ing. The NMDA receptor channel is probably more than a cellular acquisition device; it is known to undergo lasting changes in response to neuronal activation (Rosenblum et al 1996). Some of these changes may not relate to the properties of the current but rather to the interfacing of the complex with intracellular cascades. These post-translational modifications may turn the complex into a device that stores information (i.e. functional change in the nerve cell) over the first few hours after training.

Another example for the role of channels in learning

relates to *synaptic facilitation in the circuit that sub-serves *sensitization of defensive reflexes (Aplysia Byrne and Kandel 1996). In this system a major contri-

bution to synaptic facilitation, a cellular analogue of *sensitization, is made by use-dependent enhancement of excitability and neurotransmitter release in the hours.

sensory-to-motor synapses in the circuit. It involves

state- and time-dependent modulation of voltage- dependent as well as voltage-independent potassium (or simply \bar{K}) conductances. For our purpose, suffice it to note (Hones and Roizman 1974; Weinheimer and McKnight that: (a) K channels are critical for the synaptic change 1987). In mammalian cells, the expression of immediate that contributes to the behavioural change in the reflex; early genes is detectable within minutes of stimulation, (b) these channels play a part in storage (part of the followed by the expression of delayed early genes, and memory at the cellular *level is the lasting modification finally, starting a few hours after stimulation, late in K conductances, although the memory-keeping stepresponse genes (Nathans et al 1988; Lanahan et al 1992).

may not be in the channel itself, but rather in a *protein kinase that keeps modifying the re-modified as well as transcription factors, enzymes that produce other cellular the newly synthesized copies of channel molecules products (biosynthetic enzymes), enzymes that degrade and (c) K channels are also readout devices, at least in other proteins (proteases), and cytoskeletal elements.

the short-term (in retrieval, the action potential, which encodes the test stimulus in the sensory neuron, memory is commonly construed within the prevailing encounters a presynaptic membrane with modified conceptual framework, which describes *consolidation channel(s), and therefore triggers a modified sensory-of long-term memory as involving *synaptic remodelling to-motor signal). Whether the same or similar channels and growth (Goel et al 1986; Dudai 1989; Milner et al

Selected associations: Coincidence detector, Neurotransmitter, Receptor, Reduction

The reader may wonder why, if this is the case, the receptor channel is named after glutamate rather than glycine. Well, this has partially do with the history of the field, but is utterly justified: under physiological conditions the concentration of glycine is usually sufficient to occupy the glycine site, whereas the concentration of glutamate is sensitive function of incoming stimuli and hence critical in determining the activity state of the complex.

Late response genes

1998; *development). Only little, however, is currently known about the identity of the late genes that are sup-genes could be transient, whereas in others, the cell posed to subserve these postulated remodelling andould commit itself to expressing these genes differently growth processes. The problem is that, whereas the carfrom the time of consolidation on. The distinction ful analysis of the pattern of gene expression during thebetween transient and lasting modulation reflects on first hours and days after a training experience is likely tthe candidate role(s) of the late gene products in the cel-reveal many changes, determining the relevance of thecellular machinery of learning. If the modulation of the changes to learning and memory is a tricky business. expression of the late response genes is only transient,

Here are a few examples of genes whose modulatethe products of these genes could function as cellular expression following training lags after that of the switches that trigger the shift of the cell from one stable immediate early genes. In *Aplysia* BiP/GRP78, an endoplasmic-reticulum resident protein involved in folding and assembly of newly synthesized proteinsswitches into a different lasting state, this implies that (a type of protein termed ÔchaperonÕ), was found to bbe products of the late genes could be storage or read-synthesized in neurons 3 hours after the onset ofbut components in the neuronal machinery of memory. long-term facilitation, which is considered the cellular analogue of long-term *sensitization (Kurtal 1992). This fits the time course expected of a delayed early gene product. In the same *system, calreticulin, a major *cal-cium-binding protein in the endoplasmic reticulum, also displayed a delayed time course of post-trainingmolecular neurobiology ensures that pretty soon, re-expression (Kennedy et al 1992). In the mammalian brain, 24 hours after the induction of *LTP in the rat hippocampus, a transient increase was observed in the expression of the messenger RNA (mRNA) of ERK-2(*conditioned taste aversion), fear a tone (*fear conditioning), or navigate in space (*hippocampus). signal transduction cascade (Thomasset al 1994). Two gene products with the kinetics of late genes were also reported to increase transiently in the rat hippocampus after water *maze training (Cavallari et al 1997). One of these genes encodes the enzyme glutamate dehydrogenase (mRNA peaking at 6 h post-training), the other a ryanodine *receptor (an intracellular *ion channel involved in *homeostasis of cellular calcium; its mRNA peaked at 6D12 hours post-training).

Although it is rather straightforward to try and incorporate the aforementioned findings and the like into *models of synaptic *plasticity and neuronal remodelling, the truth is that the real function of the identified late genes in consolidation and memory is yet unclear. Do their products fulfil a causal role in altering the *internal representations in the neuronal circuits that encode memory? Are they ultimately stabilizing or augmenting the molecular machinery that is altered in the short term, e.g. post-translationally modified ion channels, enzymes (e.g. *protein kinase), or receptors? Are they required for growth processes to supply active neurons with sufficient synaptic space for future computations? Or, alternatively, are they only manifestations of homeostatic processes that provide *nutrients and restore function to the exhausted, *systems as well (Moravec 1988; Wengl 2001). We stressed cells?

In some potential scenarios, the expression of the late known about the identity of the late genes that are sup-genes could be transient, whereas in others, the cell posed to subserve these postulated remodelling andould commit itself to expressing these genes differently growth processes. The problem is that, whereas the carfrom the time of consolidation on. The distinction ful analysis of the pattern of gene expression during thebetween transient and lasting modulation reflects on first hours and days after a training experience is likely tthe candidate role(s) of the late gene products in the cel-reveal many changes, determining the relevance of thecellular machinery of learning. If the modulation of the changes to learning and memory is a tricky business. expression of the late response genes is only transient,

In contrast, if the expression of these genes itself state to another, but not as storage or *retrieval devices. The investigation of identified neurons in identified circuits that subserve identified behaviours, e.g. in The concrete role of late response genes in the formation of persistent memories. The fast developments in analysis of identified circuits in the brain of behaving vant information will become available from *situ* analysis of identified circuits in the brain of behaving mammals, which learn, for example, to avoid a taste and raf-B, two components of a major *intracellular tioning), or navigate in space (*hippocampus).

Selected associations: Consolidation, Development, Immediate early genes, Phase, Protein synthesis

¹For what transcription factors are, see *CREB and *immediate early genes.

Learning

1. The act or process of induction of a lasting alteration in behaviour or in the behavioural potential, due to the individualÕs behavioural experience.
2. The *acquisition of information, or the reorganization of information that results in new knowledge.
3. Experience-dependent generation of enduring *internal representations, or lasting modifications in such representations.

The above definitions apply to smart inanimate systems as well (Moravec 1988; Wengl 2001). We limit our discussion, however, to learning in biological

organisms with nervous systems. Definition 1 is of L_j. For example, suppose a *neurotransmitter activates the *classical, ÔbehaviouralÕ type (e.g. Bower and *receptor in a synapse. The downstream cascade Hilgard 1981). The term Ôbehavioural experienceÕ culminates in modification of an *ion channel. The refers to the wide gamut of sensory, motor, emotional, identity of the modified channel, determined by the and cognitive events that take place in a lifetime; the stimulus and its context, conveys a specific meaning to modifier ÔbehaviouralÕ is introduced to eliminate the synaptic state, e.g. modified channel X synapses need to exclude specifically the experience of disease excitability. But this altered synaptic state could be injury, and poisoning, which is not traditionally considered to result in learning. Definitions 2 and 3 are circuit level; for example, it means something very different if the synapse is inhibitory or excitatory, or, at a behavioural *performance and behavioural capacity of higher level, if the circuit enhances or suppresses the the organism in terms of ÔknowledgeÕ (Plato; James 1890; Squire 1987). Definition 3 (Dudai 1989, 1992) the representational meanings (ÔsemanticsÕ) hence expresses information in terms of internal representations, which are neuronally encoded structured synapse, depends on the synaptic context, and that of the tations, which are neuronally encoded structured synapse, on the circuit context.

*models of the world that could potentially guide behaviour. This is the preferred definition of learning in this book. This definition implies that learning, be it in *Aplysia or human, is alteration in an internal representation of some type or another.

The pursuit of internal representations and their modification by experience is thus identified as the crux of learning research, at all the *levels of analysis of learning. In the *reductive analysis of learning, the focus on representational properties is meant to guide the investigator to identify those changes in one level, e.g. the cellular, that cause or reflect the representational alterations in another level, e.g. the circuit. Changes that do not contribute to the representational alteration are irrelevant to learning, although, of course, they may still be critical for other functions of the nervous system, such as *homeostasis. Further, the assumption in this book is that internal representations are encoded in the spatiotemporal activity of neuronal circuits. Hence, molecules, isolated *synapses, and in many cases even individual nerve cells, are not expected to encode independently appreciable chunks of behaviourally meaningful models of the world. In order to gain behavioural meaning, the contribution of the molecular and cellular change must be construed within the *context of the circuit (Dudai 1989, 1994).¹

A caveat is appropriate here. Molecular states within an individual nerve cell clearly have a meaning as well. But this meaning is at a level of organization that does not suffice to guide directly behaviour and cognition. ÔMeaningÕ is level-dependent, and levels transmit only limited information to other levels (Simon and Ando 1961). Therefore, although states at level c build embody unique meaning at level these states only provide elementary building blocks, or terms, that are used to construct a variety of meanings at a higher level

1. Innateness Some types of learning involve information that is constrained *a priori by innate predispositions. These types of learning are termed Ôprepared learningÕ. They could be ubiquitous in the animal kingdom, for example, *conditioned taste aversion, or species-specific, for example, filial *imprinting, *bird song. Imprinting and bird-song are good examples for the role of *development in learning. Some behavioural definitions of learning explicitly exclude the role of rigid, autonomous developmental programmes, which do not require interaction with the environment, in the modification of behaviour. But it is doubtful whether genuine use-independent programs exist in real-life. The demarcation line between ÔdevelopmentÕ and ÔlearningÕ is inherently blurred. The two types of processes share molecular and cellular hardware (e.g. *immediate early genes), and it is possible to consider learning as an extension of brain development. Still, the position of different types of learning on the ÔdeterministicÕ, ÔpreparednessÕ or ÔdevelopmentalÕ axes vary. example is provided by *classical conditioning. Some instances of classical conditioning involve only augmentation by experience of the response to the conditioned stimulus. This is called conditioning (*Aplysia). In other instances there is no significant pre-conditioning response to the conditioned stimulus. This is bona fide classical conditioning. These two types of classical conditioning are hence separable on the axis of ÔpreparednessÕ.
2. Strategy There are two major strategies by which a ÔteacherÕ stimulus could modify internal representations (Young 1979; Changeux 1985; Edelman 1987; Dudai 1989). First, the teacher could impose new

- order in the system by directly structuring it to modify in a certain way. Secondly, it could induce the new structure by selecting internal representation among multiple endogenous variations, i.e. existing Ôpre-representationsÕ. The instructive and the selective mechanisms of learning could coexist.
3. Domain. Learning may involve the acquisition of motor, sensory, emotional, or cognitive information, or to all of the above.
 4. Associativity Certain types of learning are governed solely by the parameters of the unconditioned stimulus. These types of learning therefore do not result in the association of the unconditioned stimulus with other stimuli. Examples are provided by *habituation and *sensitization. Most types of learning involve the formation of association among stimuli or among stimuli and actions. Examples are provided by classical and *instrumental conditioning.
 5. Specificity Types and instances of learning differ in the specificity of the acquired information (*generalization, *transfer).
 6. Intention We learn about the world either incidentally or intentionally. The term Ôincidental learningÕ has come with time to acquire multiple meanings (Hilgard and Marquis 1940; Spence et al 1950; Morton 1967; Hyde and Jenkins 1973; Craik and Tulving 1975; Glass and Holyoak 1986; Reigl 1997; Berma et al 1998). These are: (a) learning that occurs unintentionally as a by-product of a sensory, motor, or cognitive process; (b) learning in the absence of *attention; (c) learning in the absence of an identified *reinforcer; and (d) an experimental situation in which the *subject is not told that memory would be tested later. Note that in (c) the lack of an identified *reinforcer is used as a *criterion; however, in real life, the reinforcer is always there, only hidden, either in the context or in the endogenous activity of brain circuits.
 7. Awareness The presence or absence of *conscious awareness is a major criterion in the *zeitgeist *taxonomy of learning and memory. Suffice it to note in the present context that conscious awareness in learning does not entail conscious awareness in retention and *retrieval, and vice versa (*declarative memory). When information is acquired in an incidental manner, without awareness of what has been learned, the process is termed Ôimplicit learningÕ, as opposed to Ôexplicit learningÕ (Seger 1994; Whittlesea and Wright 1997). The distinction between ÔimplicitÕ and ÔexplicitÕ learning has been extensively used in tasks involving rule learning in humans, e.g. grammar learning. In these experiments ÔexplicitÕ came to mean that deliberate instructions are given to search for rules that underlie the presented material, whereas ÔimplicitÕ is when the subject learns without such instructions but acquires information about the underlying rules nevertheless (Reber 1967; Berry and Broadbent 1988). The term Ôlatent learningÕ is occasionally applied to either incidental or implicit learning (Stevenson 1954), but this is not recommended, because ÔlatencyÕ does not necessarily imply neither incidental nor implicitness of learning (Dudai 1989; *insight).
 8. Novelty Certain types or tokens of information are unexpected, others are. A useful rule of thumb is that the more *surprising the information, the better it is learned (*algorithm). The novelty dimension of the stimulus to be learned should not, however, be confused with naivete of the subject. Even when the role of innateness is recognized (1 above), many investigators still err to think that the subject's brain enters the new experimental situation as a blank surface (ula rasa, Locke 1690). This rarely is the case; almost always the subject brings to the task knowledge and expectations (*a priori). This is now evident even at the cellular level. For example, whether a modest input induces a long-term change in the target neuron (*long-term potentiation) depends on what the same cell has experienced 2-3 h before (Frey and Morris 1998). It is hence appropriate to consider even new learning experiments as manipulations of an already opinionated brain (*palimpsest).
 9. Rate Certain types or instances of learning occur in a single trial, as a step function (*flashbulb memory). Others are incremental and require repetitive training. An example for the latter is rote learning (Hebb 1949; Irion 1959), manifested in the acquisition of *skill. The kinetics of learning is commonly depicted as a learning curve. This is the representation of performance, which itself is taken to represent learning, as a function of the amount of experience (e.g. Figure 41, p. 144).
 10. Fate Depending on its type and on the parameters of acquisition, learning could result in *engrams that last from seconds up to engrams that last for a lifetime (*percept, *consolidation, *taxonomy). Furthermore, in some types of learning the information is a priori intended to subserve only the transient task and then be *forgotten (*working memory).

The multiplicity of dimensions clearly hints at the it (ÖAufgabeÖGerman) imposed certain constraints richness of the computational theories, neuronal on *attention and thought, yielding a tendency to use a algorithms and their cellular and molecular implemen- particular mental strategy. This learned tendency to tation, which one should expect to identify in neuronal respond in a particular manner to a type of stimulus circuits that learn. It also implies that a master solution was termed ÖEinstellungÖGerman for ÖsetÖ, ÖattitudeÖ). to the mechanisms of learning is unlikely to exist.

Selected associations: Acquisition, Engram, Development, Internal representation, Memory

¹Although there is no doubt that the contribution of individual neurons to a representation must be evaluated in the context of the entire circuit, the role of single neurons in encoding representations is still unsettled. In any case, this role is circuit and task dependent. Single neurons may execute meaningful computations, but it is unlikely that they encode meaningful parts of complex representations. For further discussion, including estimates of the number of neurons that encode a representation, see *cell assembly.

²Theoretically, one might envisage a computational system with practically unlimited *capacity that could read simultaneously all the information in all the levels of a biological system. Such a system is however impractical, and, most importantly, disposes of the advantage of being able to save computational resources by using only important information extracted at each level.

³It is doubtful, however, whether pure nonassociativity exists in nature; see discussion in *habituation.

For a while, the concept of a cognitive or mental ÖsetÖ had been used rather liberally by multiple schools in psychology, dealing with topics as diverse as perception, conditioning, volition, or neurosis. This cast some doubts on the usefulness of ÖsetÖ, leading Gibson (1941) to comment that ÖThe concept of set or attitude is a nearly universal one in psychological thinking despite the fact that the underlying meaning is indefinite, the terminology chaotic, and the usage by psychologists highly individualisticÖ. It was Harlow (1949) who reinvigorated the concept by focusing on one aspect of it, which he termed Ölearning setÖ, and devising *assays to quantify it. Harlow felt uneasy with the fact that many in the contemporary field of animal learning study their subjects in short, isolated learning episodes only. He called this approach the ÖBüzkriegÖ technique. Animals, say from his argument, do not learn about the world merely by taking isolated snapshots of it; they are expected to benefit from *transfer from one situation to another and ultimately form some *generalizations and predictive ÖhypothesesÖ that facilitate the proper response to familiar types of situations. This, at least, is the way we humans behave, and there is no reason to assume *a priori that other species are radically different.

What Harlow did was to place *monkeys in a special test enclosure (ÖWisconsin general test apparatusÖ *delay task), and present them with a series of visual discrimination foodÖreward problems. In each problem, the monkey was required to choose on a front tray the rewarded one of two different objects. Different pairs of objects were used for each individual problem, and the leftÖright position of the rewarded object was varied in an overall balanced manner. Each of the problems was run for multiple trials. At the beginning, it took the monkeys many trials to respond correctly. But then, a remarkable increase was noted in *performance,

Learning set

1. A learned tendency to follow a particular cognitive strategy in response to a particular type of *stimulus.
2. Learning to learn.
3. Progressive improvement in the rate of learning of successive object discrimination problems of a given type, culminating in single-trial learning of novel problems of that type.

The roots of Ölearning setÖ can be traced back to the beginning of the twentieth century, to a group of psychologists at Würzburg University, Germany, known collectively as ÖThe Würzburg SchoolÖ. They pioneered experimental approaches to thought processes (Boring 1950). In the course of their investigation they noted a Ölearning setÖ. Harlow further found that the monkey that with proper preparation of a *subject for a mental task, upon the presentation of the stimulus thoughts of the subject would run off automatically to perform the task. This was taken to indicate that the subject was particular task and the instructions that have preceded for a number of trials, but then the reward value of the

Learning set

stimuli was reversed for another series of trials, i.e. the first trial required to acquire the specific habit. Hence the stimulus previously correct was made incorrect and former yields an interproblem learning curve ("learning vice versa). After experiencing a number of problems of this type, the monkey learned to respond correctly. It is also noteworthy that the formation of a learning set already in the second trial on the discrimination reversal task might be gradual improvement in performance, and this reversal type of problem. It is noteworthy that in spite of the fact that the discrimination reversal task might be conceptually different from "insight," in which an hypothesis or the formation of a learning set was actually formed more rapidly (Figure 41); this was attributed to interproblem "transfer" from the earlier discrimination training.

What is it that is actually acquired in a learning set? Harlow himself entertained the idea that the subject

The experimental procedure developed by Harlow, acquires the "skill" of eliminating inappropriate response tendencies (error factors), Harlow 1959). Other successive discrimination problems, gave rise to the idea that in forming a learning set, the subject acquires a conceptual understanding of the type of discrimination reversal task. However, definitions 1962; Warren 1966). In the case of the types of discrimination reversal tasks, 1 and 2 are more comprehensive and capture the essential features of the concept better. For the change in behaviour noted in other types of problems, the evidence points to the acquisition of an hypothesis, or abstract "algorithm," of 1970) could be safely construed as manifestation of the type of "win-stay, lose-shift": the subject remembers the ability of the organism to acquire a response strategy—the outcome of the preceding trial as being either rewarded or unrewarded (reinforcer associated with the particular stimulus) and selects the next trial the same cue if previously rewarded (shift). It is important to appreciate that the acquisition of the "win-stay" or the alternative cue if unrewarded ("lose-shift"). Note that this requires the use of "working memory," and is expected to be sensitive to intertrial intervals. The number of problems solved before the subject has formed a learning set is conventionally measured in terms of the number of trials required to form a set, just as the interval in each problem (e.g. Kamil and Mauldin 1975).

formation of "habit" is measured in terms of the number of trials required to form a set, just as the interval in each problem (e.g. Kamil and Mauldin 1975).

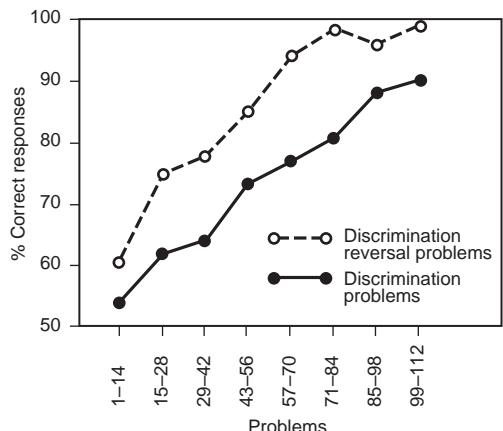


Fig. 41 The acquisition of learning sets. Learning curves of discrimination (closed circles) and discrimination reversal problems (open circles) in the monkey are plotted as responses on trial 2 in each problem as a function of successive groups of problems. The discrimination reversal learning set was formed more rapidly, probably due to interproblem training ("transfer" (reproduced from Harlow 1949)).

As the acquisition of a learning set implies mastering some type or another of abstract rules, it was soon adapted as an intelligence test in comparative animal psychology. For the purpose of comparison, a useful convention is to measure the mean per cent correct on trial 2 of a given problem as a function of the number of problems experienced of the same type (Figure 41; success on trial 2 reflects single trial learning because trial 1 is the instruction trial). The idea is that the more problems required to form a set, the duller is the brain. This type of assay has been applied to estimate the difference in intelligence in phylogeny, ontogeny, and among individual members of a species, even *Homosapiens* (Hayes et al 1953; Harlow 1959; Warren 1966; Doty et al 1967; Hodos 1970). Learning sets have also been used as model behaviours to explore the role of identified brain organs, such as cortex, hippocampus, thalamus and striatum, in advanced learning capabilities in various species (Ropponen 1953; Chow 1954; Staubli et al 1984; Eichenbaum et al 1986; Lu and Slatnick 1990; Tremblay et al 1998).

However, several caveats are appropriate. First, it is advisable to keep Dehaan's razor in mind, and scrutinize the data even if they do suggest a learning set. Over the years, some

interesting debates have taken place in the scientific literature concerning the question whether a marked improvement in performance by a given species can be attributed to other things being equal¹ a risky heuristic that must be retested from time to time by using the appropriate control procedures.

cessive presentation of a given type of problem indeed proves the formation of a bona fide learning set (Menzel and Juno 1982; Schrier and Thompson 1984; Reid and Morris 1992; Slotnick 1994). Second, the above notwithstanding, it is important to remember that tion refers to the structural hierarchy in the nervous system they assign to different kinds of problems. It is the most common usage of Level in the importance they assign to different kinds of problems. popularization of science. A conventional top-down approach will do justice to the intelligence of different species. For example, primates are visual animals whereas for the rat the world is mostly smell and taste, ranging from metres (behaviour) to angstroms and touch. It is hence not surprising to discover that if (molecules). It is useful to note that on the one hand, a learning sets are at all formed in the rat, *performance higher level of organization means a higher complexity on series of odour discriminations rather than visual of the system as a whole, but on the other, the complex discriminations is the place to look for them (Slotnick and Katz 1974).

Selected associations: A Priori, Classic, Habit, Subject Transfer

¹For more on this and similar types of response strategies, see the highly simplifying; hence one should not confuse Ôreductive stepsÕ with Ôsimplifying stepsÕ (Dudek 1989; *reduction).

Level

1. A stratum in a hierarchy.
2. A bounded interval on a scale of structural, functional, or conceptual complexity.

ÔLevelÕ originated in Latin. It was adapted to denote gadgets used to establish flat surfaces. That led to the use of ÔlevelÕ to denote a stratum in a hierarchy, because components at the same level are considered, mostly *metaphorically, to be at the same height or rank. The question whether the *tax-Picturing of levels in a *system follows natural divisions or is merely a convenient *artefact of human cognition, supporting higher ones, is thus considered today as an issue that needs to be addressed separately in each case. Whatever the particular answer is, in real-life systems the variables at other levels are dependent on each other. But in practice, in the analysis and *modelling of systems, the Òis also a concept used, initially without explicit neural borders between the levels are delineated in an attempt to optimize their apparent segregation and permit their theory of memory (Craik and Lockhart 1972). The assumption that variables at other levels are for the most part constant or irrelevant. This is ÔdeeperÕ, cognitive ones, and that the deeper the process referred to as the *paribus* assumption (Latin for *assuming*, the more robust is the resulting *engram.

composed of behavioural, brain, organ, circuit, cellular, and molecular levels. These levels differ in their physical complexity within each of the levels is still immense. For example, it is evident that the biophysical properties of single neurons, and the molecular networks within a single cell, are amazingly intricate (Alberts 1994; Aidley 1998). Therefore, transition from the brain or the circuit to the cellular or the molecular level does not necessarily imply simplification; hence one should not confuse Ôreductive stepsÕ with Ôsimplifying stepsÕ (Dudek 1989; *reduction).

ÔLevels of processingÕ refer to the neuroanatomical and physiological hierarchy of information processing in the nervous system. A bottom-up view depicts them from the lower to the higher. ÔHigherÕ means a larger distance from sensory receptors, or a more global representation of an item. Brain systems that process sensory information used to be portrayed as strictly hierarchical, whereby information from Ôlow levelÕ centres

converges on Ôhigh levelÕ centres (*homunculus). This picture is currently replaced with the one that portrays central sensory systems as concurrent streams of processing, with Ôlow levelÕ *cortical areas already dealing with rather complex attributes (e.g. De Vetaal 1994). The question whether the *tax-Picturing of perceptual systems in the brain as neuromony of levels in a *system follows natural divisions or is merely a convenient *artefact of human cognition, supporting higher ones, is thus considered today as an issue that needs to be addressed separately in each case. Whatever the particular answer is, in real-life systems the processing is expected to culminate in a more global representation (*binding). ÔLevels of processingÕ is also a concept used, initially without explicit neural borders between the levels are delineated in an attempt to optimize their apparent segregation and permit their theory of memory (Craik and Lockhart 1972). The process referred to as the *paribus* assumption (Latin for *assuming*, the more robust is the resulting *engram.

For example, phonological processing of a word could be regarded as ÔshallowÕ and semantic as ÔdeepÕ, and literature in a more colloquial manner, to simply latter is bound to generate stronger memories than indicate the level in which the research is performed by the former. A major conclusion from such a model an experimenter. In this context, reference to the afores is hence that the levels of processing engaged in the mentioned Ôorganizational levelsÕ is the most common. first second in the life of a memory determine much. The choice of the level of experimental analysis depends about the whole future of that memory (*acquisition, on a personal *bias, anchored in philosophical attitudes, *retrieval).

Note that the term Ôlevels of analysisÕ is also used in training, expertise, *paradigms, zeitgeist, opportunities,

ÔLevels of descriptionÕ or ÔanalysisÕ are concepts and chance not necessarily in that order. The choice of refer to the operation of the brain as an information- the level of experimental analysis places constraints on processing, problem-solving machine. An influential account of such levels is that of Marr (1982). He distinguished three levels in the operation of any machine: research, adherence to a molecular level of analysis carrying out information-processing tasks: (a) the level means that the research will yield, if successful, insight on of the computational theory, involving the goals of general building blocks of *plasticity and on synaptic computations and the logic of the strategy to carry out information-storage mechanisms, but probably not on them out; (b) the level of *representations and the specific mechanisms that embody a specific internal *algorithms, i.e. how can the computations be implemented; (c) the level hardware implementation of synaptic algorithms. A tion, i.e. the way the representations and algorithms are implemented in terms of ÔinputÕ and ÔoutputÕ (Andai 1989, 1992). And vice versa choice of a brain and of the algorithms for the transformation of ÔinputÕ and organ level is not expected to illuminate the physio-to ÔoutputÕ; and (c) the level hardware implementation of synaptic algorithms. A research programme that aims at elucidating learning implemented in the Ônuts and boltsÕ, or Ôsilicon add memory as they really are, i.e. multilevel phenomena-wiresÕ, or Ôneurons and *channelsÕ of the machine. *Ergo*, must therefore combine the expertise of multiple example, consider the implementation in a brain circuit subdisciplines, ranging from molecular biology to experience of a Hebbian algorithm by an *long-term potentiation- mental psychology to modelling. How to integrate all like *synaptic mechanism that involves *calcium currents and subtypes of *glutamate receptors. to make their practitioners talk the same language and

Three comments are appropriate here: first, the same comprehend each other, is itself not an easy problem. It computation can be performed in different species, or surely cannot be solved at the administrative level. in different circuits in the same species, by different Selected associations: Binding, Homunculus, Reduction, algorithms. Similarly, the same algorithm may be System, Taxonomy implemented by different molecular, cellular, and circuit devices. For example, an algorithm of multiplication may be implemented in an AND gate in two The *ceteris paribus* assumption is further encountered in *system. different systems, but the AND gates may be realized by For selected approaches to levels, their taxonomy, decomposability, and other assumptions required in dealing with them in a variety different *coincidence detectors in each of the systems system types, see Bunge (1960), Simon and Ando (1961), Simon Second, the complexity of algorithm should not be (1962), Fisher and Ando (1963), *Vitagli* (1969), Mesarovica expected to be a function of the complexity of the brain (1970), and Yagil (1999).

or the behaviour. This means that a certain task may be For the application of this concept in *functional neuroimaging implemented by a cumbersome algorithm in a simple studies, see *Kapta* (1994).

brain but by a simple algorithm in a complex brain. In other words, *simple systems are not guaranteed to yield simple solutions. And third, the different conceptual levels of analysis, i.e. the computational, algorith-

mic, and implementational levels, could be identified at any level of processing or organization in the nervous

system. This means that even cellular and molecular A disputed concept, referring to an inter-neurobiologists will soon have to learn to struggle with connected collection of cortical and subcortical information-processing theories, representations, and structures in the medial parts of the mammalian algorithms, if they ever wish to understand what brain that are implicated in autonomic, emotional, neurons do (e.g. Bray 1995).

Limbic system

A disputed concept, referring to an inter-connected collection of cortical and subcortical structures in the medial parts of the mammalian brain that are implicated in autonomic, emotional, and cognitive functions.

Limbus rim or border in Latin. Already in 1664, Willis described the brain area that surrounds the brainstem sensory integration (MacLean 1952, 1970), as well as as the limbus (cited in Wile 1989). He was followed by Broca, who termed more or less the same part of the brain as the great limbic lobe (Broca 1878; also Schiller 1992). Later, MacLean (1952) referred the limbic lobe together with subcortical structures to both non-declarative (Pavlovian fear conditioning) and declarative memory (e.g. see Fernandez interconnected to it as the limbic system, or Visceral 1999 for a recent study of real-time tracking of brain. MacLean further suggested that this visceral declarative memory formation in limbic circuits). One brain processes emotions and guides some types of behaviour essential for the preservation of the evaluation of saliency and importance of neocortical and the species (MacLean 1970). With time, cal input, and instruct neocortical circuits whether to multiple lines of evidence have led to the notion that form lasting internal representations of that input the limbic system plays a central part in learning and memory (Dudai 1989).

memory. Interestingly, the idea that the limbic system is associated with memory echoes Dante's Inferno, and according to an hermeneutic analysis made between the circles and the human body with the original limbic components, up to a stage in Limbo was the site of memory (Dante 1314/1996). A second trend, a natural outcome of the first, involved the expansion of the limbic system concept to circle in Inferno, and according to an hermeneutic analysis made between the circles and the human body with the original limbic components, up to a stage in Limbo was the site of memory (Dante 1314/1996).

The definition of the limbic system given above is included (LeDoux 1991; Kotter and Meyer 1992). This rather vague. This is intentionally so. Almost from the growing scope of the limbic system concept, combined outset, no two authorities agreed on the preciseness with the generality and fuzziness of the functions anatomy and function of the limbic system (Swanson attributed to the system, have contributed to a growing 1987; LeDoux 1991; Kotter and Meyer 1992). A popular concern whether the limbic system represents a natural lar, *classical morphological description of the limbic structure or rather is an artificial concept (*taxony). system portrayed it as being composed of two interconnected circuits (Livingston and Escobar 1971). One circuit is centred on the hippocampal formation, and is called the medial or Papez circuit (Papez 1937). In this current knowledge of the functional anatomy of the circuit, information flows from the entorhinal cortex to the hippocampal formation, from there through the fornix to the anterior thalamus (directly or via the iour, the conclusion might indeed be reached that mammillary bodies), from the anterior thalamus to the cingulate gyrus, and from there back to the entorhinal cortex via the cingulum bundle. The other major limbic circuit, called the basolateral or Yakovlev circuit (Yakovlev 1948), is centred on the amygdala. It includes the orbitofrontal, insular, and anterior temporal cortical areas, together with their interconnections of the modifier limbic system does not exist in reality as such. As the popular press.

Over the years, two major trends have characterized the research on the limbic system. The first involved the going? Some suggest that whatever the real attribution of a growing number of physiological and behavioural deficits to limbic dysfunction. This was (Isaacson 1992), which refers to basic and *homeostatic damage resulting from disease, injuries, and lesionistic behaviour, and phylogenetically ancient drives such as hunger and sex (e.g. MacLean 1970). This limbic of normal functions. At first the emphasis was on emotionality is different from the oneocorticalness, which involves emotion and sociopathology (Papez 1937; Kluver and Bucy 1938). These limbic functions are now attributed cognitive representations. Others may claim that such mostly to the amygdala (LeDoux 1991). Later the a division is artificial, simplistic, and misleading.

Limbic system

For example, the *hippocampus is a classical limbic structure, but is involved in functions that are characterized by more Óneocortical-nessÓ than Ólimbic-nessÓ and are ÓlimbicÓ cortici (e.g. Sutcliffe 1993).

a mechanism that implements learning, short-term and intermediate-term memory at the cellular level. But by no means is this accepted by all. To gain

After so many viable years it is unlikely that the insight into the phenomenon and the controversy that limbic system notion will suddenly disappear. It will encircles it, it helps to recall the original observation. probably give way to more sophisticated classifications. Bliss and Lomo (1973) stimulated the perforant path of brain structure and function. But in that respect it leading from the entorhinal *cortex to the dentate gyrus does not differ from some other concepts of brain in the hippocampal formation of the anaesthetized rabbit organization and function, that may reflect an artificial entity rather than a natural one (e.g. Kirkpatrick 1996). for 30 s or 100 Hz for 10–15, the dentate response to

a single afferent volley was potentiated for hours, and in the unanaesthetized rabbit, even for weeks (Bliss and Gardner-Medwin 1973). This change was noted in the amplitude of the excitatory postsynaptic potential (EPSP) and in the amplitude and latency of the population spike (EPSP-to-spike potentiation, abbreviated EDS potentiation). This implied that both the synaptic strength and postsynaptic excitability have changed. LTP was hence discovered by applying non-physiological stimuli in a paradigm that did not involve learning. Bliss and Lomo (1973) were well aware of that, but also realized the potential of their finding: ÔOur experiments show that there exists at least one group of synapses

Selected associations: Amygdala, Amnesia, Fear conditioning, Hippocampus

Long-term potentiation

An increase in *synaptic efficacy that persists for hours to more than days after the delivery of a brief induction *stimulus.

In the field of memory research, interest in activity dependent lasting synaptic *plasticity is a natural sequela to the tenet that learning involves synaptic modifications. Over the years, cellular physiologists have identified a number of stimulation protocols that unveil intact animal makes use in real life of a property which synaptic plasticity (Johnston and Wu 1995). For example, in many types of synapses, when a pair of stimuli are delivered sequentially within a fraction of a second, the response to the second stimulus is larger than that to the first (del Castillo and Katz 1954). This is Ôpaired-synapses in area CA1 and the mossy fibres synapses in pulse facilitationÓ (PPF). Stimulation by a train of stimuli (Ôtetanic stimulationÓ) could result in augmentation of synaptic response that lasts seconds to minutes. LTP remained the dominant *model of activity (Larrabee and Bronk 1947; Lloyd 1949). This is Ôpost-tetanic potentiationÓ (PTP). The short life of PPF and LTP, and the fact that they were initially investigated in 1947 and 1949 respectively, led to the belief that they were not useful for information storage. Whether or not the hippocampal synapses that do not connote learning such as the long-term depression (LTD), elicited after specific stimulation protocols in neuromuscular junction, did not stir much excitement in the memory community. This situation changed in 1994 (Malenka 1994; Lisberger 1998). A dominant model when investigators in the laboratory of Per Andersen in Oslo noted that in the *hippocampus, certain tetanic stimulation protocols resulted in enhanced synaptic efficacy (Lomo 1966; Andersen and Lomo 1967), which merge when the analysis shifted from the macroscopic to the microscopic level. This benefited from the use of Bliss and Gardner-Medwin 1973) Enter long-term potentiation (LTP).

LTP is a generic term. It is now used to refer to biology, and *neurogenetics. In the hippocampus, LTP appears in two major forms, one in which induction is

dependent on N-methyl-D-aspartate (NMDA) receptors (NMDAR, *glutamate), the other on which it does not. The original dentate LTP as well as CA1 LTP are NMDAR dependent, whereas CA3 LTP is NMDAR independent. Here is a partial sketch of the current picture of NMDAR-dependent LTP, with a few comparisons with NMDAR-independent LTP.

1. Induction LTP is induced by glutamate activation of NMDAR under conditions that remove the magnesium block from the NMDAR-*ion channel (*coincidence detector). This leads to calcium (Ca^{2+}) flux, resulting in activation of Ca/calmodulin-activated protein kinase (CaMKII) and other kinase systems, and in the modulation of activity of a variety of *intracellular signal transduction cascades. Other types of glutamate receptors, such as the metabotropic receptors, might also be required in the induction phase. The site of induction is postsynaptic. In contrast, strong presynaptic NMDAR-independent LTP is probably induced by

Still, it conveys the flavour of the core mechanisms involved. The \$64 000 question (inflation notwithstanding, Stevens 1998) is whether LTP implements NMDAR memory. The phenomenology of LTP does look attractive. In addition to the initiation by a brief stimulus and poststimulus persistence, other properties of LTP are frequently taken as evidence that it is indeed related to

learning. These properties include: (a) specificity (LTP is restricted to the conditioning path; Andersen et al. 1977; Lynch et al. 1977); (b) cooperativity (LTP has a stimulus intensity threshold, below which only PTP may develop, and above which LTP is a function of the number of activated fibres; McNaughton et al. 1978); and (c) associativity (activation of adjacent, convergent afferents can yield greater LTP in one of these afferents, furthermore, a weak input, incapable of sustaining LTP, can sustain it if activated concurrently with a The site of induction is postsynaptic. In contrast, strong presynaptic Ca influx.

however, that the similarity argument suffers from the homunculus fallacy: it assumes that within the brain

(early LTP, less than an hour) involve modification of existing proteins. Longer-lasting LTP (late LTP) involves modulation in gene expression (Frey et al. 1988; Nguyen et al. 1994; *immediate early genes, *late part displays the properties of the whole. We must look response genes, *protein synthesis). In both phases, major part is played by glutamatergic receptors of the -amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) type (APMAs). They are phosphorylated (Barria et al. 1997), and their density in the synapse (Hayashita et al. 2000) increase. This results in enhanced AMPAR-mediated transmission. In addition, growth processes possibly contribute to enhanced synaptic efficacy (e.g. Andersen and Soleng 1998). All in all, the long-term processes involve an intricate step-wise dialogue among synaptic and cell-wide mechanisms (Frey and Morris 1997; Dudai and Morris 2000). Although the focus of change in NMDAR-dependent LTP is postsynaptic, presynaptic mechanisms, possibly regulated by a message that travels from the postsynaptic to the presynaptic terminal (retrograde message, e.g. nitric oxide), also contribute to potentiation. In contrast, in NMDAR-independent LTP, the major site of expression is assumed to be presynaptic, involving enhanced transmitter release, which is induced by activation of intracellular signal transduction cascades such as the cAMP cascade (Nicoll and Malenka 1995).

The aforementioned sketch does no justice to the potential complexity of LTP (to tell the truth, discovering that a molecule is involved in LTP is now the rule rather than the exception; Sanes and Lichtman 1999).

1. Correlation. Auditory *fear conditioning, which is subserved by the *amygdala, alters the auditory evoked responses in the amygdala in the same way as LTP induction. The change parallels the acquisition of the fear behaviour, and does not occur if the tone and the shock remain unpaired (Rogers et al. 1997).
2. Perturbation. This is a popular approach. Drugs that block NMDAR also block certain types of learning, including *maze tasks that depend on hippocampal function (Morris et al. 1986). Some versions of these tasks are, however, unaffected (Bannerman et al. 1995). A few mutations that impair LTP impair learning (Silva et al. 1992), others do not (Zamudio et al. 1999). The pharmacological and genetic data can be used to show that certain cellular components and mechanisms are shared by LTP and learning, but not that both are the same. A different type of interventional approach is based on the prediction that if learning is subserved by LTP, driving all the synapses to their maximal LTP might saturate the *capacity of the system and block the ability to acquire new information. Saturation of hippocampal LTP in the rat was indeed found to impair maze learning (E.I. Moser et al. 1998). The inverse is

Long-term potentiation

also true: training rats on a reach-and-grasp motor task results in reduced ability of the neurons in the motor cortex to sustain LTP, as if learning has exploited a part of the LTP capacity in that region (Rioult-Pedouet et al 2000).

- Modelling The concept of LTP is useful in some models that mimic the performance of brain circuits (e.g. Mehta et al 2000).

So what are the conclusions? It is heated debate. The participants are divided into three congregations: those that adhere to St Anselm's motto *do ut intelligam* (Anselm 1100), Unless I believe I shall not understand; the opposing atheists, admittedly a minority and in between, those that do not feel that questioning the role of LTP in learning is blasphemy. All in all, the

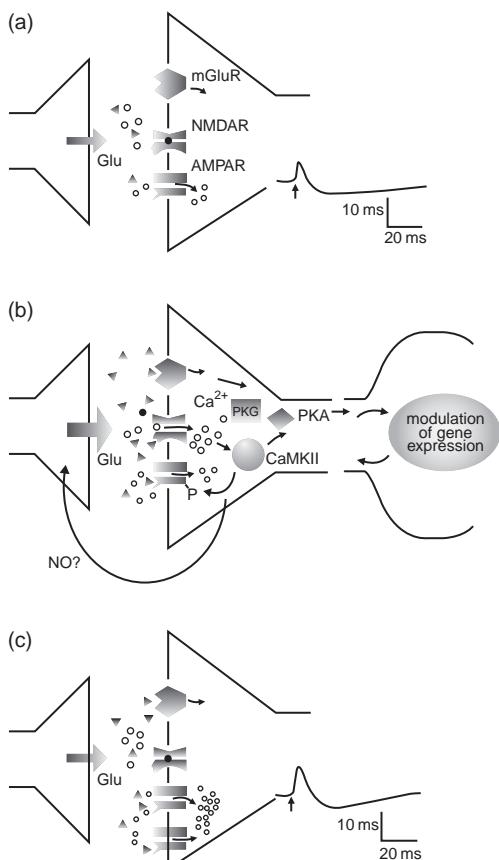


Fig. 42 A highly simplified scheme of the cellular mechanisms at a synapse (c), releases glutamate again, but now the transmission in the hippocampal area CA1. In the absence of an LTP induction (whose release may be augmented because of the aforementioned stimulus (a)), excitatory neurotransmission is mediated via two major presynaptic modifications) encounters additional AMPAR, resulting of glutamate receptors: AMPA (AMPA) and metabotropic (mGluR) receptors. The first is an ion channel preferentially permeable to sodium (small open circles), the latter is linked to intracellular calcium (large open circles). (Based on Nicoll and Malenka 1995; Hayman et al 2000).

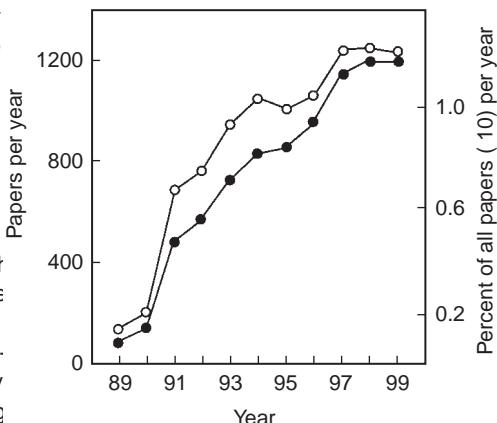


Fig. 43 Long-term potentiation in the popularity of LTP. The graph depicts the number of papers that mentioned either long-term potentiation or LTP in their title, abstract or keywords, per year period 1989–1999 (Full circles). The percentage of these papers of the papers listed in the Science Citation Index throughout this period is also presented (open circles). Both plots show a more than an order of magnitude increase in the popularity of LTP over that decade, with an almost step function increase in popularity between 1990 and 1991. Note, however, the plateau in the last years in the graph, which appears also to be retained in the year 2000 (data not shown). This indicates that the interest in LTP, or the capacity of the neuroscience community to deal with it, may have reached at least a temporary saturation. About a third of all the papers that have mentioned LTP throughout the above decade also referred specifically to learning and memory. See also *zeitgeist. (Compiled from the Science Citation Index Expanded, Web of Science V. 4.1, ©ISI, Institute for Scientific Information.)

signal transduction cascades. A third type of glutamatergic receptor, the NMDA receptor channel (NMDAR), is a cation channel, blocked under resting conditions by magnesium (closed circle). Induction of LTP (b) involves removal of the magnesium block, resulting in an NMDAR-mediated Ca²⁺ influx (large open circles). This activates, either directly or indirectly, a number of signal transduction cascades involving a number of protein kinases. A key role is played by the Ca²⁺-dependent kinase CaMKII. This leads to phosphorylation and activation of AMPAR, and, furthermore, to translocation of new functional AMPAR molecules into the synapse. A retrograde messenger (nitric oxide, NO?) could modify presynaptic activity. The potentiation involves additional processes, including, in the case of long-lasting (late) LTP, modulation of gene expression (see *immediate early genes, *late response genes, *protein synthesis). Proliferation of synaptic contacts may also ensue (*development, not shown for simplicity). A stimulus arriving at the presynaptic terminal of the potentiating

jury is yet out (e.g. Shors and Matzel 1997). As it is stay in lotus land. The fabulous lotus, never identified, an umbrella term, the simplistic question Ôis LTP is hence the ancient counterpart of modern *amnestic memoryÕ is meaningless; one must specify exactly drugs. Actually, lotus was not the only potion renown in which LTP. In each system, the relevance of the pheancient times for its alleged amnestic powers. Drinking nomenon to learning should be assessed on the basis ~~the~~ water of the River Lethe (forgetfulness) in the Plain physiological and behavioural data that are relevant to of Oblivion in Hades (the underworld, to which the this same system. Next, one should consider the possisouls travel) was supposed to erase all memory of ble role of LTP in learning at the computational, earthly life (Plato Republic 621).

algorithmic, and implementational levels. The compu- A variety of real agents interfere with memory. Some tational level is a tricky issue, because in spite of there physical treatments, such as electric shock (Duncan intuitive idea that a stronger synapse means stronger¹ 1948), including electroconvulsive therapy (ECT, memory, the ultimate contribution of enhanced synap- Daniel and Crovitz 1983). In laboratory animals, a brief tic efficacy to the representational properties of circuitselectric shock produces amnesia for a recently acquired is far from simple (e.g. Markram and Tsodyks 1996). Antask, provided that the treatment is administered during example of a role at the algorithmic level is the ANDing the first few hours after training. In humans, ECT gate function provided by NMDAR-dependent LTP, induces a gradient of retrograde amnesia that may And as to implementation, similar algorithms may be cover memories acquired up to 3 years before treatment implemented in different neurons by different recep- (Squire et al 1975). The effect of electric shock is tors and signalling cascades. In most cases we are stillnstrued as interference with *consolidation (Duncan ignorant as to what the crucial parameters of intracellu- 1948; McGaugh 1966; Squire et al 1975). lar molecular networks are, and what they actually rep- Certain types of drugs produce amnestic effects as resent (e.g. Barkai and Leibler 1997). Nevertheless, it is well. This could be due to their effect on arousal, or safe to conclude that multiple receptors and signalling² attention, or on *acquisition, consolidation, or cascades are shared by LTP and other processes of use³. retrieval of information. Drugs that impair recent dependent synaptic plasticity that are not LTP (e.g. memory when administered immediately after train-⁴*Aplysia *development; Constantine-Paton and Cline 1998). In other words, LTP itself may not be learning, *protein kinases, are highly useful in dissecting but it surely unveils cellular mechanisms that are usedhemory into *phases and in identifying the molecular in learning.

Selected associations: Associative learning, Model Plasticity, Synapse

Certain types of drugs produce amnestic effects as well. This could be due to their effect on arousal, or safe to conclude that multiple receptors and signalling² attention, or on *acquisition, consolidation, or cascades are shared by LTP and other processes of use³. retrieval of information. Drugs that impair recent dependent synaptic plasticity that are not LTP (e.g. memory when administered immediately after train-⁴*Aplysia *development; Constantine-Paton and Cline 1998). In other words, LTP itself may not be learning, *protein kinases, are highly useful in dissecting but it surely unveils cellular mechanisms that are usedhemory into *phases and in identifying the molecular in learning.

and cellular mechanisms of short- and long-term *plasticity (Davis and Squire 1984; Montarolo et al 1986; Rosenzweig et al 1993). In general, if a drug enhances attention or *learning (Hock 1995; *nootropics), the antagonist has the opposite effect. Furthermore, the effects are dose dependent; some compounds that have beneficial effects on learning and memory have an opposite effect at higher concentrations. For example, caffeine at moderate doses is used to increase alertness and attention and hence creates favourable conditions for learning (Weiss and Laties 1962); but at high doses it impairs learning (Lashley 1917). The same is seen with other stimulants (e.g. Wetzel et al 1981).

Perhaps most interesting for the general public is the amnestic effect of drugs widely prescribed in medical practice. ÔSedatives or hypnoticsÕ taken in large doses retard the circulation. A clergyman was obliged to discontinue its use; he had very nearly lost his memory,

which returned when the medicine was suspendedÔ (Ribot 1882). Nowadays, anxiolytics of the benzodiazepine family (e.g. Valium) stand out as the most striking example. Benzodiazepines augment the efficacy of the flowering lotus, forgot the way home and desired to inhibititory neurotransmission by interacting with the

Lotus

An imaginary fruit that makes its eaters forget their way home.

The Lotophagi~~l~~² (Greek) were encountered by Odysseus and his sailors on an island in the troubled sea, shortly before facing the Cyclope (Hom³ Odyssey IX 83Ð104). Whoever tasted the honey-sweet fruit of the flowering lotus, forgot the way home and desired to

GABA_A receptor complex in brain (Coopet al 1996).

They are widely used as anxiolytics, hypnotics, muscle relaxants, and anticonvulsants. They also impair some cognitive abilities (Ghoneim and Mewaldt 1990; Izquierdo and Medina 1991; Danion et. al 1993; Gorenstein et al 1995). Benzodiazepines are capable

of interfering with long-term encoding of new episodic information without significantly affecting previously stored memory. They have little effect if at all on semantic memory or on non-declarative memory (*taxonony). The amnestic effect is not correlated with the sedative and hypnotic effects of the drugs. Repeated administration results in some tolerance to the amnestic effect but does not abolish it (Ghoneim and Mewaldt 1990). Members of the benzodiazepine family have qualitatively similar effects on cognition, but in practice, some have more severe effects than

others (bid.). The most renown in terms of its amnestic effect is Flunitrazepam (Rohypnol). This drug has been probably drawn not on cloth but rather on clay, by acquired the unflattering nickname of Ôthe rape drugÕ. In the neurosciences, the term is occasionally used in its everyday connotation (definition 2), in which it was used as a prelude to sexual assault. Denote functional architecture and spatiotemporal (Anglin et al 1997). Flunitrazepam induces drowsiness, activity patterns in discrete brain areas (e.g. in *functional neuroimaging), without necessarily making sleep, impairs motor function, and, most importantly, is remarkably amnestic. As the compound is water soluble, colourless, tasteless, and odourless, it can be slipped into a drink and afterwards, the victim may be unable to recall details of the assault. Owing to its abuse potential, flunitrazepam is now illegal in some countries.

With proper use, amnestic drugs do have a benefit of the world (definition 5). The first requires potential. They could be considered in severe shock and reductive analysis of brains, the latter may even satisfy trauma. It is likely that in the years to come medicine psychologists and philosophers who prefer not to map will be equipped with an arsenal of specific memory tools.

erasers side by side with memory enhancers. In both cases, identification of specific steps in the encoding process, consolidation of new information (e.g. see maps are mental models of the world. In its most common usage, a Ôcognitive mapÕ is meant to be a development of better memory targeted agents. Againtly, the idea dates back much before scientific psychology was born, and decisive regulations should be ensured to prevent reflected, for example, in ancient methods of abuse. In the meantime, benzodiazepines are already mnemonics. It was Tolman's neo-behaviourism that employed in anaesthesia and to calm unanaesthetized patients undergoing invasive and painful medical procedures. Forgetfulness of the unpleasant experience is in this case not an undesired side-effect but rather from one place to another (Tolman 1948). The spatial

Map

1. A function that associates each member of a set A with a member of a set B .

2. Representation of space.

3. Representation of attributes of space A in space B , that keeps a systematic variation in the value of at least one salient attribute of A across a dimension of B .

4. Central sensor or central motor map A map (as in definition 3) of attributes of sensory or motor space, respectively, in a brain area.

5. Cognitive map Mental model of physical or imaginary space.

Selected associations: Amnesia, Attention, Fear conditioning, Nootropics

Let us navigate our way in the neuroscience maps, and the consolidation of new information (e.g. see maps are mental models of the world. In its most common usage, a Ôcognitive mapÕ is meant to be a development of better memory targeted agents. Againtly, the idea dates back much before scientific psychology was born, and decisive regulations should be ensured to prevent reflected, for example, in ancient methods of abuse. In the meantime, benzodiazepines are already mnemonics. It was Tolman's neo-behaviourism that employed in anaesthesia and to calm unanaesthetized patients undergoing invasive and painful medical procedures. Forgetfulness of the unpleasant experience is in this case not an undesired side-effect but rather from one place to another (Tolman 1948). The spatial map concept was later supported and much expanded in a series of elegant experiments on the role of hippocampus in guiding rats in mazes (O'Keefe and Nadel 1978). One can entertain multiple versions of such maps, differing, for example, in their resolution and behavioural control from detailed plans that

exploit salient landmarks to permit navigational plasticity, to less-detailed global representations of space (Vehner and Menzel 1990; Bennett 1996). Note that the (ibid; Gallistel 1989). Analysis of experience-dependent concept of cognitive map is not limited to representational modifications in so-called hippocampal place maps of physical space, and *generalizes to faculties that and their candidate components, place cells, is a fruitful not rely directly on sensory attributes, such as branch of the molecular neurobiology and *neurogenetic depiction of *taxonomies, or of social status netics of learning and memory (e.g. Wilson and Tonegawa 1995; Laszlo et al. 1996). Such nonspatial gawa 1997). Whether the major role of the hippocampus mapping may still involve imagery of imaginary or is to encode topography is still debated. Some authors propose that the mapping functions of the hippocampus much exceed the spatial domain (e.g. Watabe 1999). Few, though, will dispute that spatial coordinates (O'Keefe 1996).

do fulfil a major role in our cognition. The need to map Another context in which mapping is employed in space in order to navigate to food and away from predators may have provided many species, including invertebrates, with the capacity for cognitive maps. However, the risk of *anthropomorphizing in constructing animal behaviour should always be considered (Konishi 1986 complex navigational abilities in *simple species (Mays 1997) (Figure 44). A *classic example is the

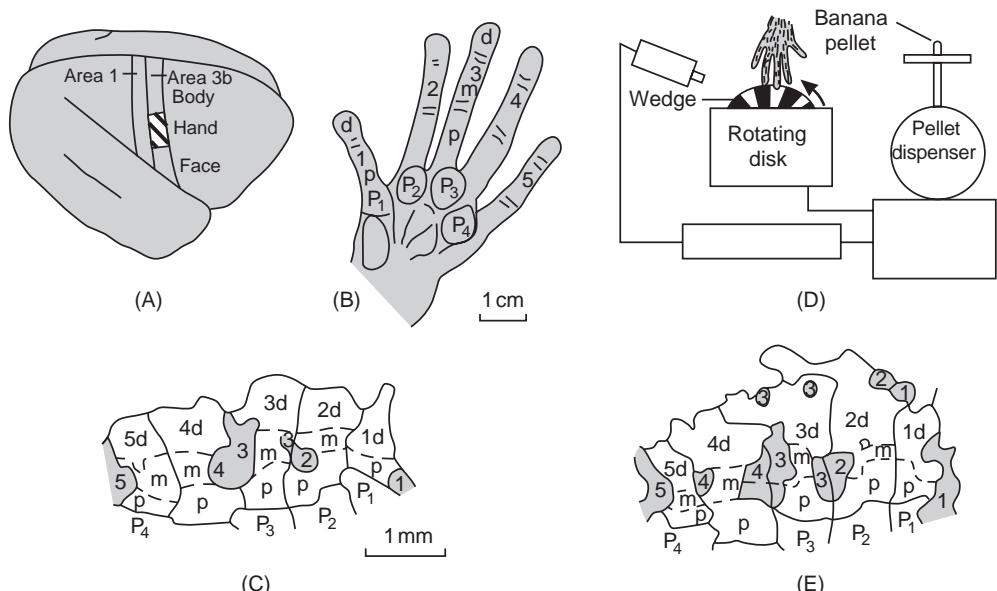


Fig. 44 A central topographical map of sensory space and its modification by experience. (A) A simplified lateral view of the right neocortex of the owl monkey. Areas 1–3b in the primary somatosensory cortex contain a somatotopic representation of the body surfaces (*homunculus). The distal aspect of the hand representation is marked by hatching. (B) The hand surface of an adult monkey. Numbers 1–5 denote the digits, d, distal (d), middle (m), and proximal (p) phalanges. Palmar pads at the base of the digits. (C) A map of the representation of hand surfaces indicated in B, in area 3b of the somatosensory cortex. The map is rotated 90° counterclockwise with respect to A. Grey areas, dorsal aspect of each digit. (D) The behavioural apparatus used for studying the effect of differential stimulation of restricted skin surfaces of the representation of these surfaces in area 3b. The monkey was trained to maintain contact with a rotating disk in order to get banana pellets. The distal aspect of the distal segment of digits 2, 3, and occasionally 4, contacted the disk. (E) The cortical hand representation of the monkey as in C, after about 20 weeks of daily training (1.5 h/day) in the apparatus depicted in D. Note the remodelling of the map with expansion of the representations of the distal aspects of digits 2, 3, and, to a lesser degree, 4. (Adapted from Jenkins and Merzenich 1990)

Map

somatotopic "homunculus in the primary sensorimotor "cortex (Penfield and Rasmussen 1968). When the map does not conserve the topography of the corresponding sensory epithelium, it is "centrally synthesized" or "computational" (Knudsen 1987). The distinction is methodologically convenient but should be taken with a pinch of salt; "projectional" mapping involves central computations as well. Examples for "computational maps" are many (e.g. Knudsen 1987; Knierim and Van Essen 1992; Schreiner 1995); although in most cases the contribution to the overall "internal representation" is still not fully appreciated. A "classic" example in which the contribution of a centrally synthesized map to an internal representation is evident, is that of the map that encodes interaural time differences of the barn owl: here spike time-code is transformed into place code by a brain-stem circuit that uses delay lines and "coincidence detectors" (Konishi 1986) (Figure 45).

Some general issues concerning sensory maps are noteworthy:

1. Traditionally, "central maps" are expected to display systematic variation in the value of at least one sensory attribute across at least one dimension of neural structure. The lack of apparent systematicity was actually taken to indicate that mapping is not indispensable for neural computation (Knudsen et al 1987). However, in some brain circuits we cannot yet conclude whether there is an orderly, systematic variation in the encoding of an important attribute across a dimension of neural structure. In other cases, miniature ordered maps are discovered dispersed in a seemingly irregular mosaic (e.g. pinwheel-like patterns of orientation selectivity in the mammalian visual cortex; Bonhoeffer and Grinvald 1993). Declaring a representation "non-map" by the criteria of definition 3 may therefore prove premature. It might be useful to relax the constraints and extend the concept of "brain map" to all cases in which world attributes are represented in a confined, dedicated brain area (definitions 1 and 2). In that case, "map" becomes more of a generic term for localized candidate internal representations (that can of course map into each other) but see 6 below.

2. Mapping involves transformation of codes, for example from time code (see above, Figure 45) or chemical code (e.g. Rubin and Katz 1999) into place code.
3. Maps recombine to produce higher-order maps. In the process, topographical and computational maps of different modalities interact and align,

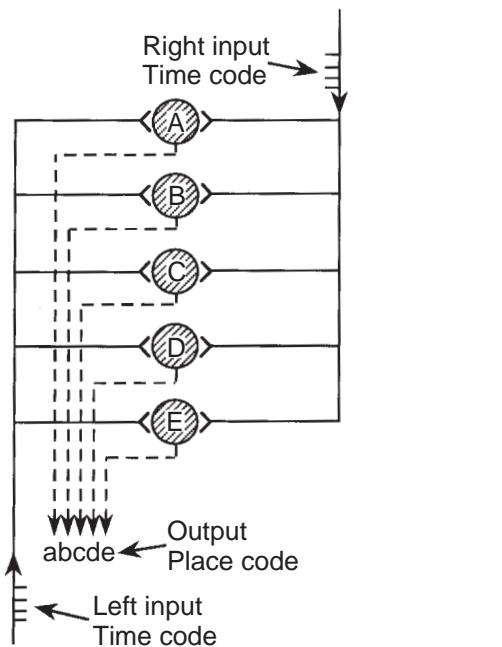


Fig. 45 A schematic model of a computational map of acoustic representation in the brainstem of the barn owl. The map converts spike time code into place code. The circuit uses delay lines and coincidence detection for measuring and encoding interaural time differences. Neurons A–E are arranged in an array and fire maximally only when signals from the left and from the right arrive simultaneously. Temporal information about the acoustic signal is encoded in spike timing. The axonal path increases in opposite directions for two sources, thus creating a left/right asymmetry in transmission delays. When binaural disparities in the acoustic signals exceed a certain threshold, the neurons fire maximally. The output of the neurons does not use spike timing to encode time, but rather the position of the neuron in the array signals the interaural time differences for which the neuron responds maximally. (Adapted from Konishi 1986.)

4. The shape of maps may reflect developmental constraints, or phylogenetic pressures to optimize wiring or facilitate computations (Konishi 1986; Schreiner 1995; Kaas 1997; Van Essen 1997). The possibility should, however, be considered that in some maps topography has little to do with the ultimate representational meaning (see 6 below).

5. Suppose the spatiotemporal states of brain map\$homeÖ (the title of his PhD thesis, admittedly rather could be recorded in physiologically meaningful poetic). The idea to use the laboratory *rat and the time windowsÑwill we be able to read in individual maze for Ôhome findingÖ experiments was suggested to maps only typef computations, or also tokens him by Sanford (Miles 1930). Furthermore, Sanford namely statements with a specific representationalsuggested specifically to model the Hampton Court ÔsemanticsÖ which encode a unique physiologicallabyrinth in London for these experiments. Up and behavioural situatioñ? to that stage all this had nothing to do with learning
6. Ample evidence now indicates that central mapsresearch. But soon after, Small (1901), in the same can be altered by experience (e.g. Weinberger 1995; Kilgard and Merzenich 1998; Faber et al 1999). for learning experiments. With time, rats in mazes What is the relevance of such changes to learninbecame highly popular in studies of behaviour and and memory? Does the observed experiencelearning. By the 1930sÐ1950s, they almost monopolized dependent modifications in the map reflect lasting experimental psychology. The contemporary *zeitgeist representational alterations, or solely changes auxilculminated in *paradigmatic statements such as Ôevery- iary to the representational change, for example,thing important in psychology (except such matters as expansion of computational space (Dudai 1999)?building of a super-egoÉ) can be investigated in With the impressive advances in *methods such asessence throughÉ determinants of rat behavior at a functional neuroimaging and molecular neurobiol- choice point in the mazeÖ (Tolman 1938). ogy, more and more experience-dependent alter- There was reason behind the mazomania. Against a tions are bound to be detected in brain maps. Thebackground of some rather artificial and sometimes temptation to declare each of these a manifestatiorbizarre paradigms of *instrumental learning, mazes of learning should be better quenched until we have provided a reproducible experimental environment adapted to the rodent sensory-motor ecological disposition: Ô(for the rat)Ö, said Small (1901), ÔÉthe experiments were couched in a familiar languageÖ. Inter alia, mazes became a major test ground for two rivalling types of theories in the psychology of learning. One, the stimulusÐresponse (SDR) type, trusted that whatever an animal learns is due to *reinforcement by trial and error of atomistic sensory stimulusÐmotor response connections. The other type of theory was cognitive, claiming that with experience, animals accumulate structured bodies of knowledge that they use to construe, react to, and even anticipate the world. Hence, whereas the first type of theories denied the existence of inferred mental processes that bridge S to R (*behaviourism), the second type deemed such internal intervening processes as obligatory; and whereas SDR theories portrayed laboratory animals as having a somewhat impoverished picture of their milieu, the cognitive

Selected associations: Internal representation, Model, Plasticity, System

¹For more on type vs. token, see *system.

Maze

1. An intricate, usually confusing network of interconnecting pathways.
2. Physical space containing multiple potential routes to a goal, at least one of which is productive or optimal.

Mazes (amasian, Ôto confoundÖ in old English) are ftheories were ready to endow them with a much more some current students of learning what the pen is for antricate psyche (Boakes 1984).

literary critic: indispensable but occasionally abused. Proponents of the cognitive view have tried to con- Although employed mainly to probe the memory of vince themselves and their opponents that when a rat rodents (Olton 1979), over the years, mazes have beenuns a maze, its behaviour reflects a molar cognitive applied to the analysis of other species as well, rangingpurpose (as opposed to reacting to local cues like a from flies (Dudai 1988) to monkeys (Murray et al 1988) and humans (Woodworth and Schlosberg 1954)the rat to navigate in space (*a priori), combined with The systematic use of mazes in the psychological labdthe varied complexity of the task and the substantial ratory was initiated by Kline in Clark University in number of response strategies permitted in certain 1898. He was searching for an appropriate *system tonazes, rendered maze paradigms especially fit to be experiment on Ôthe migratory impulse vs. the love ofused in the attempts to resolve the aforementioned

Maze

debate (e.g. Tolman 1938; Olton 1979). The mazephysical paths within the maze enclosure (conforming studies matured into a dynamic, multifaceted researchto the more inclusive definition 2 above). Such mazes field, addressing cognitive *maps and brain regions that are thus of an Ôopen-fieldÕ type. The term ÔenclosedÕ or retain *engrams of such maps. Sophisticated cellulaÔclosedÕ field is sometimes used to denote defined paths physiology, molecular biology, and computational mazes within a closed environment (Hebb and science now permit, for the first time, attempts to close Williams 1946), but this is questionable because unless the gap between the observed behaviour, the postulated virtual (Maguire et al 1998), all mazes are enclosed in cognitive maps, the circuits that are assumed to encode physical space in one way or another. In their shape, the maps, and the cellular and molecular mechanisms defined path mazes range from a straightforward L, T, or Y, useful for example in simple discrimination or circuits (e.g. Burgess and OÕKeefe 1996; Wilson and Burgess 1997; *reduction).

mazes, permitting sophisticated spatial and *working

Mazes come in many variants. A convenient distinction is between Ôdefined pathsÕ and Ôopen-fieldÕ mazes, for example in *habit. An Ôopen-fieldÕ type of maze that The former (definition 1) have bordered passages and have gained impressive usefulness and popularity in cul-de-sacs as intuitively expected of labyrinths. Therecent years is the water maze (also known as the ÔMorris passagess could be delineated by walls (in which case it is a maze); Morris 1981). In this type of maze rodents are an Ôalley mazeÕ or by elevated paths (Ôelevated mazesÕ) to escape from water on to a hidden platform with the dead ends being the termination of the located within a large unobstructed pool (for earlier elevated alley into open space rather than a wallyvariants of water mazes, although with defined paths, Olton 1979). Alternatively, mazes may have no defined see Glaser 1910; Rosvold and Mirsky 1954). The ÔMorris

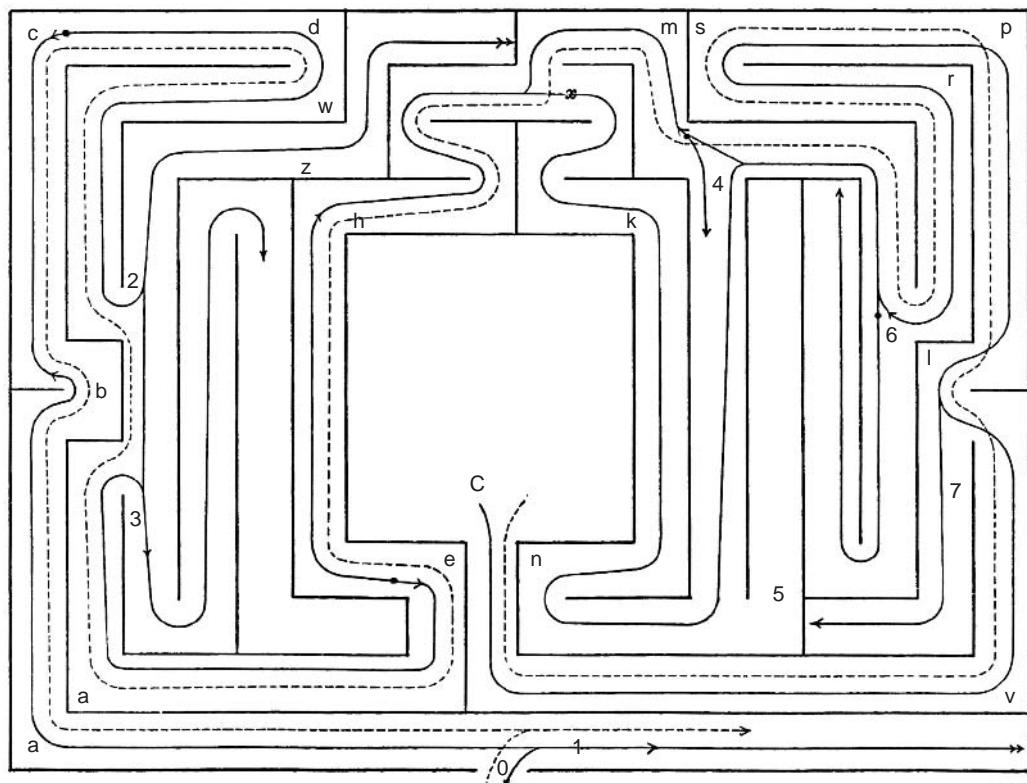


Fig. 46 The first maze in experimental psychology: the Hampton Court Garden maze, used by Small (1901; *classic).

maze¹ has been seminal in reinforcing the notion that organisms with a nervous system. As in the case of rodents can form stable overall spatial maps of their learning, the term 'behavioural experience' in definition 1 refers to the wide gamut of sensory, motor, emotional, and cognitive events that take place throughout a lifetime. Other types of experience, such as the unfolding relevance of long-term potentiation to behavioural development of a rigid developmental programme independent plasticity (e.g. Bannerman et al 1995; Wilson and Tonegawa 1997). Many other types of maze are, however, excluded. The term 'enduring' means longer than highly useful as well in such studies (e.g. O'Keefe and Burgess 1996; Speakman 1987; Mark et al 1995).

of the environment, or disease, injury and poisoning, fraction of a second to a few seconds at most (*phase).

The rapid and impressive advances in molecular neurobiology in general, and in mice *neurogenetics in information (definition 2). It is noteworthy that brains in particular, have promoted the popularity of mazes and nervous systems are not at all mentioned in the among neurobiologists at large, because mazes could behavioural or informational types of definitions. This provide a seemingly simple learning assay. Thus, it lack of reference to the biological substrate of behaviour become almost routine for new transgenic and knock-out mice to be declared either smart or stupid on the psychology, information, and system theory (reviewed basis of passing or flunking the test in the water maze in Bower and Hilgard 1981; Baddeley 1997). Over the However, the simplicity of the procedures facing the years, only rarely were complaints expressed in the literature experimenter may mask the complexities facing the mouse (e.g. Bannerman et al 1995; Day et al 1999). It may also blur the finesse of species-specific innate behaviours (Wolfer et al 1998). A maze is clearly not an instant assay kit, and the experimenter should devote attention to the performance of the subject and to what this performance really means.

Selected associations: ~~At~~ hippocampus, Map, Mouse, Rat, Paradigm

¹For a beautiful distinction between alley and open field mazes in fiction, see Borges (1949).

Another type of definition refers to memory in terms of the combined heritage of multiple schools in the psychology, information, and system theory (reviewed by Young 1987). Over the years, only rarely were complaints expressed in the literature that few dictionaries contain any reference to memory as a feature of a physical system (Young 1987). Definition 3 refers to memory as retention over time of experience-dependent modifications in internal representations, where internal representations are neuronally encoded models of the world that could guide behaviour (Dudai 1989). The focus on the representational properties of neural systems is meant to guide the identification of the relevance of memory findings at multiple levels of analysis (*reduction). This attitude fits the multilevel nature of research in the neurosciences better than the attitude reflected in the behavioural and/or the informational definitions (Dudai 1989, 1992; Crick 1994).

The view taken here is that memories, regardless of the species and the task, are biological internal representations. Similarly to 'learning', the difference among types of memory is in the ecological function, computational theory, algorithms, and neural implementation of the internal representation. The pursuit of internal representations and their modification by experience is thus tagged as the gist of memory research. Internal representations are assumed to be encoded in the spatiotemporal states of neural circuits (*cell assembly, *homunculus). In contemporary neurobiology, quite a few research programmes that claim to target memory concentrate solely on the molecular and the isolated single-cell level. Such programmes address cellular information storage, or neuronal plasticity, not 'memory'. This of course should not belittle the huge excitement, signal importance, and immense usefulness of the molecular and cellular approach; it only means that molecular and cellular

Memory

1. An enduring change in behaviour, or in the behavioural potential, that results from the individual's behavioural experience.
2. The retention over time of learned information.
3. The retention over time of experience-dependent internal representations, or of the capacity to reactivate or reconstruct such representations.

Memory, the mother of all the muses (Hesiod & C *mnemonics), resides in many types of systems, including inanimates (Moravec 1988; West et al 2001). We will refer here solely to memory in biological approach;

Memory

neurobiologists shall aim at integrating their programs learning or previous retrieval. Further, retrieval itself with higher level approaches if they wish to focus on could induce use-dependent alterations in the circuit, memory. And vice versa: system neurobiologists should including re-*consolidation of the modified anew tune to molecular and cellular biology, and exploit its trace. Add to this the *association of the *context at the tools, if they wish to understand the nuts and bolts of time of retrieval with the retrieved *engram, and the biological information-storage machinery in the brain. result is the potential *falsification of memory.

Memory could be subjected to multiple *taxonomies, 3. A balance is expected in the evolution of biological based on different *dimensions, such as duration, association between universal processes and components, creativity, *conscious awareness, and behavioural functions that subserve many types of memory systems, and particularly (e.g. Augustine 400; de Biran 1804; James 1890; Bergström 1908; Hebb 1949; Ryle 1949; Tolman 1949; Miller 1998). Such taxonomies are exemplified under *learning evolution could favour universals, the need to endow the above. The rationale and evidence for selected classification with new capabilities, as well as opportunism in tions of memory are detailed in the relevant entries in evolution, could favour the addition of particular this book. At this point, it is useful to consider briefly only molecular, cellular, or system *algorithms and devices. a few general properties of memory.

The point to note is that even if two learned behav-

1. By definition, not all internal representations that iours seem to share the phenomenology, or two mem- guide behaviour are memories. Internal representationsory circuits seem to share algorithms, such as the could also be *a priori, innate constructs, encoded by Hebbian, and hardware devices, such as the *glutamate genes and established by developmental proN-methyl-D-aspartate receptor, a closer look may unveil grammes even in the absence of learning. *Percepts are any particulars among the apparent universals. In any also internal representations but not memory. Memo- case, as memory refers to so many different types of ries are only those species of internal representationinternal representations, neuronal systems, functions, that result from learning. At the same time, it is impor- and behaviours, as in the case of learning, it is unlikely to tant to note that the concept of ÔlearningÕ used in the book is comprehensive, and includes not only physio- logical or behavioural experience but also rearrange- Selected associations: Engram, Internal representationments of internal representations that yield new Learning, Palimpsest, Plasticity knowledge. Therefore, in brains, probably also in very simple brains and ganglia, even the innate internal representations are expected to undergo a process of change with experience and become fidememory.

Metamemory

2. In contrast with what is connoted by popular *metaphors, memories, being spatiotemporal activity Self-appreciation, monitoring, and control of states of the nervous system, are unlikely to be stored one's own memory. over time as such. Rather, they are probably reactivated or reconstructed each time anew, to regain their meaning. Although some authors consider the study of meta- ing, content-wise, only in *retrieval (Tulving 1991). memory a newcomer to the field of memory research, Retrieval is any *stimulus-induced or spontaneous act-its roots are rather ancient. Already St Augustine (400) vation of the representation, whether accompanied by referred to ÔMemory of memories. I have remem- behavioural *performance or not. So what is it that I have remembered. Interest in the self- stored over time? This profound issue is discussed appreciation of one's own knowledge and performance under *persistence; suffice it to note here only two basic was shared by introspectionists during the early days of types of scenarios. One, that *recognition or *recall is experimental psychology, especially the so-called the activation of a dedicated circuit, probably identical ÔWürzburg school of Ôsystematic experimental intro- to the one activated in training. One could expect to speculate (Boring 1950). However, systematic reports encounter this scenario in simple circuits that subserve *subjects' ability to predict their own learning ability simple behaviours, such as reflexes. Another had to await the development of more rigorous research possibility is that what is stored is only a compressed methods (e.g. Underwood 1966). Soon after, Tulving Ôcore memory, or index, that permits the reactivation and Madigan (1970) noted that Ôone of the truly unique reconstruction of a full-blown representation. The acti- characteristics of human memory (is) its own knowl- vated circuit could be different from that employed in edge, and added that Ôif there is ever going to be

a genuine breakthrough in the psychological study of memory – it will relate the knowledge stored in the individual's memory to his knowledge of that. Finally, the term "Metamemory" itself (meta Greek for "beyond", "after") was coined by Flavell (1971). This was in the context of research on the development of learning and memory in children in general, and children's knowledge about their own memory in particular. Flavell and his coworkers became interested in questions such as whether kids appreciate that some types of material are harder to remember than others, and whether they have any

idea of how to improve their learning performance. The self-belief and predictions about one's own memory For example, do kindergarten kids realize that it is easier to remember the gist of a short story rather than its exact wording? In suggesting "Metamemory", Flavell had in mind the analogy with "Metalinguage" (a language used to describe a language under study), thus, while keeping in mind occasional criticism concerning the research methodology and the conclusions (Flavell and Wellman 1977). "Metamemory" is hence concerning the research methodology and the conclusions of higher-order memory, and as such is "Metacognition" (Cavanaugh and Perlmuter 1982), metamemory is faculty ("Metacognition"), the ability to reflect on one's own cognitive processes and performance, e.g. Yzerbyt et al 1998). Viewed this way, metamemory is part of a belief system that comprises a "private theory" of mind.

The research on metamemory still occupies a central position in developmental psychology (reviewed in Schneider 1999), but has long transcended into other subdisciplines of memory research. There are multiple facets to metamemory, some implicit, others explicit. Understanding the processes and mechanisms involved is key to appreciating and monitoring of performance, and retrieval really work in a complex brain. For example, in self-appreciation and self-monitoring of performance, are FOK and control of retrieval due to some interference, others in controlling it. Here are some measures that have been used to infer that metamemory does exist and to then analyse it:

1. Ease of learning, refers to the subject's judgement of how easy is the task to be learned (Underwood 1966)
2. Judgement of learning, refers to the subject's prediction of whether the information was indeed acquired and whether it will be successfully retrieved (Arbuckle and Cuddy 1969).
3. Feeling of knowing (FOK) refers to the subject's feeling that what is known is based on familiarity of the problem rather than judgement of whether an item is in memory despite failure to retrieve it at present time (Hart 1965, and Ritter 1992; Klier et al 1997). In that case, it is even A related term is the "metaphor depicting verbal question what is "Meta" in the "Metamemory".
4. Control of learning strategies refers to the subject's self-assessment of the effectiveness of learning strategies, their applicability to the target in aspects of memory monitoring remain intact even in

question, and their recruitment, for example, whether to use *spaced, rather than massed, training. Control of retrieval strategy, refers to the subject's self-appreciation of retrieval strategies and effectiveness. Consider, for example, the decision whether to terminate a retrieval attempt or to pursue it (as appreciated intuitively, this could be related to FOK, see above). Control of retrieval and learning strategies, as well as other facets of metamemory, were considered as a potential leverages to memory improvement (Hertzog 1992; *mnemonics).

For example, do kindergarten kids realize that it is easier to remember the gist of a short story rather than its exact wording? In suggesting "Metamemory", Flavell had in mind the analogy with "Metalinguage" (a language used to describe a language under study), thus, while keeping in mind occasional criticism concerning the research methodology and the conclusions (Flavell and Wellman 1977). "Metamemory" is hence concerning the research methodology and the conclusions of higher-order memory, and as such is "Metacognition" (Cavanaugh and Perlmuter 1982), metamemory is faculty ("Metacognition"), the ability to reflect on one's own cognitive processes and performance, e.g. Yzerbyt et al 1998). Viewed this way, metamemory is part of a belief system that comprises a "private theory" of mind.

some decline in self-confidence (Cohen 1996). How is it

possible for us to know whether we know or do not know an item in memory without specifically retrieving that item, is mostly still a mystery. Underlying all possible for us to know whether we know or do not know an item in memory without specifically retrieving that item, is mostly still a mystery. Underlying the processes and mechanisms involved is the monitoring of the system by itself, an outcome of com-

monly remains fairly stable in normal ageing, in spite of some decline in self-confidence (Cohen 1996). How is it

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dementia of the Alzheimer type (Moulet et al 2000).

Impairment in FOK is evident in Korsakoff's patients, but is not an obligatory feature of amnesia (Shimamura and Squire 1986). One of the characteristics of Korsakoff's patients is frontal cortex dysfunction.

A figure of speech in which one entity is described in terms of another.

Frontal patients that are not amnesics also show

impairment on FOK. All this has led to the proposal Metaphor is the transfer of memory (Shimamura 1995; but see doubts in O'Shea et al 1994). Another potential approach is to use formal notation, metaphors can be described as state-functional neuroimaging to observe brain areas in figurative language, composed of two juxtaposed elements, the *Tenor* and the *Vehicle*, which are presented as sharing common attributes or *Ground*. Circuits may not be easy.

(Richards 1936). The tenor is the subject of the

As noted above, Tulving and Madigan (1970) deemed metaphor, while the vehicle is the means by which the metamemory unique to human memory. Is it true? subject is referred to. (More recent discourse refers to Over the years attempts have been made to prove that the subject as the *Target domain* and to the vehicle as other species also know what they know and what they source domain (Gibbs 1994.) For example, in *Memory* don't. Verbal tests are unfortunately out of question if it is a storehouse (after Locke 1690, and see below), nonhuman subjects. The anecdotal testimony of pet *Memory* is the tenor (the target domain), *Storehouse* owners is also useless as a respectable research method. The vehicle (the source domain), and *Space* the ground.ology. All this makes it necessary to devise some sophisticated tricks to overcome the communication barrier target with the source domain, produces an emergent (e.g. Smith et al 1998; Inman and Shettleworth 1999; meaning for the entire statement.

Hampton 2001). Some will claim that this need for the Classically, metaphors were regarded as artful, poetic indirect approach is actually an advantage, because decorations: *Metaphor* gives style clearness, charm, having to rely on questionnaires, opinion polls, and and distinction as nothing else can (Aristotle subjective verbal accounts, does only good to the field (1405a8D9). But in modern psychology and linguistics, Without going too much into details, here is an illustrative approach: suppose we train a pigeon on a delayed language, language development and change, and thought matching-to-sample task (*delay task), and occasionally and conceptualization (Lakoff and Johnson 1980). allow it to choose between a test of memory for the same Three major motives were proposed for using people with a hefty reinforcement, or pecking a safe key for metaphors (Gibbs 1994). The first is similar to the classic view, namely, metaphors capture effectively a meagre reinforcement. Will the pigeon prefer the safe poetic view, namely, metaphors capture effectively key when it senses that its own memory is feeble, say the vividness of experience. The second is to provide after a long delay? As Inman and Shettleworth (1999) compactness in verbal communication. The third, to show, even when such a behaviour is observed, interpret express what is otherwise inexpressible in literal languages other than the use of metamemory are still possible. It is this latter property that endows metaphors a sible. Nevertheless, this kind of experimental design central position in musing, hypothesizing and writing might in principle be further explored and *controlled about learning and memory.

to identify metamemory. Among the nonhuman candidates for a personal theory of memory, monkeys and apes are probably a better bet than pigeons. In any case, this is definitely an area of research where the razor is an effective antidote for anthropomorphism and *red herrings.

Selected associations: Cerebral cortex, Mnemonics, Real life memory, Retrieval

Ordinarily, there are two main reasons for inexpressiveness: tenders for a personal theory of memory, the first is related to evolution: anthropoid apes are probably a better bet than pigeons. In any case, this is definitely an area of research where the razor is an effective antidote for anthropomorphism and *red herrings.

Dimensions (millimetres to kilometres, seconds to years), limited complexity (e.g. *attention, *capacity), and restricted access to inner mental processes. These segments of the universe comprise the *Mesoworld*, to be contrasted with the *Micro* and *Mesoworld* which are not accessible to the bare senses. It is also

¹On the Würzburg School see also *learning set.

²A subject is said to have a *Theory of mind* if it can impute mental states to itself and others (*observational learning).

tempting to assume that ordinary language lags beyond the Second World War was influential in shaping the potential of the human brain to transcend the metaphors of attention and working memory. In current mesoworld into the micro, the macro, as well as the discussions, working memory is occasionally referred to inner universe. Ultimately, the accumulated *insight of as the brain's desktop; this is an interesting example of our *culture is formalized in formal, scientific terminology, some of which gravitates with time toward borrowed from the computer world, which was intuitiveness. But often, an interim stage is needed imported from the pre-computer office environment. which comprehension of the unfamiliar is mediated via second-order, or *palimpsestic metaphor: desktop is son, it is tough to comprehend intuitively what an research ideas, their value is limited. A few caveats are electron is; depicting it by a process of analogical appropriate here. First, metaphors are potential source *transfer as a small planet encircling the nucleus-sunfor misunderstanding: Metaphor is the dreamwork of makes life easier. A second reason for inexpressibility language and, like all dreamwork, its interpretation simply the lack of appropriate knowledge. reflects as much on the interpreter as on the originator

Brain research uses metaphors for both aforemen(Davidson 1979). Second, in the absence of new data tioned reasons. To describe the mind and memory, and theory, merely adding or exchanging metaphors multiple classes of metaphors have been generated could simply augment confusion. This is not unique to most of them antedating the scientific era (Abrams the scientific language: it was noted that Ömixed 1953; Roediger 1980). The vehicle and ground in these metaphors (i.e. the application of two or more incon metaphors involve either space, written records, vision,sistent metaphors to a given situation) Öalways arouses or technology. Especially common are spatial derisionÖ (Fowler and Burchfield 1996). Third, domi metaphors, depicting memory as a physical repositorynant metaphors (*zeitgeist) could hinder progress by and *retrieval as a search for the location of an itemfixating conceptual *paradigms (Watkins 1990; Koriat filed in storage (for classical examples see Plato and Goldsmith 1996). For example, storage metaphors Theaetetus197cÖ; Augustine 400; Locke 1690; may lure us to think about memory as static, which is *engram, *mnemonics). Written record metaphors wrong. Only time will tell whether recent metaphors (which could be regarded as a subset of the spatial ones) at drew from computer science and modern physics advanced from etched wax tablets (Plato and Goldsmith 1996) to more fancy writing pads (Freud 1925). Inresearch, as in science in general, metaphors should an influential *model of *working memory, we better be regarded only as vehicles on the winding and encounter a subsystem termed the Övisuospatial scratchy road to formal understanding. But this is padÖ or ÖsketchpadÖ (Baddley¹⁹⁸⁶)ing memory already another metaphor. as such was also referred to as Öthe blackboard of the mindÖ (Goldman-Rakic 1996).

Selected associations: Engram, Flashbulb memory, Model, Palimpsest, Transfer

Visual metaphors of brain and memory often intermingle with spatial or written record metaphors. They

refer to *perception and *acquisition in terms of ¹For what is meant by ÖintuitionÖ, see *dimension. passively perceiving the world or actively throwing light²The Öcentral executiveÖ, used to describe the postulated super on it (Abrams 1953), and to *retrieval as illumination controlling system in working memory, could also be considered of items in mind (e.g. by an internal searchlight, metaphor, but of a different ground. It belongs to the family of the Baars 1998). Visual metaphors are common when the *homunculus metaphors.

discussion involves *attention and *conscious awareness (*ibid.*). Whereas the images in some of the above metaphors, e.g. the storehouse, remain rather similar over the ages, technological metaphors reflect the

machines and gadgets of their period. They tend to be more dynamic than spatial metaphors and describe multiple phases in learning and memory. Examples of The *plasticity of neural plasticity.

technological metaphors include hydraulic networks in the Renaissance (Descartes 1633), and electronics aMetaplasticity is the modulation by experience of computers nowadays (Churchland and Sejnowski 1992). Operational and system research by the Allies that have probably evolved to form a dynamic balance

Metaplasticity

among the need for change (*plasticity), the need to resist too much change (*homeostasis, *memory, *persistence), and the metabolic price of both, at various periods in the life of the organism (*development). Metaplasticity is commonly referred to as the plasticity of *synaptic plasticity (Abraham and Bear 1996; Abraham and Tate, 1997), but there is good reason to believe that the underlying mechanisms involve the neuronal cell body as well. The concept of metaplasticity fits to be used in the discussion of higher *levels of organization as well. For example, it is legitimate to say that the language areas of the brain undergo metaplastic changes with age. It is, however, assumed that metaplastic changes that are manifested at the circuit or *system level, are the consequence of metaplasticity at the synaptic level.

Most research on metaplasticity concerns activity that primes the expression of subsequently induced *long-term potentiation (LTP) or of long-term depression (LTD). Part of this work is conducted on *hippocampal preparations (e.g. Huang et al 1992; Christie and Abraham 1992), and part on *cortical preparations with special emphasis on developmental plasticity in the visual cortex (Kirkwood et al 1996). In

these systems, under appropriate conditions, prior the cortex following manipulation of visual experience activity can be shown to regulate the capacity to (*development).

undergo LTP and LTD (Abraham and Tate 1997).

An influential theoretical framework for metaplasticity in the mammalian brain was proposed by Bienenstock, Cooper, and Munro (known in the field as the BCM *model; Bienenstock et al 1982). This model was developed to account for the development of stimulus selectivity in the mammalian sensory cortex. The model makes two basic assumptions. One, that synaptic modification varies as a non-target, these stimuli modulate receptors, *intracellular linear function of postsynaptic activity, such that low levels of afferent activity result in LTD whereas high levels in LTP. The crossover from LTD to LTP occurs at the modification threshold m . The second assumption of the model is that m slides as a function of synaptic history, hence endowing the system with metaplasticity. This sliding threshold keeps the active synapse within a dynamic range, preventing saturation of LTP or complete depression by LTD on the synapses; during the synaptic consolidation time window (ibid.). Some experimental data echo the assumptions of the BCM model. For example, Kirkwood et al (1996) found that in the developing cortex, indeed metaplasticity depends on sensory experience (Figure 47): in the visual cortex of light-deprived rats, LTP is enhanced and LTD diminished over a range of stimulation frequencies, but the effect is reversed by brief light exposure. This shift may contribute to the experience-dependent modifications of visual receptive fields in the developing visual system. Kirkwood et al. (1996) have measured the change in synaptic responses in slices prepared from the visual cortex of light-deprived (closed circles) and control (open circles) 4D6-week-old rats. Measurement was done at 20D30 min after the stimulation. The percent change in synaptic response is depicted as a function of stimulation frequency. It can be seen that visual experience shifts long-term depression (LTD, negative change) to long-term potentiation (LTP, positive change) cross-over point (indicated by a vertical dashed line). (model, see text). (Adapted from Kirkwood et al. 1996.)

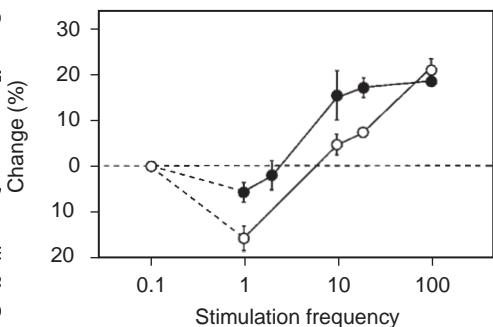


Fig. 47 Experience-dependent metaplasticity in the *developing visual system. Kirkwood et al. (1996) have measured the change in synaptic responses in slices prepared from the visual *cortex of light-deprived

(closed circles) and *control (open circles) 4D6-week-old rats. measurement was done at 20D30 min after the stimulation. The percent change in synaptic response is depicted as a function of stimulation frequency. It can be seen that visual experience shifts long-term depression (LTD, negative change) to long-term potentiation (LTP, positive change) cross-over point (indicated by a vertical dashed line). (model, see text). (Adapted from Kirkwood et al. 1996.)

Multiple molecular and cellular mechanisms may account for metaplasticity over a spectrum of developmental stages, brain regions, synaptic specificities, and growth factors and neuromodulators probably primes

the development of circuits to respond differentially to subsequent plasticity. The experience-dependent release of calcium-calmodulin dependent protein kinase type II of the enzyme CaMKII, shifts m in the hippocampus (Mayford et al 1995; see also commentary in Deisseroth et al 1995). This sliding threshold keeps the active synapse within another type of candidate mechanism for metaplasticity, preventing saturation of LTP or complete depression by LTD on the synapses; during the synaptic consolidation time window, the recent history of the neuron could determine whether a stimulus will be encoded in long-term memory or, alternatively, forgotten (Frey and Morris 1997).

Metaplasticity was also explored in an invertebrate, Aplysia. The advantage of studying this system lies in the ability to relate events at the cellular, circuit, and behavioural level, respectively. The circuits that encode the defensive withdrawal reflexes in Aplysia are composed of a number of cell types, including sensory

neurons that receive the tactile information from the skin, motor neurons that execute the withdrawal reflex, and interneurons that feed into the sensory and motor neurons information from various parts of the organism (Figure 5, p. 16). In the circuit that mediates the siphon withdrawal reflex, the L29 excitatory interneurons synapse on to the motor neurons, whereas the L30 inhibitory interneurons synapse on to L29. By inhibiting

L29, activation of L30 suppresses the ability of siphon stimulation to elicit the reflex. L30 receives input from road and embark on a journey (this indeed is the the excitatory interneurons that relay tactile information from the siphon skin; this forms a negative feedback loop, which limits the activation of the reflex. Activation of L30 can induce multiple types of plasticity. One type, *a priori limits on the frequency facilitation (FF), involves a steady increase in the strength of the synaptic connection during the burst of nerve impulses. Another type of plasticity, short-term that outlasts the stimulus by about 1 min. The most important findings in the context of this discussion is that L30 is also influenced by tactile information from the tail. If a weak tactile stimulus is applied to the tail

Selecting a method and following it is like choosing a road and embarking on a journey (this indeed is the origin of the word:meta, which is Greek for beyond, after, along with, antłodos, which is way, journey). The loop, which limits the activation of the reflex. Activation of L30 can induce multiple types of plasticity. One type, *a priori limits on the frequency facilitation (FF), involves a steady increase in the strength of the synaptic connection during the burst of nerve impulses. Another type of plasticity, short-term that outlasts the stimulus by about 1 min. The most important findings in the context of this discussion is that L30 is also influenced by tactile information from the tail. If a weak tactile stimulus is applied to the tail

serotonin is applied in an imitation experiment, Despite the fact that experimental science is wonderful

*method), the capacity for STE in the L30DL29 fully rich and heterogeneous, the number of elementary inhibitory synapse is suppressed, while leaving the capacity of methods, or better ÔmetamethodsÕ, is modesty for FF intact (Fischer et al. 1997). In other words, the tail shock selectively modulates the ability of the synapses and undergo short-term use-dependent plasticity, i.e. it induces metaplasticity. Similarly, in the behaving animal, (Hesiod 8Cbc); the practical muses of experimental tail shock suppresses the inhibitory modulation of the siphon withdrawal reflex after tactile stimulation of the tail. This phenomenon was termed Ômodulatory metamethods are observational intervention and simulation.

plasticityÕ, because its induction does not require activity, these one should add complementary analytical

of the synapse whose plasticity is being regulated, as tail methods, mostly comparison and correlation. The data

shock itself does not activate L30.). that all these methods generate are further analysed and

A valuable take-home message from the metaplasticity studies relates to the importance of the history of thesesexperimental *subject or preparation and to the influence which temporarily govern mainstream knowledge in a of this history on the outcome of the experiment. The given domain of science. If influential, these hypothesestudies of metaplasticity reminds us that individual subjects or preparations, even if *controlled for age, gender, *nutrition, or *context at the time of experiment, etc., could still differ not only in terms of their particular past or an entire scientific discipline may start at any point experience on a specific activity or item of information, along this never-ending methodological ritual. The but also in their activity dependent *capacity to undergo plastic changes at any particular moment in time.

the point of view of the history and the philosophy of science, but it does encapsulate the essence Selected associations: Development, Homeostasis, Long-term potentiation, Plasticity

The reality of scientific practice and *culture. The ÔmetamethodsÕ are shared by different scientific

Method

disciplines. In addition, distinct disciplines have their experimental approach, phenomena/processes, or own sets of domain-specific methods, which transform mechanisms are imitated or simulated by discrete the general methods into specific procedures and experimental manipulation *in situ*. Examples include techniques.

substitution of a *percept by electrical activity in the

So let's encounter the metamethods, one by onbrain (Loucas 1936; Ronal et al 2000); of a conditioned First come the core experimental methods. stimulus (*classical conditioning) by *long-term

1. Observation. This is the most fundamental of all potentiation (LTP; Skelton et al 1985); of other types of the experimental methods, clearly preceding modern learned input by identified molecular agents (Acosta-science. "Observation" sometimes connotes nddridi et al 1984; Kabat et al 1994); and of "consolidation" controlled as opposed to controlled experimental tion by the activation of *CREB (Yi et al 1995). Some situations (e.g. Freedman et al 1998). This is not the of these manipulations could also be considered "inter-intention here. Careful observation in the course of vention (see 2 above), but their aim is specifically to controlled experiments could yield highly valuable and imitate or simulate candidate biological processes and sometimes ground-breaking discoveries. Unfortunately, mechanisms of learning in order to prove their postulated the good old practice of observation, which requires ample patience, openness, and experience, tends now to be neglected by too many hyper-active investigators aiming at imitating as well as testing the natural phe-tors in their rush for tenure ("scoopophobia). Heuristic nomenon or parts of it (*algorithm, *model). In the classifications, longer-lived *taxonomies, and signalnear future we should expect to see more and more hypotheses may emanate from smart observations attempts to mimic or simulate living organisms, includ-(Hodgkin et al 1977; for a notable example, see Darwin ing their learning and memory capabilities, by elec-1871). However, to contribute usefully to a scientific dis-tronic devices, creating Galileo's addition to "vivo" cipline, observations must usually be followed by the "systems (Normile 1999; "enigma). Simulation experi-additional methods of intervention and simulation, to ments could also involve "thought experiments" test hypotheses and generate *models. (On a special type of Gedanken experiments, see controlled speculative type of "Observation", "introspection", which occupies days, in which the entire "experimental" manipulation prominent position in the methodology of the early days of memory research, see "behaviourism.) rather than on the bench or in the field (Sorensen

2. Intervention. This is a very popular type of research (1992). However, fruitful thought experiments may method. It is adored in *reductive research pro- require a more robust theoretical infrastructure than grammes. The aim of interventional methods is to infer currently available in the neuroscience of memory. function from dysfunction or hyperfunction. It is hence All the above experimental methods are comple-the *classical generic type of scientific experiment that mented and augmented by several analytical methods involves active interference with nature to see what will happen. In the brain sciences, the agents used include comparison and correlation (additional ones, related to interference in perception or in behavioural *perform- hypothesizing exceed the scope of this brief pragmatic ance; perturbation of metabolic cascades (e.g. *intra-discussion). cellular signal transduction cascades), using drugs or 4. Comparison of sets of observations of the same mutations; perturbation of the electrical activity of variable under different conditions (e.g. memory as a neurons and neuronal circuits; and anatomical lesions function of *synaptic activity, drug treatment, age, *con-Concrete examples are to be found in many entries in this book; e.g. *amnesia, *consolidation, *neurogenetic mechanisms in the system. This requires selection of ics, to cite merely a few. For selected methodological issues related to the use and misuse of interventionalental design (including controls), and statistics studies, see Bechtel 1982, Glassman 1978. (e.g. Martin and Bateson 1993; Freedman et al 1998;

3. Simulation. This type of methods attempts to Kerlinger and Lee 2000). Quantification, which is imitate or simulate natural phenomena, processes, essential for scientific comparisons but also for other or candidate mechanisms. This is done in order to methods, deserves a special comment. The introduction verify assumptions concerning structure and func- of quantifiable variables is usually taken to mark the tion, test models, predict performance, and generate transformation of a field of interest into a scientific new hypotheses. Simulation experiments come in discipline. Sometimes the ingenuity of the forefathers of two flavours, experimental and theoretical. In the a scientific discipline is not in identifying the important

questions, but rather in identifying or devising the variables that could be quantified and used in order to address these questions. For example, Ebbinghaus made it possible to first quantify the capacity and the stability of human memory by introducing retention of nonsense syllables as a measured quantity (see also Jacobs 1887; for the first quantitative measures of animal memory, see in Boakes 1984; Gorfein and Hoffman 1987).

(1885) made it possible to first quantify reproducibly the *capacity and the stability of human memory by introducing retention of nonsense syllables as a measured quantity (see also Jacobs 1887; for the first quantitative measures of animal memory, see in Boakes 1984; Gorfein and Hoffman 1987). Selected associations: Control, Criterion, Reduction, Simple system

Ebbinghaus' method was very efficient and influential, but not without opponents. For a revolt against the use of nonsense materials to test the faculties of human learning and memory, see Bartlett (1934).

5. Correlation Here a natural or manipulated phenomenon is correlated, in time or space, with other phenomena in the same or another *level of analysis, in order to identify links among phenomena. In an important subtype of correlative experiments, and as part of reductive memory research programmes, behavioural phenomena are correlated with neuronal plasticity. Selected examples are correlation of *fear conditioning with *amygdala LTP (Rogers et al 1997), or correlation of learning with neurogenesis in the hippocampus (Gould et al 1999). In such cases, the aim is to pinpoint cross-level mechanistic inter dependency.

On the general problematics of the attempt to conclude causality from correlations, see Irzik (1996; also thefor the sake of the notorious spy organization Ô39 StepsÕ pitfalls of post-hoc argumentation in *criteria).

Hitchcock's master of facts, earned his living by performing feats of trivia pursuit in nightclubs, while in parallel trusting to memory information

(Hitchcock 1935). Most mnemonists, both in fiction

It is easy to notice the affinity of the above Ômetamethod in real life, are engaged in much more innocent acts than the *criteria used to assess the contribution of activities.

In modern times mnemonists are either experimental data to the resolution of a given research regarded as curiosities or at most as interesting *subjects

problem. Observations correlate phenomena, identify for research. But only a few centuries ago, mnemonists similarity, and hint at necessity; interventions identify were still masters of an important and respectable art.

necessity; and simulations yield information on similarity, usefulness, sufficiency, and even exclusiveness.

Mnemeis ÔmemoryÕ in Greek (Mnemosyne was the mother of the muses; Hesiod 80). Before writing

general, whereas the methods provide us with the became widespread (and surely before recording knowledge, the criteria tell us about the relevance of devices became inexpensive), the ability to trust data to this knowledge to the question posed.

Mnemonics

memory was highly valuable, and mnemotechniques

The field of memory research is equipped with its own special repertoire of methods. These are exemplified in *classical conditioning, *cue revaluation, *delay most practical purposes. This was clearly appreciated task, *fear conditioning, *habituation, *instrumental by philosophers and teachers. Socrates tells us that conditioning, *LTP, *maze, *priming, *real-life memory, *sensitization, *transfer, and *working memory. when the God Theuth praised the newly invented art of writing, claiming that it will make people wiser, the But brain research in general is in a special situation. If Egyptian King Thamus responded: ÔO man full of arts, is a truly multidisciplinary enterprise. The more it advances, the more it is quick to incorporate knowledge another to judge what measure of harm and of profit and methods from a great variety of other disciplines. they have for those that shall employ them.É If men These range from molecular, cellular, and *develop-learn this, it will implant forgetfulness in their souls; mental biology, via physiology and anatomy, clinical neurology and *neuroimaging, psychology, and ethology, to computational science and information theory

King Thamus panicked prematurely. In practice, for a (Dudai 1989; Martin and Bateson 1993; Baddeley 1997) very long period after its introduction, writing was used mostly for administrative purposes, and most of the

Manning and Dawkins 1998; Zigmundal 1999; Kan-del et al 2000). Not surprisingly, a recent textbook in the neurosciences is authored by no less than 150 anyway. Thousands of years after Socrates, in medieval

Mnemonics

Europe, it was still common practice to regard written documents with suspicion because texts could not be ÔÉon his travels, he does not cease to make new places challenged to defend their statements whereas people some monastery or church, remembering through could (*false memory was clearly not on the mind of them histories, or fables, or Lenten sermons. É He can people as it is now). In societies all around the globe repeat from memory the whole of the canon law, text epics and ballads continued to rely for many genera-and gloss É two hundred speeches or sayings of Cicero; tions on oral traditions. Even after the invention of three hundred sayings of the philosophers; twenty printing, printed bibles and books of prayers were con-thousands legal points ÉÔ (Yates 1966). Superb mem-considered primarily as aids to memorization by heart ory and mnemotechniques were considered highly use-(Clanchy 1979; Ong 1982; Rubin 1995). Mnemonics, ful in church and government, and therefore, in *classic therefore, was not abandoned for a long time. On the contrary, great intellects devoted their energy to the curriculum of language arts, side by side with grammar, development and improvement of Ôartificial memory logic, and rhetoric. It was told of Thomas Aquinas, the systemsÔ composed of mnemonic techniques and procehoolastic philosopher and theologian of the thirteenth dures (Yates 1966; Carruthers 1990).

century, that he was able to dictate simultaneously to

In a popular type of artificial memory systems, four secretaries on four different subjects, and even go images of physical items or loci (e.g. rooms in palaces) dictating while asleep; in that he excelled Julius Ômemory theatersÔ; Figure 48), were associated in meaesar, who, fourteen centuries earlier, was said to be ory with specific items or meanings, and later used as aapable of dictating to four people while writing a fifth code to *retrieve them. Some expert mnemonists letter in his own hand, but no mention was made of his became legends in exploiting these techniques. Foaibility to keep on dictating from memory after falling example, Peter of Ravenna (fifteenth century) was said to sleep (Carruthers 1990).

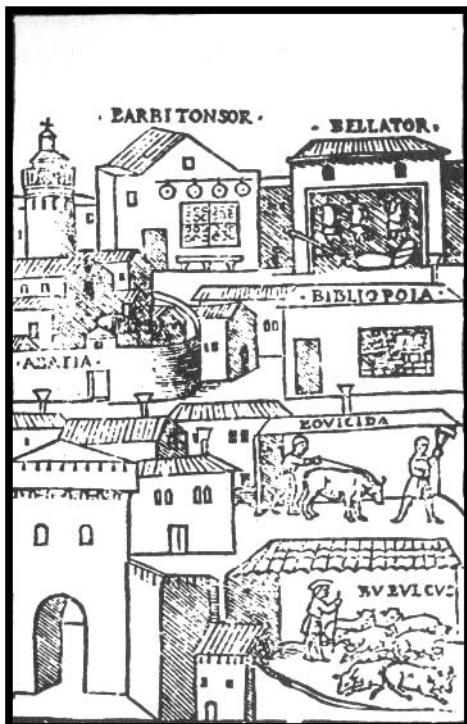


Fig. 48 A popular type of mental Ôartificial memory systemsÔ was based on the allocation of items in memory to spatial maps of In this one, items are associated with buildings, rooms, and items in an abbey. (Johannes Bumbantificiose merterice 1533; reprinted in Yates 1966.)

Whether Aquinas was indeed capable of dictating memory, so good? The elementary *capacity of something legible from sleep is questionable; he could memory probably remains the same, but the use of have appeared as if in sleep at a state of extreme ~~conceit~~^{metamemory}, the chunking of information, the tration. This is at least an explanation that would be retrieval from long-term stores, and the switching from favoured nowadays by those scientists who doze off ~~is~~^{short-term} to long-term stores and back, could research seminars and then wake up to the applause ~~to~~^{improve} tremendously (Chase and Simon 1973; Hirst ask a question. Naturally, information about past mem- 1988; Pesenti et al 2001; *working memory). An ory feats and mnemonists is mostly anecdotal. How improvement in chunking and retrieval rather than in ever, we do have data on more recent cases (Strattorcapacity was also detected in controlled laboratory 1917; Luria 1969; Hunter 1977, 1978; Thompson experiments, in which subjects succeeded in improving 1993; Brown and Deffenbacher 1995). From this infor- 10-fold their performance on digit span tests (Chase mation, based on only a small number of mnemonists, and Ericsson 1982).

one could draw a conclusion that there are different All this suggests that practice, combined with mnemonic strategies. Compare, for example, the sonal mnemonic strategies for chunking, tagging, and patient Shereshevskii of Luria (1969), and Professor association, could improve an average memory Aitken, a mathematician, mental calculator, and (Loisette 1899; Rawles 1978; Hirst 1988; Herzog 1992). mnemonist (Hunter 1977). Whereas Shereshevskii^Öere are some hints. *Spaced training could be useful. mnemonics was of the classical type (see above), usint^{Test-type} rehearsals instead of straightforward repeti- imagery and forming a rich perceptual chain to link and tions could be useful as well, for example, in assigning retrieve information, Aitken formed a rich conceptual names to faces and thus preventing social embarrass- map to encode and retain his memory (*ibid*). Another ment in parties (Landauer 1988). In the future, memory conclusion is that some exceptional mnemonists enhancing chemicals (*nootropics) and bionic gadgets display pathological traits, even to the degree of becoming available as well, but this is not really ing Öidiot savants^Öhereas others are apparently nor- bona fide mnemonics any more.

mal. For example, Shereshevskii led a rather miserable Do we really wish to expand our memory, and if life and couldnt adjust to any profession (Luria 1969)so, to what extent? A modest memory improvement is Aitken was a professor of mathematics and it is left fortlikely to be beneficial. But remembering too much the reader to judge whether this is entirely normal. And could mean a decline in the ability to *generalize and Rajan Srinivasan Mahadevan, who in 1981 recited fronto focus on important data. This is another manifesta- memory the first 31 811 digits of and entered the tion of the general maxim of *performance, which Guinness Book of World Records, was described as states that moderation is the key to success. The sad Ödecently normalÖ Öaverage to above-average student^Ö of Shereshevskii, who was overwhelmed by details cognitive psychology (Thompson et 1993). It would and could not generalize, hints at the potential disad- be of great interest to find out which brain systems sub-vantage of remembering much too much (Luria 1969; serve the performance of mnemonic feats like these oDudai 1997a).

Shereshevskii, Aitken or Mahadevan. Do they use the Selected associations: Capacity, Metamemory, Nootrop- same brain systems as do individuals with an average ics, Performance, Real-life memory memory on the same task? *Functional neuroimaging of mnemonists could provide the answer (Pesenti _____ et al 2001).

Can ordinary individuals with an average memory become memory experts? It is useful to remember that practice and the perfection of *skill are bound to improve the skill-related aspects of memory. Experts do usually have a markedly larger task-related memory than novices in their field of expertise. Take chess as an extreme example. Master chess players clearly outperform novices or middle-range players, and some chess experts can remember as many chess positions as the above mentioned number of loci in the memory of the legendary Peter of Ravenna (Chase and Simon 1973). What is it that turns the expertÖs memory, or the use of

¹Borges, in the marvellous story about Ireneo Funes who lost

ability to forget after being thrown off a horse (1944), endowed that fictitious hero with a mnemonic system in between that of Aitken a that of Shereshevskii: a mental idiosyncratic vocabulary of all mental images ever encoded in the brain.

²Idiot savant (French for Ölearned idiotÖ) is a mentally impaired individual who exhibits genius in a highly specialized area, such as calculation or painting (Treffert 2000).

Model

1. An abstract or concrete *system that represents another, usually more complex or less familiar system.
2. A schematic representation that accounts for properties of a system, often used to infer additional properties and to predict the outcome of manipulations.

All models (*nodus*, Latin for ‘a measure’; ‘standard of measurement’) are analogies (things similar but not identical, Greek for ‘proportionate’). Some are only *metaphors, others sets of quantitative relations among components of the modelled system, and yet others somewhere in between. In the context of the present discussion, it is useful to distinguish among (a) mathematical models, (b) diagrammatic models, and (c) the use of the term ‘model’ to describe a *simple system that could potentially illuminate phenomena of interest in what is considered a more complex system. Although different in type and complexity, all models share some elementary methodological aims, pros and cons.

Basically, models are heuristics devised to explain and predict (Lakatos 1978; *paradigm). A profound question is whether we can do without them, i.e. are they only mental aids, or an inherent necessity for human understanding of nature (Duhem 1914; Hesse 1963). Some will argue that even what seems to us the most accurate depiction of a natural phenomenon is still a schematic model distilled through human cognition (*internal representation). Another issue is when does a detailed representation loses its modelness, hence usefulness as a simplifying and explanatory agent. Borges (1964) has something to say about it:

‘In that Empire, the Art of Cartography reached such Perfection that the map of one Province alone took up the whole of a city, and the map of the empire, the whole of a Province. In time, those Unconscionable Maps did not satisfy and the Colleges of Cartographers set up a Map of the Empire which had the size of the Empire itself and coincided with it point by point. Less Addicted to the Study of Cartography, Succeeding Generations understood that this Widespread Map was Useless and not without Impiety they abandoned it to the Inclemencies of the Sun and the Winters. In the Deserts of the West some mangled Ruins of the Map lasted on, inhabited by Animals and Beggars; in the whole Country there are no other relics of the Disciplines of Geography.’

It is not uncommon to find great minds captivated by their pet model to such an extent that they lose sight of the initial question and reach a stage where the model must be modelled to simplify it. This, of course, is still an utterly legitimate and potentially rewarding intellectual pursuit, only that its relevance to the original research objective deserves scrutiny.

1. Mathematical models. These usually combine an attempt to *reduce biology into the exact sciences with the quest for a powerful descriptive and predictive language. In disciplines such as physics, models could refer to a theory (Nagel 1979). As there aren’t yet real comprehensive formal theories with theory-derived laws in the neurosciences, even the most ‘formal’ models of learning and memory are not formal in the full sense of the term, but rather an hypothesis or experimental *generalization expressed in mathematical notations. In the field of memory research, there are influential formal models at different *levels of analysis.

An example at the level of *synaptic *plasticity is provided by models that employ the Hebb type of algorithm (Hebb 1949), which assumes that the alteration in synaptic weight is a function of the correlation of pre- and postsynaptic activity. An example at the level of behavioural learning is provided by models that employ the Recorla-Wagner algorithm (Recorla and Wagner 1972), which proposes that in associative learning, the change in the associative strength of a stimulus with a *reinforcer, depends upon the concurrent associative strength of all present stimuli with that reinforcer. Many other examples exist of semiquantitative models at the system and behavioural level (e.g. Raaijmakers and Shiffrin 1992).

A particularly important class of mathematical models is that of artificial neural networks (ANN; McCulloch and Pitts 1943; Amit 1989; Fausett 1994; Mehrotra et al 1997). These models deal with the collective behaviour of systems that consist of a large number of interconnected computational units (‘neurons’). Signals are passed between units over connections, which manipulate the signal in a typical way. Each unit applies an activation function to its net input to determine the output signal. Networks are characterized by the architecture of connectivity, the algorithm that determines the weight on the connections, and the activation function of the units. The collective behaviours of such networks appears to mimic various dynamic properties of neuronal circuits, such as representation of *percepts, learning and *retrieval. Certain types of ANN are implemented in technological systems that need to perceive, recognize, and learn from experience.

2. Diagrammatic models. These are rather common, often intended as a didactic tool or as a rudimentary

functional explanation in familiar terms. Such models run the danger of being perceived as the real world as models rather than an analytic tool. Textbooks and papers proclaim systems. A most popular example is *long-term vide many examples of such models: block and flow-potentiation (Bliss and Collingridge 1993). Such model chart diagrams of *intracellular signal transduction systems unravel processes and mechanisms that might cascades (Figure 39, p. 136), graphs of *phases serve as candidate components of the real thing, e.g. of *acquisition, *consolidation, and *retrieval of learned synaptic plasticity in the behaving brain under physio-information, or *maps of interconnecting brain circuits logical conditions. A common problem in this type of (e.g. *limbic system). Models of this kind commonly echo the contemporary technological *zeitgeist, bor-in the *homunculus fallacy: trusting that the *reduced rowing, for example, from electrical engineering and model system should display properties of the complex computer science (*metaphor).

system that it is supposed to model. Parts of a whole are

3. Simple systems as models. Here ÔmodelÕ is usually not expected to display the properties of the whole, and figure of speech more than a real model. The justification if they do, one should suspect the simplification has

tion of the usage of the term is sometimes questionable gone too far. and the outcome of this usage potentially problematic. Despite all the caveats, models of all the three There are two major types of so-called Ôsimple models'. The aforementioned types are indispensable both as con- One is organisms or naturally occurring biological phe- ceptual and as practical tools. They unveil phenomena, nomena that are used to cast light on properties of processes, and mechanisms that could later be pursued other organisms or phenomena. Examples include then the more complex and less tangible system. The trick use of animal systems in studying human cognition and is probably in always remembering to distinguish disease (e.g. *dementia), the use of one species as between the role of a system as a model and what it ÔmodelÕ for learning and memory in remote species, really is, and in having the courage to abandon the of a simple type of learning as a ÔmodelÕ for other, more model, in spite of the great investment and affection, complex types of learning (for selected examples, see when its use invokes too many discrepancies with the Thompson and Spencer 1966; Clause 1993; Seppl's original research goal.

1994; DÔMello and Steckler 1996; Eichenbaum 1997a;

Eisenstein 1997; Gallagher and Rapp 1997; Mihalek 1998; Robbins 1998; als Aplysia *Drosophila*mon-

key, *mouse, *rat). It should not be forgotten that

Ôsimple organismsÕ did not evolve to serve as models

Selected associations: Metaphor, Map, Paradigm, Simple system, System

for other organisms. Although one does expect some

similarity to increase in an inverse proportion to the

phylogenetic distance, rats and mice are not models for

humans; they are rats and mice. If forgotten, this trivial

truth may lead to erroneous conclusions on the proper-

ties of human brain, behaviour, and pathology, and

promote fishing expeditions for *red herrings.

[For the history and usage of this term, see Donoghue (1992).

Monkey

Any of various members of the order Primates,

Another caveat concerning the use of simple excluding the anthropoid apes and humans.

organisms as models involves the distinction between

homology and analogy. Homology (Greek for Ôsamê') This is what I see in my dreams about final exams: /Two reasonÔ, Ôin agreementÔ) refers to having the same phylogenetic origin but not necessarily theThe sky behind them flutters,/The sea is taking its same form or function. Analogy refers to having the bath./The exam is History of Mankind./I stammer and same form or function but not the same phylogenetic hedge./One monkey stares and listens with mocking or ontogenetic origin. Whether one should expect to disdain,/the other seems to be dreaming away/But unveil homologies or analogies depends on the specieswhen itÔs clear I donÔt know what to say/He prompts me used as a model, the physiology and behaviourwith a gentle/Clinking of his chainÔ (Szymborska 1995). modelled, and the level of analysis. For example, using it is the appreciation that monkeys are our closest invertebrate learning to model mammalian learning phylogenetic relatives and share some of our intimate may unveil homology at the molecular and cellular biological secrets, that fuels SzymborskaÔs irony. Among level but only analogy at best at the circuit and all the species around us, the monkeyÔs brain resembles behavioural level.

ours the most. It is there that we often go in search for

the rudiments of our higher cognitive faculties (*a priori, *declarative memory). ÔPlatoÕ, remarked Darwin (1838a), ÔÉ says in ÔPhaedoÕ that our Ônecessary ideasÕ arise from the preexistence of the soul, are not derivable from experienceÑread monkeys for preexistenceÓ. And he also noted, musing relativity in the universe: ÔIf all men were dead then monkeys make men.ÑMen makes anglesÓ (Darwin 1838)

Monkeys belong to the order Primates, which has two major suborders (Bennett et al 1995): The Prosimii (ÔpreÕ or ÔearlyÕ monkeys) and the Anthropoidea (Ôhuman-likeÕ). In general, prosimians have a long, wet nose, slightly sideways eyes, prominent muzzle and brow whiskers, and large mobile ears. Many of them are nocturnal species that rely on smell and hearing. Anthropoids have flatter faces, a dry short nose, no2 prominent whiskers, forward-facing eyes, and they rely mostly on vision. The prosimians and the anthropoids each are further classified into suborders: The prosimians into the Lemuriforms and the Lorisiformes, and the anthropoids into the Platyrhini (Ôbroad noseÕ, New World Monkeys) and the Catarrhini (Ôhooked noseÕ, Old World monkeys, apes and humans). The term ÔmonkeyÕ is conventionally reserved to denote only the long-tailed, medium-sized primates, always excluding the anthropoids apes and humans, and frequently excluding also the prosimians. This classification also fits the term Ônonhominoïd primatesÕ. The monkey species most commonly used in medical and biological research are the macaques, which are Old World monkeys. They include the rhesus Macaca mulatta (Bourne 1975), the Japanese macaque Macaca fuscata, and the cynomolgus monkey Macaca fascicularis. But other species are used as well.

Monkeys became occasional pets since times unknown. Their resemblance to humans also led to their use in early anatomical investigations (Morris and Morris 1966). They were among the first species to be systematically used in the early days of brain research and experimental psychology. Generally speaking, monkeys are employed in neurobiology for four main purposes:

1. As *models for human brain pathology. The contribution of the monkey to our understanding of the consequences of brain damage cannot be underestimated. The effect of circumscribed brain lesions on monkeyÕs physiology and behaviour was systematically studied already more than a century ago (Brown and Schafer 1888). These studies have led to the discovery that the temporal lobe (Kluver and Bucy 1938) and frontal lobe (Jacobsen and Nissen 1937; Pribram et al 1952; Fuster 2000) play a key

part in higher brain function, learning, memory, and cognition (*cortex, *limbic system, *working memory). In recent decades, extensive efforts have been devoted to the development of monkey models of human *amnesia. This has led to remarkable sophistication in lesion techniques on the one hand and behavioural testing on the other (e.g. Mishkin 1982; Zola-Morgan and Squire 1985; *delay tasks). Attempts to resolve the debate over the role of hippocampus, *amygdala, and various adjacent cortical areas in memory are still largely based on lesions in monkeys (e.g. Suzuki et al 1993). Even the fast developments in the functional neuroimaging of human brain do not yet provide a satisfactory alternative.

As systems for the investigation of the role of discrete brain areas and circuits in normal physiology and behaviour, of the alteration of these roles with development and experience, and, ultimately, of the nature of neural codes and *internal representations. Such research programmes rely on a variety of neuronal activity recording methods, including the use of single and multiple invasive electrodes as well as invasive or noninvasive functional neuroimaging, combined with behavioural protocols on the one hand and with modelling on the other (e.g. Miller and Desimone 1994; Vaadia 1995; Bitter et al 1996; Goldman-Rakic 1996; Georgopoulos 1996; Malonek and Grinvald 1996; Nudo et al 1996; Tanaka 1997; Logothetis et al 1999).

3. As systems for exploring the capability and applicability of top-notch research and clinical methods, before they can be safely applied to humans (e.g. Logothetis et al 1999).
4. Monkeys as well as hominoid primates are used to unveil the evolution of human cognitive abilities, including social interactions, self-recognition, tool usage, communication and language, and even rudimentary math (Anderson 1990; Greenfield and Savage-Rumbaugh 1993; Swartz 1997; Brannon and Terrace 1998; Kawai and Matsuzawa 2000; Ramus et al 2000; on the criticism of the studies of human language in the apes, see Pinker 1994; *anthropomorphism).

Although monkeys are indispensable for multiple facets of brain research, they are not the easiest species to use. They require special handling, infrastructure, attitude, and quality time. They learn at a very slow rate some tasks that look so simple to humans; it may take many months to a year to teach a monkey to master certain *instrumental tasks. This

may attest to the remoteness of the experimental protocols from *real life. The frustrated investigator should also ask himself or herself how long would it take for a naive, perplexed human *subject to acquire such tasks in the complete absence of verbal instructions. On top of it all, monkeys are prone to evoke human-like emotions, which may give rise under certain conditions to hesitations and scruples on the side of some human experimenters. Monkeys are also quick to draw the aggression of the so-called 'animal-rights' group. Whoever subjects animals to invasive manipulations should always keep in mind ample respect for the well-being of the other species; in the case of the monkey, this is even more so warranted.

Selected associations: Amnesia, Anthropomorphism, Declarative memory, Model, Subject

Mouse

A small mammal of the genus *Mus*, family *Muridae*, order *Rodentia* (rodents).

The common mouse (*Mus musculus* L.) is a pest for householders, a pet for animal lovers, a blessing for molecular biologists, and a hero for some psychologists. It even shared an Oscar: Cliff Robertson won his 1968 Best-Actor award for beating Algernon, a cute albino mouse, in racing in a *maze (Nelson *et al.* 1968). It is not clear, though, whether Algernon made it to the ceremony. Mice have accompanied human populations since prehistoric times. Similar to rats, they originated in Asia, and from there spread to the rest of the world. They were occasionally used for amusement in both East and West, and a mutant, the 'waltzing' mouse (see below), had been bred in China and Japan specifically for this purpose. Throughout the Middle Ages, mice were used in magic and folk medicine (Thorndike 1923). The first documented use in scientific investigation was by Robert Hook, who in 1663/64 experimented on the survival of the mouse in compressed air, hoping to gain some insight about the ability of man to breathe under water (Nichols 1994). But mice only found their way into the routines of laboratory life during the nineteenth century, when they were started to be employed in large numbers in the study of genetics. Many laboratory strains used today can be traced almost a century back to a few commercial colonies in the USA (Green *et al.* 1966; Hogan *et al.* 1994). DNA analysis shows that several of these strains originated

from a single female of the subspecies *Mus musculus domesticus*, the common house mouse. But as genetic material from other subspecies has been introduced over time into the genetic pool of the laboratory mouse, standard inbred strains are referred to as *M. musculus* only. The genetic making of the mouse can now be easily manipulated (see below), and new strains are produced on demand (mice were also already cloned from somatic cells; Wakayama *et al.* 1998).

The mouse has a lot to offer to biologists and psychologists alike. It is a small mammal (20–35 g), but not small enough to make the life of anatomists and physiologists miserable. The size of the brain is manageable. The generation time is 3–4 months, and the litter size six to eight in inbred lines. Handling is easy and the food inexpensive. Only the smell of the mouse colony is a potential obstacle. The mouse is an agile, social animal (Williams and Scott 1953). It has a rich behavioural repertoire, and is quick to learn, especially in natural situations that involve the chemical senses, spatial information, and social interactions. Perhaps the *classic example of mouse behavioural analysis is that of the dancing (waltzing) mouse by Yerkes (1907). Even Pavlov, whose favourite experimental *subject was the dog (*classical conditioning), switched to the mouse to study the inheritance of conditioned reflexes (Razran 1958). Since those early days, mice have been used extensively in the study of learning and memory (for a useful selection of paradigms, see Crawley and Paylor 1997). During a certain period, though, they seemed to have lost their priority in animal psychology laboratories to the *rat, which is larger and under certain situations less erratic in its behaviour. The undeclared battle was re-won only recently, with the resurrection of the mouse as the king of the *maze, due to the developments in molecular genetics.

Mice clearly beat rats in the field of genetics. For a mammal, the mouse is an impressive genetic machine. Sophisticated *methods have been developed in recent years for the application of reverse genetics to the mouse, i.e. targeting mutations to identified genes or altering gene dosage (*neurogenetics). These techniques are advancing at a very rapid pace, and the literature is almost overwhelmed with the description and analysis of mutant mice and their *development, physiology, pathology, and behaviour (Blake *et al.* 1997; Keverne 1997; Silva *et al.* 1997a; Nelson and Young 1998; Tang *et al.* 1999; Price *et al.* 2000; also the Mouse Genome sites on the Web). Furthermore, novel techniques now permit the generation of tissue-, cell type- and temporally restricted gene knockouts (for the particular application to memory research, see Tsien *et al.* 1996a,b;

Mouse

Wilson and Tonegawa 1997; Shimizu *et al.* 2000; also *dementia, *hippocampus, *LTP). These techniques offer considerable advantages to the study of learning and memory, because they could be used to dissociate the effect of a mutation on development from those on behavioural plasticity, and, furthermore, localize the defect to specific brain regions and circuits.

The impressive pace of mouse neurogenetics, and the unavoidable (yet frequently justified) hype, turn it pertinent to pin-point several caveats. First, the novelty and smartness of a research method should not be confused with its usefulness. For example, in certain experiments that aim at establishing the specific role of an identified brain region in a narrow temporal *phase of memory *acquisition, *consolidation, or *retrieval, targeted microinfusion of a selective short-lived drug could be as useful as a knockout. It is also cheaper. Second, almost trivial but sometimes forgotten, careful attention must be devoted to the genetic background of mutant mice, because only if the same background is used, can the difference between the phenotype of the wild type and that of the mutant be ascribed to the mutation rather than the background (Silva *et al.* 1997b). This is particularly important in the study of behaviour, which, as a rule, is a polygenic trait, hence highly sensitive to modifier genes. Third, those who switch from rats to mice because of the genetic advantages of the latter, should be reminded that mice are not tiny rats. They have their own species-specific physiology and behaviour, and the interpretation of their *performance in learning and memory tasks depends on understanding what is it that the mouse really *perceives and does (e.g. Wolfer *et al.* 1998). And fourth, behavioural paradigms are not a pH indicator paper. You don't insert a mouse and get a reading. Before deciding on the basis of behavioural tests that a mutant, lesion, or drug has a specific effect on memory, one must carefully evaluate and exclude multiple genetic, developmental, environmental, as well as physiological and behavioural parameters that are not directly relevant to memory. This is not easy (e.g. Deutsch 1993; Gingrich and Hen 2000).

Selected associations: Dementia, Maze, Model, Neurogenetics, Subject

Already in its infancy, psychobiology became fascinated by the role of heredity in behaviour. Foci of interest ranged from the inheritance of blushing (Darwin 1872) to that of exceptional talent (Galton 1869).¹ At first the approach was only observational (*method), and mostly anecdotal. But hardly half a century later, leading investigators were already engaged in the systematic selection of 'bright' vs. 'dull' strains in the rodent-in-a-*maze *paradigm (Tolman 1924). This approach was usually 'top-down', from the population and the behaviour to the individual and its genetics; the study of specific mutants, and the analysis of the effect of the mutation on the physical structure of the nervous system was still a rarity (Yerkes 1907). The newly formed discipline of behavioural genetics combined methods from ethology, experimental psychology, and quantitative genetics (Falconer 1960; Hirsch 1963). Only little was known at that time about the physical nature and structure of the genetic material and about the mechanisms by which the genetic information is transformed into physiological processes.

The revolution that has converted neurogenetics into the success story it is today, took place only after the overall strategy has been changed to 'bottom-up', i.e. searching for the role of identified single genes in physiology and behaviour (Benzer 1967). Single-gene analysis of learning and memory started in the fruit fly, *Drosophila (Dudai *et al.* 1976; Dudai 1988; Tully 1996; Dubnau and Tully 1998). Over the years, learning mutants of *Drosophila* have contributed significantly to our current knowledge about the molecular mechanisms of *acquisition and *consolidation of simple memory (*CREB, *intracellular signal transduction cascade). Yet *Drosophila*, in spite of offering unique advantages to the geneticist, is not the dream machine of the neurophysiologist. With time it became indeed possible to identify the effect of specific mutations in identified brain regions and even single neurons that subserve learning (Corfas and Dudai 1990; Waddell *et al.* 2000; Zars *et al.* 2000; Dubnau *et al.* 2001), but central neurons in the fruit fly do not yet succumb to the electrode in the same way that central mammalian neurons do. Furthermore, being an invertebrate, *Drosophila* is incapable of providing clues to the operation of the mammalian brain at the circuit and *system *level. Neither does it disclose anything about issues such as emotional memory (*amygdala, *fear conditioning) or *declarative memory.

Enters the *mouse. In the past decade or so several spectacular developments have taken place in the field of mouse genetics, which now make it possible to add engineered genes to the mouse genome or remove other

Neurogenetics

The use of genetics in the investigation of the structure and function of the nervous system.

genes at will, and generate mouse lines that will express the mutation and propagate it in their progeny. Genes can be added or lesioned in other organisms as well, e.g. *Drosophila* or zebrafish, using a variety of methods. The point is, however, that the ability to engineer the mouse genome in an efficient, flexible, and reproducible manner has swept the mammalian brain for the first time to the forefront of neurogenetic analysis. Among mammals, the mouse is still unique in this respect; appropriate neurogenetic techniques are not yet available, for example, in the rat.

In the present context we need to become familiar with two specific terms only, 'transgenic' (TG) and 'knockout' (KO) mice. Without going into the methods in which TGs and KOs are actually generated (Jaenisch 1988; Joyner 1993; Wassarman and DePamphilis 1993; Nagy 1996; Torres and Kuhn 1997), suffice it to say that TG is the generic term for an organism with foreign pieces of DNA incorporated into its genome, and KO for an organism in which a gene is ablated *in situ*. TGs are used to test the effect on physiology and behaviour of extra genes, normal or mutated. KOs are used for the analysis of the loss of normal gene function. 'First generation KOs' affect the expression of the gene throughout the body, during *development and in adulthood. The absence of regional and temporal specificity makes it impossible to conclude that the effect of

the KO on learning and memory is independent of developmental or general anatomical and physiological impairments. In 'second generation KOs', the KO is targeted to a specific region or cell type (Tsien *et al.* 1996a; Wilson and Tonegawa 1997). In 'third generation KOs', the expression of the mutation is also regulated in time in a reversible manner (Mayford *et al.* 1996; Shimizu *et al.* 2000). This permits exploration of the role of the gene in discrete *phases of learning and memory. At the time of writing, the onset or offset time of gene expression in third generation KOs is measured in hours, which is not terrific for the analysis of acquisition, consolidation, or *retrieval of memory, but this is likely to improve.²

The use of transgenic mice has already contributed markedly to our knowledge on the role of identified molecular processes in *plasticity, learning, and memory. To name just a few selected examples, KOs have been used to identify the role of types of a variety of *protein kinases, of subtypes *glutamatergic receptors, and of *CREB and other transcription factors in *long-term potentiation and in a variety of *classical and *instrumental learning situations. They have also proved useful in probing the relations between *long-term potentiation and learning, and the role of *hippocampus in learning and memory (Grant *et al.* 1992; Silva *et al.* 1992; Abeliovich *et al.* 1993;



Fig. 49 A suspected case of reverse genetics. The group that has isolated *dunce*, the first memory mutant in the fruit fly, **Drosophila*, headed by Seymour Benzer, shortly after making their discovery at the California Institute of Technology (Dudai *et al.* 1976). This discovery started the now flourishing discipline of the molecular–genetic analysis of learning and memory.

Neurogenetics

Bourtchuladze *et al.* 1994; Mayford *et al.* 1996; Rotenberg *et al.* 1996; Tsien *et al.* 1996b; Wilson and Tonegawa 1997; Shimizu *et al.* 2000). Interestingly, the overexpression of the glutamatergic *N*-methyl-D-aspartate receptor in the forebrain of a transgenic mouse was shown to enhance the performance of some learning tasks (Tang *et al.* 1999), indicating that genetic engineering could potentially be used not only to investigate memory, but also to improve it. In addition to their use in research of neuronal plasticity and elementary learning mechanisms, transgenic mice are employed to *model the aetiology and mechanisms of Alzheimer's disease (Price *et al.* 2000; *dementia).

There is no doubt that state-of-the-art neurogenetics is extremely useful in elucidating the molecular and cellular machinery of developmental and behavioural plasticity. The sophistication of the current molecular neurogenetic methodologies is really impressive. However, from the point of view of learning research, similarly to other cutting-edge techniques such as *functional neuroimaging, it is only a tool, not the goal. To become really useful, it must be teamed with additional methodologies and levels of analysis, such as cellular and circuit physiology, neuroimaging, and, clearly, fine behavioural analysis.

Another point to remember is the distinction between neurogenetics as a research tool and neurogenetics as a philosophy. There is a big gap between the demonstration that a gene product influences learning, memory, or any other cognitive faculty, and the conclusion that the gene product is deterministic for the behaviour in question (Rose 1995a). The more we learn about the role of development in moulding physiology and behaviour, the more we understand the complexity of the genome, the more we realize how complicated is the behaviour~*f*(genes) equation. The impressive success of the Human Genome project (International Human Genome Sequencing Consortium 2001; Venter *et al.* 2001), provides us with new powerful experimental tools, and with a marvellous potential for further understanding of the brain. But they also call for proper humbleness: we still have to travel a long way to unravel the real contribution of identified genes to learning, memory, and other aspects of cognition in humans (e.g. Flint 1999; Plomin 1999).

Selected associations: Development, Drosophila, Immediate early genes, Intracellular signal transduction cascade, Mouse

pet lovers, circus owners, and other entrepreneurs, who were collecting and breeding useful mutations and strains for commercial purposes or just for fun.

²For comparison, the onset and offset time of conditional, temperature-sensitive mutations in *Drosophila* is only a few minutes (Kitamoto 2001).

Neurotransmitter

1. **A chemical substance that is secreted from the pre*synaptic nerve terminal into the synaptic cleft and acts as a *stimulus on the post-synaptic terminal.**
2. **A chemical substance that is released by a neuron and acts as a stimulus on a cellular target.**

'Neurotransmitter' is a term nowadays in use not only by neuroscientists but also by the lay person citing from the popular science columns. Yet both the concept and the term were nonexistent only a century ago. At that time it was thought that nerve–nerve and nerve–muscle communication is always electrical (*synapse). The first to propose explicitly that a chemical substance, adrenaline, is liberated from the sympathetic nerve terminal to act upon its muscle target, was Elliott (1904). But the story actually starts earlier. The mere idea that a nerve may release a chemical substance for communicating with other cells was proposed by Du Bois-Reymond in 1877 (cited in Dale 1938). The first hints of evidence were provided by an English physician, George Oliver, who spent his leisure time inventing clinical instruments and testing them on his own family members (Dale 1948). One of these instruments was designed to measure the thickness of an artery under the skin. Oliver (how horrible) injected extracts of various animal glands into his young son. Using his new instrument, he observed that an extract of the adrenal gland altered the diameter of the artery. He rushed to tell the story to Professor Schafer in London, who was experimenting on blood pressure in dogs. Together they replicated the experiment, this time without Oliver's son, whose name somehow did not enter the scientific literature (Oliver and Schafer 1894). This has led to the identification of some physiological effects of the extract, which was later to become known as 'adrenaline'. Lewandowsky, Langley, and others subsequently described additional physiological properties

¹Scientists were not, of course, the first to pay attention to the genetics of behaviour. They were preceded by countless animal breeders,

of adrenaline (e.g. Langley 1905). This was the background for Elliot's suggestion that adrenaline relays information from the nerve to the muscle.

Adrenaline was indeed the first substance to be proposed as a transmitter, but the first transmitter substance to be isolated as such from living tissue was *acetylcholine (Loewi 1936; Dale 1954). Synthesized by chemists and extracted from the rye fungus (ergot), acetylcholine was found to be a potent cardiac blocker. The trail of experiments that had culminated in its identification in the nervous system started with an instance of *state-dependent memory. The person beyond the critical experiment, Otto Loewi, was a restless sleeper. One night he awoke suddenly with the idea that if the vagus nerve inhibits the heart by liberating a chemical substance, this substance might diffuse out into a solution left in contact with the heart, and then transferred to inhibit another heart. He scrawled the plan of the experiment on a scrap of paper and went to sleep again. Alas, the next morning he could not decipher his scribbles. He spent the whole day trying to understand what he wrote, but in vain. The next night he awoke again, with vivid recall of the experimental plan. There are two versions on what actually happened later (Cannon 1934; Finger 2000). In the more romantic version, which clearly fits a movie script, Loewi dashed off to his lab in the middle of the night to perform the experiment. In the second, more mundane version, he wrote a detailed account of what he had in mind and went to sleep again. In any case, by the subsequent day the experiment was done. Loewi took two frogs, removed their heart, and placed each in a salt solution. He left the terminal of the vagus nerve on one heart but removed it from the other. He then stimulated the vagus nerve on the first heart, collected aliquots of the bath solution, and transferred it to the chamber containing the second heart. The denervated heart slowed down. This meant that the stimulation of the vagus secreted into the solution a compound that was capable of controlling the heart in the absence of the nerve. After much additional work, the compound, first dubbed *Vagusstoff* ('vagus substance'), was identified as acetylcholine. It is told that since that discovery, Loewi became ardently interested in dreams (Finger 2000). But this is another story.

The *classic view of a neurotransmitter is provided in definition 1 above: a substance released from the presynaptic on to the postsynaptic terminal, triggering there a cascade of events that result in excitation (excitatory neurotransmitter) or inhibition (inhibitory neurotransmitter). This is a point-to-point, or one-to-one, unidirectional communication. With time, the

concept of 'neurotransmission' was expanded. First, it was found that neurotransmitter molecules could act on the same neuron that releases them, usually to modulate transmitter release (reviewed in Powis and Bunn 1995). This is still a one-to-one communication, but the cellular target is also the source of the signal, i.e. the presynaptic rather than the postsynaptic terminal. Second, it was found that neurotransmitters could act by diffusion on distant targets in the absence of direct synaptic contacts. This one-to-many communication is termed 'volume transmission' (Zoli *et al.* 1999). It is especially relevant to the concept of 'neuromodulation' (see below). Third, it was discovered that some compounds that transmit information between neurons, such as the gas nitric oxide (NO, Zhang and Snyder 1995), are not released via specific synaptic sites to bind to membrane receptors, but instead diffuse out of the membrane to adjacent cells to interact with intracellular receptors. This is either one-to-one or one-to-few communication. Further, these compounds convey information from the postsynaptic into the presynaptic terminal, contrary to the conventional wisdom of neurotransmission; they are therefore termed 'retrograde messengers' (e.g. Figure 42b, p. 150). Finally, neurotransmitters act on and are released by glia cells as well, although only little is so far known on this topic (Araque *et al.* 1999).¹ All these modes of transmission are accommodated by the more comprehensive definition 2 above.

We are currently familiar with scores of transmitter substances, and even the simplest nervous system contains a surprising number of them (Brownlee and Fairweather 1999). The classical transmitters are small molecules, such as acetylcholine or *glutamate. About 10 are identified, most of which are amino acids (the building blocks of proteins) or their derivatives (acetylcholine is an exception). To these we should add the neuroactive peptides, which are much more numerous (Cooper *et al.* 1996). Endogenous opioids are only one example. And to these we should add the 'nonconventional' transmitters such as gases and small lipid molecules (Medina and Izquierdo 1995; Zhang and Snyder 1995). At this point in our discussion, two additional points deserve attention. First, how do we decide whether a compound is a neurotransmitter? Several attempts have been made to identify the relevant *criteria (e.g. Werman 1966). These criteria must fit not only the classical view of chemical transmission (definition 1) but also the more modern views (definition 2). The only universal criteria are probably the release from a neuron and the action as a stimulus on a target cell. Of course, the transmitter must be synthesized, and later

Neurotransmitter

degraded or removed from its site of action, but these functions must not necessarily be carried out by the source and the target cell, respectively.

Another point is the distinction between a ‘neurotransmitter’ and a ‘neuromodulator’ (Kaczmarek and Levitan 1987; Harris-Warrick and Marder 1991; Lopez and Brown 1992; Katz and Frost 1996). Conventionally, when this distinction is used, the term ‘neurotransmitter’ is reserved to those stimuli that transmit fast information between one neuron and another in a one-to-one mode (definition 1 above). They exert their effect by directly gating *ion channels ('ionotropic *receptors') in the target neuron. In contrast, ‘neuromodulators’ modify the ability of neurons to respond to neurotransmitters and by other stimuli, commonly by indirectly modulating ionic channel complexes, for example, via ‘metabotropic *receptors’, their downstream *intracellular signal transduction cascades and *protein kinases. Neuromodulators alter the intrinsic properties of neurons, affect their excitability and ability to extract signal from noise, and hence gate, rescale, and bias incoming information. This enriches the computational and representational *capacity of the circuit and, furthermore, encodes at the cellular *level parameters such as *attention, *context, and internal states (e.g. Hasselmo 1995; Shulz *et al.* 2000). However, in the literature, and apparently also in real life, the distinction between neurotransmitters and neuromodulators is not rigorous. For example, is glycine acting on the regulatory site of the *glutamatergic *N*-methyl-D-aspartate receptor, a modulator or transmitter? Or, most authors would consider NO as a transmitter, but it is not limited to a one-to-one communication mode, and does not directly gate channels. It is therefore useful to consider types of transmitter substances as components of a whole spectrum, ranging from fast-acting, *bona fide* transmitters, to slow-acting, diffusing, *bona-fide* modulators.

In the context of memory research, we should note that neurotransmitters and neuromodulators are molecular stimuli that in their concerted activity convey to the target neurons and circuit information about *percepts, activated *internal representations, and endogenous brain states (e.g. Hasselmo 1995; McGaugh and Cahill 1997; Arnsten 1998; Fellous 1999). Therefore they are particularly relevant to the *acquisition and *retrieval phases in the operation of those circuits that encode the relevant representations. The specific combination of neurotransmitters and neuromodulators arriving at the synapse at any given point in time is critical in determining whether the synapse will change as a consequence of the experience,

and if so, for how long (e.g. *coincidence detection, *long-term potentiation). But the role of the transmitters themselves is transient. Even in those cases in which the retention of learned information in a circuit is believed to be based on the modulation of transmitter release (e.g. **Aplysia*), the transmitter molecules do not store information over a prolonged time; the persistent alteration in their availability is a consequence of a lasting changes in other cellular components, such as channels, receptors, or cytoskeletal elements and transmitter-release mechanisms.

Selected associations: Acetylcholine, Acquisition, Glutamate, Receptor, Synapse

¹Glia (Greek for ‘glue’), or neuroglia, is a generic term that refers to multiple types of non-neuronal cells in the nervous system, which fulfil multiple roles in providing a proper microenvironment, and metabolic and functional support for neuronal function. The possibility that glia cells have a computational role in the brain should not be excluded. See also *synapse.

Nootropics

Compounds that enhance cognitive function.

The term ‘nootropics’ (from Greek, *noos*—mind, *tropos*—turn) was originally coined to denote chemical compounds that were reported to enhance cognitive function, including learning and memory, without possessing other significant effects (Giurgea 1973). The best known are piracetam and structurally related compounds (Giurgea 1973; Goulaev and Senning 1994). Over the years, however, the term has acquired a peculiar flavour. Many authors reserve it for compounds that are reputed to boost cognition, but were not rigorously proven to do so. Others use it to refer to compounds that have proven beneficial effects on cognition but whose mechanism of action is yet unknown. There is actually no reason why ‘nootropics’ shouldn’t be used as a generic term to denote compounds that enhance cognition, whether their mechanism of action is known or not. But this is a matter of taste.

The search for a memory potion clearly antedated the introduction of the term ‘nootropics’. It was mostly disappointing. Even the literary imagination did not come up with a simple solution. To learn the fine details of the collective past, the poet in the Divine Comedy, much like Odysseus before him, had to go through Hell

(Dante 1314; *limbic system); and in modern times, Borges' Funes, the ultimate memorizer, was endowed with limitless memory only after knocking his head in an almost fatal horse accident (Borges 1944; *mnemonics). A more realistic and systematic approach to memory enhancement began by the same Lashley who was searching for the *engram. He found that strychnine (a poison that interacts with the *receptor for the *neurotransmitter glycine) accelerates the learning *performance of rats in a maze, albeit only in concentrations that produce tremor and motor incoordination (Lashley 1917). More recent research has provided evidence that other stimulants as well could enhance memory if administered around the time of training (McGaugh 1966; McGaugh *et al.* 1993), but toxicity prevents these drugs from being used as cognitive enhancers.

In the late 1960s, a new compound with a structural resemblance to the inhibitory neurotransmitter -aminobutyric acid (GABA), piracetam (2-pyrrollidoneacetamide), was tested for its effects on motion sickness, and subsequently reported to enhance learning and protect against *amnesic treatments in rats (Giurgea 1973; Gouliaev and Senning 1994). Soon afterwards, additional pyrrollidone derivatives were synthesized and tested, and some reported to improve learning and memory in both rats and humans (Mondadori 1993; Deberdt 1994; Gouliaev and Senning 1994). In parallel, compounds unrelated to the piracetam family were also added to the nootropic list, among them newly synthesized chemicals (e.g. Mondadori *et al.* 1991), and natural preparations with a respectable history in traditional medicines (e.g. ginkgo biloba extracts; Deberdt 1994). The nootropic efficacy of most of these compounds was, however, debated from the outset. Furthermore, no agreement has been reached on their mechanism of action in the brain. Interactions with neurotransmitter and neuromodulatory systems (and see below), *ion channels, membrane fluidity, steroid hormones, and neuronal energy supply, have all been suggested (Olpe and Lynch 1982; Mondadori 1993; Gouliaev and Senning 1994).

Meanwhile, rational design has led to the development and identification of new classes of cognitive boosters (Staubli *et al.* 1994; Ingram *et al.* 1996; Giacobini and McGeer 2000). The first drugs to be approved for alleviating some early symptoms of *dementia act by enhancing transmission via

*acetylcholine (Crimson 1994; Giacobini and McGeer 2000). The identification of the role of the -amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) type of *glutamatergic receptors in *plasticity resulted in the synthesis of ampakines, AMPA agonists that cross the blood-brain barrier, enhance excitatory synaptic response and *LTP, and improve memory in rats (Staubli *et al.* 1994) and humans (Ingvar *et al.* 1997). In the latter, an ampakine was reported to improve performance on several sensory and spatial learning tasks, but not on cued *recall of verbal information and on tasks that measure arousal and *attention only. Interestingly, facilitation of AMPA receptors is one of the effects seen with piracetams (Gouliaev and Senning 1994). *In vivo* this glutamatergic effect is probably limited because of the rapid metabolism of piracetam in peripheral tissues (Staubli *et al.* 1994). Research on agonists of the benzodiazepine binding sites on GABAergic receptors was also considered (Raffalli-Sebille *et al.* 1990; Izquierdo and Medina 1991; *lotus). The anxiogenic effects of these compounds could pose, however, a severe problem.

Drugs that interact with the cholinergic, glutamatergic, and additional neurotransmitter systems are expected to enhance *acquisition and possibly *retrieval of learned information. Other compounds might boost *consolidation. An appealing target for consolidation boosters is the *CREB system. Other transcription factors and *immediate early genes could be targeted as well. At the time of writing, nootropics that act on these targets are still unavailable. To develop them is not an easy task, because one must identify those elements of the transcriptional and translational regulatory systems in neurons that are critical for learning and memory, but not for other essential cellular processes (e.g. *homeostasis).

Whichever their mechanism of action, either on acquisition, on consolidation or on retrieval, it is likely that safe and effective nootropics will ultimately become available, even as over-the-counter medications. Their effect on the *capacity of *real-life memory, on cognitive functions such as categorization and decision making, and on emotion, should make an interesting topic for countless PhD theses.

Selected associations: CREB, Glutamate, Lotus, Mnemonics, Nutrient

Noradrenaline

A biogenic amine that functions as a *neurotransmitter and a hormone.

Noradrenaline (NA, alias norepinephrine, 2-amino-1-(3,4-dihydroxyphenyl)ethanol) belongs to a family of compounds called catecholamines (see also *dopamine). It is synthesized from dopamine in the brain, sympathetic nerve, adrenal medulla, and heart by the enzyme dopamine- β -hydroxylase (DBH; Cooper *et al.* 1996). Noradrenaline fulfils multiple roles in *development, physiology, and behaviour (Mason 1984; Thomas *et al.* 1995; Thomas and Palmiter 1997a). A related catecholamine, adrenaline (AD, alias epinephrine) is synthesized from NA by the enzyme phenylethanolamine N-methyltransferase. Adrenaline was the first substance to be proposed as a neurotransmitter (Elliott 1904). In the periphery both NA and AD act as transmitters and hormones. In the brain, NA is much more abundant than AD, and less is known about the function of the latter.

The noradrenergic innervation in the brain is diffused and reaches a large variety of targets. The majority of the noradrenergic innervation originates in the locus ceruleus, in the pontine central grey (Figure 50). This cluster contains about 3000 neurons in the rat and 25,000 in human. Several major noradrenergic tracts travel from the locus ceruleus and innervate targets in most of the brain. Noradrenergic neurons also reside outside the locus ceruleus, in the lateroventral tegmentum. Much of their output intermingles with that of the locus ceruleus but the targets are not identical.

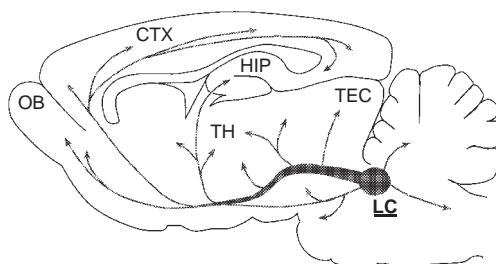


Fig. 50 A schematic diagram of the central noradrenergic projections from the locus ceruleus (LC) in the mammalian brain. Only selected targets are marked. CTX, cerebral cortex; HIP, hippocampus; OB, olfactory bulb; TEC, tectum; TH, thalamus. (Adapted from Cooper *et al.* 1996.)

NA released from nerve terminals interacts with adrenergic *receptors (adrenoreceptors). These exist in multiple types, which differ in their localization, ligand binding properties, and downstream *intracellular signal-transduction cascades. A major classification of noradrenergic receptors is on the basis of rank affinity for NA, AD, and the synthetic agonist isoprenaline (ISO); α -adrenoreceptors are defined as NA>AD>>ISO, and β -adrenoreceptors as ISO>AD=NA. All the adrenoreceptors are targets for potent drugs (Milligan *et al.* 1994). As is the case with many other neurotransmitters and neuromodulators, additional NA binding-proteins exist in brain, including cross-membrane transporters, active in reuptake (Blakely and Bauman 2000). The transporters are also targets for efficient neuroactive drugs.

The fact that noradrenergic drugs affect performance on memory tasks, and that the turnover of NA in the nervous system correlates with certain behavioural states, has led already more than 30 years ago to the suggestion that NA plays a part in learning and memory (Kety 1970). It is now agreed that in a variety behavioural paradigms, memory is enhanced by treatments that induce NA release or activate NA receptors, and impaired by treatments that reduce NA release or block NA receptors (Mason 1984; McGaugh and Cahill 1997; Roulet and Sara 1998). There is especially strong evidence for the involvement of adrenoreceptors in the *amygdala in the storage of information for inhibitory avoidance (McGaugh and Cahill 1997; Ferry *et al.* 1999). Adrenoreceptors are also obligatory in the *cortex for the formation of memory in another avoidance paradigm, *conditioned taste aversion (Berman *et al.* 2000). In some other learning situations NA ligands were reported to have no effect (Pontecorvo *et al.* 1988). Similarly, mice lacking NA because of a knockout (*neurogenetics) in the DBH gene, display only mild defects in some learning and memory tasks and perform normally in others (Thomas and Palmiter 1997*b,c*). All in all, the pharmacological, neuroanatomical and genetic interventions suggest that NA affects functions that are obligatory for memory formation only in certain situations.

What could these functions be? There is evidence that the noradrenergic system contributes to the encoding of selective *attention, vigilance and novelty detection, stress, emotion, and motivation (Steketee *et al.* 1989; Decker and McGaugh 1991; Aston-Jones *et al.* 1994; Smith and Nutt 1996). NA does this in concert with other neuromodulatory systems, such as *acetylcholine and dopamine (Hasselmo 1995; McGaugh and Cahill 1997). At the system level, the

aforementioned functions could be achieved via noradrenergic activation of the amygdala (McGaugh and Cahill 1997), of the cortex, and of the reciprocal thalamocortical processing (McCormick 1989; the modulation of thalamocortical information could specifically subserve novelty detection, Ahissar *et al.* 1997; *surprise). At the cellular level, it is noteworthy that NA was found to modulate *glutamatergic N-methyl-D-aspartate receptors in *hippocampus, via the cyclic adenosine monophosphate cascade (Gereau and Conn 1994; Raman *et al.* 1996). This fits with the idea that NA contributes to the encoding of *context, which modulates glutamatergic input, affects cellular signal-to-noise ratio (Segal and Bloom 1976; Hasselmo 1995; Jiang *et al.* 1996), and contributes to the overall decision made by the neuron and the circuit, whether or not to retain the incoming information.

The possibility could be raised that the activity of the noradrenergic system, similarly to that of the cholinergic and the dopaminergic systems, is not essential for the operation of the 'core' molecular machinery that embodies lasting *synaptic changes in some systems of the mammalian brain. The distinction between a 'core' and an 'accessory' synaptic storage system is not self-evident. Generally speaking, it implies that there are molecular cascades that are essential for synaptic storage and there are others that are indispensable for encoding distinct cellular and circuit states but dispensable for the storage process *per se*. For example, certain subtypes of the intracellular signalling cascades that lead to the modulation of gene expression and to *protein synthesis in *consolidation of long-term memory, could be regarded as components of the core machinery of synaptic storage. It is likely that in a variety of areas of the mammalian brain, glutamatergic transmission is essential for the *in vivo* triggering of this core machinery. In contrast, certain neuromodulatory systems may trigger state-dependent activation of the core machinery or set the threshold of its activation, but storage could take place in their absence, provided the core machinery was set into action by other means. The identity of the core machinery itself, however, may still depend on the task.

Selected associations: Context, Dopamine, Neurotransmitter, Receptor, Synapse

Nutrients

Substances and compounds required by living tissues for metabolism and energy production, growth, maintenance and reproduction, remodelling, and communication.

'Food for thought' is not merely a cliché. The discussion of the association of satisfactory nutrition with efficient cognition has transcended long ago the domains of folk psychology. Ribot, one of the forefathers of modern neurology (see *amnesia), postulated that '... the basis of memory is... nutrition; that is to say, the vital process per excellence' (Ribot 1882). It is now established that even without too much mental effort, our brain consumes an impressive amount of energy. The adult human brain, while weighing only 2% of the total body weight, consumes 15–20% of the total resting oxygen consumption (Guyton 1991; Ganong 1993); in a 6-year-old child the value is about 50% (Kennedy and Sokoloff 1957). In the resting brain, energy is generated almost exclusively by the oxidation of glucose (Siesjo 1978). A substantial proportion of this energy is used up by molecular pumps that maintain proper concentration gradient of ions, such as *calcium, across the neuronal membrane, thus ensuring neuronal excitability and responsiveness (Guyton 1991; *ion channel). Glucose is derived continuously from the capillary blood, as only a tiny supply of glucose is normally stored as glycogen in the neurons at any given time (*ibid.*). In periods of activity, local metabolic rate and blood flow increase dramatically in the activated area (Roy and Sherrington 1890; Fox *et al.* 1988; Sokoloff 1989; Malonek and Grinvald 1996). These fast activity dependent processes provide the biological basis for a variety of *functional neuroimaging techniques (Raichle 1994). They are also reflected in the intense molecular turnover that is detected in neurons immediately after a physiological or behavioural experience (*consolidation, *homeostasis, *immediate early genes, *protein synthesis). Which metabolic pathways supply the instantaneous surge of energy in activated neural circuits, is still a subject of controversy. Whereas some investigators favour the view that hard-pressed neurons resort to anaerobic metabolism, similarly to exercising muscles (Fox *et al.* 1988), others report that active neurons, similar to resting ones, stick to oxidative metabolism (Malonek and Grinvald 1996).

The fact that a working mind consumes much energy, has led to the idea that the lack of proper food-stuff might impair intelligence. Many types of nutrients

Nutrients

in addition to energy sources are also very important for brain and cognition. Vitamins or minerals are examples. Deficiency in these may cause severe neurological and cognitive disorders. For example, thiamine deficiency in chronic alcoholism results in *dementia (Korsakoff's syndrome, Butters 1985). Many other vitamins as well as minerals (e.g. iodine, iron) are also essential for a healthy brain (Ganong 1993; Scrimshaw 1998). Improper intake of vitamins, minerals, and essential amino acids is a pressing problem in undernourished societies, where it may adversely affect child *development and cognitive achievements (Scrimshaw 1998). Lipids, which are required among others in intercellular and *intracellular signal transduction and in regulation of membrane fluidity and excitability, are also important for proper cognitive function. Some lipid preparations were claimed to act as cognitive boosters (*nootropics) and memory enhancers (Yehuda and Carasso 1993, Yehuda *et al.* 1996).

The composition of the diet should also not be ignored by investigators who experiment on laboratory animals. A change of a diet may affect *performance on learning tasks, and under certain conditions, an imbalanced or poor diet may ultimately result in amnesia (e.g. Guo *et al.* 1996).

Even in healthy individuals on a balanced diet, what is placed into the mouth, and especially when it is placed there, may make a lot of difference as far as cognition is considered. This, at least, is the conclusion that emerges from a number of reports in recent years. For example, drinking a glucose-rich beverage was found to improve learning and recall in healthy adults (Manning *et al.* 1998). Similarly, in healthy students, failure to eat breakfast impaired learning and memory throughout the day; the problem was easily amended by drinking a glucose-supplemented drink (Benton and Parker 1998). The improvement in memory performance correlated with blood glucose. It has yet to be determined whether the beneficial effect of sugar on cognition is a consequence of a boost to the energy of the brain, or of augmentation of neurotransmitter synthesis (e.g. *acetylcholine), or other metabolic processes. Nevertheless, all in all, the data imply that children should not be sent to school without breakfast; that politicians should not decide on state matters without ensuring that their blood glucose has reached a sufficiently high level; and that elderly people should pay proper attention to what they eat and when they do that. It also argues against diets that reduce calorie intake to absurdity—unless definitely deemed a must by an expert physician.

Selected associations: Dementia, Development, Homeostasis, Nootropics

Observational learning

1. The *acquisition of novel behaviour by observing its *performance by a model.
2. The generation or modification of lasting *internal representations of actions, or actions and their consequences, by observing the behaviour of a model.

'Whatever you see me do, do like-wise', said Gid'on to his selected three hundred men, blew the shofar, waved the torch, and surprised the Midyanites in their camp (*Judges* 7: 17–22). He was a master demonstrator in an observational learning class. A lot of what we learn in our lifetime, from others we learn, frequently by observing a model and adapting its actions. In *real-life, the model is a conspecific; in the lab it could be an individual of another species or a behaving inanimate.¹ This capability, to gain from the experience of others, clearly expands the behavioural repertoire of individuals much beyond the limits of their own innate (**a priori*) responses and solo experience combined.

Behaviours emitted or acquired via social interaction are termed 'socially dependent'. They are widespread and observational learning is but one type. Socially dependent behaviours include: (a) *socially released* behaviour; (b) *socially facilitated* behaviour; (c) *social learning*, which includes imitation and observational learning, instructed learning, and collaborative learning.² In socially released behaviour an innately predisposed response pattern, such as courtship or attack, is triggered by the *perception of a specific *stimulus (Lorenz 1981). In socially facilitated behaviour, there is an increase in the frequency or intensity of response that is already in the individual's active repertoire, e.g. eating or locomotion, when in the presence of others that are engaged in the same behaviour (Clayton 1978). In contrast, in social learning, the interaction results in new behaviour. This interaction could be between a model and a learner (imitation and observational learning), an intentional teacher and a learner (instructed learning), or two or more learners (collaborative learning; Tomasello *et al.* 1993). The differentiation among observational, collaborative, and instructed learning is appropriate in the discussion of social learning in humans, but not necessarily in other species, in

which the parties in the learning process might be unaware of their 'formal' role in it. Collaborative and instructive learning will not be further discussed here.

Many authors use the terms 'imitation' (or 'imitative learning') and 'observational learning' interchangeably. This should not, however, blur the wide spectrum of complexity of the behaviours involved. Others prefer to reserve 'imitation' to describe a subtype of observational learning, in which the learner faithfully duplicates the behavioural performance of the model. In the more flexible forms of observational learning, the learner emulates the behavioural strategy involved, not only the overt motor acts, and is clearly capable of adapting and improving the learned behaviour to attain the goal. Another point to note is that 'observational learning' connotes visual learning, whereas 'imitation' covers all the sensory modalities. In the rest of this discussion, for the sake of convenience, the term used will be 'imitation and observational learning' (abbreviated IOL).

Our knowledge of IOL draws from research in multiple disciplines: behavioural psychology and ethology; education, developmental and social psychology; and cognitive psychology and the philosophy of mind. The systematic discussion of IOL in behavioural psychology and ethology was initiated already in the nineteenth century; examples from this period are provided in Darwin (1871, 1872), Romanes (1882), and Morgan (1896). Most contemporary reports on species other than humans were mostly anecdotal (*anthropomorphism). The interpretation of the factual or the alleged data was at first rather shaky. In this context, even Darwin erred: he suggested that in evolution, the dog has started to bark in an attempt to imitate its talkative human master (Darwin 1872). Since then, IOL has been documented in a great variety of species, ranging from guppies and octopi, via birds and cats, to *monkeys and apes (John *et al.* 1968; Griffin 1984; Anderson 1990; Cheney and Seyfarth 1990; Fiorito and Scotto 1992; Barresi and Moore 1996; Whiten *et al.* 1996; Marler 1997; Laland and Williams 1997; Templeton 1998). And, reassuringly enough, not only humans find it more rewarding to learn from other's mistakes than from their successes (Templeton 1998).

Research in education and social psychology has contributed tremendously to our understanding of the role of IOL in human *culture (Deahl 1900; Miller and Dollard 1941; Bandura 1962; Bandura and Walters 1963; Bandura 1986). A major question is how much of children's behaviour is moulded by observing their parents, their siblings, their classmates, or TV? The answer is simple: a lot. IOL starts already in the neonate (Meltzoff and Moore 1977), and plays a central part in

shaping behaviour throughout the critical periods of emotional and cognitive *development (Piaget 1962). For example, in a *classic, influential set of studies, it was found that children who observe a model rewarded for aggressive behaviour tend to exhibit more aggressive responses than children who see the model punished (Bandura *et al.* 1963) (Figure 51). This is a case of 'vicarious learning', so called because the *subject sympathizes with the reward or punishment of the model without experiencing it itself (Bandura and Walters 1963). It is difficult to overemphasize the importance of the findings on the role of IOL in children, especially in a TV-dominated society. Some kids may be misled to think that jumping in front of a car is safe and kicking another guy is good, because on TV stuntmen/women are never hurt and villains live happily forever (Potts *et al.* 1996). IOL keeps working throughout life, even in situations in which we are utterly unaware of it; for example, in a restaurant, what we order is influenced by incidental observation of the reaction of others to the food (Bayenes *et al.* 1996).



Fig. 51 A *classic study of observational learning: children imitate the aggressive behaviour of an adult model they had observed torturing an inflated doll on film. In this study, on the average, gender had a clear effect: boys displayed more acute aggression toward the doll, whereas girls were more inclined to sit on the doll rather than punch it. (From Bandura *et al.* 1963.)

Observational learning

There used to be in the literature a temptation to use complex forms of IOL as evidence that subhuman species have, similarly to **Homo sapiens*, a ‘theory of mind’, i.e. that the individual of the species can impute mental states to itself and to others.³ This is because in some situations it seems as if the observer really ‘reads the mind’ of the model. This is why cognitive psychologists and philosophers of the mind discuss IOL (e.g. Gallese and Goldman 1998). A caveat is, however, appropriate: even a remarkable capability to learn from the other is not sufficient to prove a ‘theory of mind’, as the behaviour might still be explained by *associative conditioning, rendering the theory of mind explanation superfluous (*criterion, *Ockham’s razor). The acid test for a ‘theory of mind’ is the ability to compute what the other subject will do on the basis of *false belief*, not *physical reality*, because *cues in physical reality could govern the behaviour of the observer without the need to access the mental state of the other individual. Possibly, in addition to humans, only great apes have a (rudimentary) ‘theory of mind’ (Barresi and Moore 1996; Frith and Frith 1999).

What brain mechanisms subserve IOL? Given the rich repertoire of IOL performances in various species, no single solution should be expected, at neither the computational, nor the neuronal hardware *level. The problem is easier to approach in the laboratory in tasks that involve elementary motor acts, such as imitation of reaching or grasping in humans and monkeys. The *methods used to analyse the imitating brain are cellular physiology in the behaving monkey, and *functional neuroimaging in humans. A useful conceptual starting point is that IOL of simple motor movements exploits elementary motor subroutines of the learner. The learning therefore does not involve *de novo* generation of the entire movement on the basis of the information received by observation of the model. In other words, here is another example of the rule ‘to learn something, you must already know a lot’ (*a priori). An appealing hypothesis is that the learner matches the *percept with its own motor representations of motor action, in order to understand (Jeannerod 1994) and learn (Rizzolatti *et al.* 1996; all this is done implicitly; no *declarativity required).

Evidence from both humans and the monkey concur with this ‘matching’ or ‘resonance’ hypothesis. In the monkey, neurons were detected in the pre-motor area in the frontal cortex, which fire both when the monkey performs an action and when it observes a similar action made by another monkey or by the experimenter (di Pellegrino *et al.* 1992; Rizzolatti *et al.* 1996). These neurons are termed ‘mirror neurons’. Similarly, in humans, areas were identified in the frontal and parietal

lobe that are activated both when a movement is performed by instruction or by imitation (Iacoboni *et al.* 1999). In another study, brain regions involved in *planning and generation of action, including frontal cortex, were activated in humans that observed an action with the intention to imitate it, as opposed to observation only (Decety *et al.* 1997). These data indicate that the neuronal circuits that subserve the perception and learning of the action-to-be-imitated overlap with circuits that subserve the preparation and the execution of the same action. If we *generalize a bit, and look at the other facet of the coin, this conclusion echoes the so-called ‘motor theories’ of speech perception (*birdsong, *performance): in order to understand an action, we must be able to perform it.⁴

Selected associations: Acquisition, Birdsong, Cerebral Cortex, Internal representation, Planning

¹Using inanimate models could be tricky, as animals often distinguish between animates and their inanimate replicas, and might fail to imitate in the absence of the live model; e.g. see discussion in Rizzolatti *et al.* (1996).

²Some socially dependent behaviours do not fit easily into this *taxonomy. For example, the transfer of food information from one rat to another via odours (Galef *et al.* 1984) is social learning, but could hardly be considered observational, or *bona fide* collaborative, or instructive. Also, relevant to socially dependent behaviours is biological communication, which includes many types of vocal, visual, olfactory, and somatosensory species-specific communication systems, and, of course, human language.

³The ‘theory of mind’ is termed ‘theory’ because the mental states are not directly observable but inferred, and this inference is used to make predictions. The term in this meaning was introduced by Premack and Woodruff (1978), in the context of their studies of the chimpanzee. Similar notions are ‘mentalizing’, and an ‘intentional stance’: having an ‘intentional stance’ means treating the other subject as an agent with intentionality (Dennett 1987; on intentionality as a *criterion for mental systems, see *system).

⁴This also echoes a maxim of scholastic philosophy, resurging in Vico (1710): only the one who makes something can fully understand it. Alas, the generalization of this wisdom to most human behaviours is clearly questionable.

Ockham’s razor

The maxim that entities are not to be multiplied beyond necessity.

The Franciscan theologian William of Ockham (also spelled Occam; 1285–1347), later of Oxford, was a most

influential medieval scholastic (Adams McCord 1987; Colish 1997). In his analysis of the Universe and human ability to perceive it, Ockham proposed that phenomena should be better explained in terms of the simplest causes rather than the more complex ones. Admittedly, he was not the first to suggest such a principle of parsimony. Even more so, his principle was rather qualified: 'No plurality should be assumed', said Ockham, 'unless it can be proved (a) by reason, or (b) by experience, or (c) by some infallible authority' (Adams McCord 1987), meaning that the Bible, the Saints, and the Church can make exceptions, and, furthermore, God is not in the game: 'There are many things that God does with more than he could do with fewer' (*ibid.*). In spite of his hesitation to regard the principle as a sweeping universal, Ockham's name became associated with it forever. Almost half a millennium later, the French philosopher de Condillac referred to Ockham's principle *metaphorically as 'the razor of the Nominalists',¹ paving the way to the current idiom 'Ockham's razor' (Safire 1999). It became and remained 'a most fruitful principle in logical analysis' (Russell 1945).

Ockham's razor has a derivative in the behavioural sciences, termed Lloyd Morgan's Canon: 'In no case may we interpret an action as the outcome of the exercise of a higher psychical faculty, if it can be interpreted as the outcome of the exercise of one which stands lower in the psychological scale' (Morgan 1894). Lord Morgan's canon was a cautionary reaction to overenthusiastic accounts of animal intelligence, that have dominated late nineteenth century psychology as a consequence of Darwin's theory of evolution. 'There is no fundamental difference between man and the higher mammals in their mental faculties. With respect to animals very low on the scale... their mental powers are much higher than might have been expected' (Darwin 1971). *Anthropomorphism became a trend in leading circles of the discipline of animal behaviour. It attained its pinnacle in the *classic book on animal intelligence by Romanes (1882), in which the author based generous interpretations of animal cognition on anecdotes obtained from secondary sources. Against that background, a canon of parsimony was utterly justified.

To the neuroscientist at the turn of the twenty-first century, Ockham's canon is still a useful guideline, but in practice is easier to quote than to use, and in any case, must not be followed blindly. The major initial successes in modern biology relied on an Ockham's razor-guided world view; modern *neurogenetics drew from the same conceptual source (Benzer 1967). *Models of artificial neuron-like networks focused in their early days on minimalistic neuronal units, but soon afterwards appreciated the need for at least a partial mimicking of

real-life complexity (Segev 1992). The problem is that in general, when scratched beyond the surface, biological *systems display much more complexity than first expected. For example, a brief period of naive hopes that the map of *intracellular signal transduction cascades is around the corner, gave way to the realization that the intricacy and complexity of these signalling networks and their interactions is overwhelming, and that their analysis requires radical rethinking not only of the methodologies but also of the education of biologists (Alberts 1998). Enzymes and *receptors are amazingly intricate machines with multiple regulatory sites and permutational states. The same holds for the regulatory apparatuses of gene expression (Lewin 1994; *immediate early genes). The living cell is hence packed with highly elaborate miniature machines and their understanding in great detail is the subject matter of gargantuan efforts (Alberts and Miake-Lye 1992; Bray 1995). And on top of it all, organisms and neural preparations initially regarded as *simple systems' soon ceased to be simple anymore (Byrne and Kandel 1996; Wolpaw 1997; see also on the demise of simple explanations of *classical conditioning; Wasserman and Miller 1997). Even the rejection of anthropomorphism is not so trivial nowadays; for example, is the suggestion that in certain conditioning protocols the rabbit becomes *consciously aware of the associated events, in conflict with Ockham's razor (Clark and Squire 1998; *declarative memory)?

The difficulty beyond all this is that we simply do not know whether the complexity that we detect is real and non-parsimonious. In Ockham's own words, we cannot determine whether 'God (did) with more than he could do with fewer' (see above). We also cannot simply conclude that a biological system, assumed to be moulded by aeons of opportunistic evolution, had evolved to take the simplest route to its goal. The remedy to this dilemma is to identify what information a system encodes at each *level of its organization, be it a molecular ensemble within the neuron or a neuronal ensemble within the brain, and then find out whether the so-called 'complexity' is indeed essential for the representation of the relevant information. If it turns out that many detected variations in individual elements, say enzymes in signalling networks, are irrelevant to the encoding of critical information (e.g. Barkai and Liebler 1997), then there is a better hope for a simple explanation of the operation of the seemingly complex system. Admittedly, it is hard to believe that nature has taken all these pains to ensure highly intricate regulation of proteins and cells in order to end up in systems in which this complexity is not important. We are thus back to square one.



Fig. 52 Proponents of parsimony: William of Ockham (*left*) and Lloyd Morgan. Seven hundred years after the introduction of Ockham's maxim, the student of memory struggles to navigate properly between the lure of simple explanations and the complex reality of biological *systems.

So may be the solution to the dilemma presented by Ockham's razor is on the pragmatic level: we should adhere to the maxim of parsimony merely as a reminder that we had better focus first on the simplest facets of our experimental systems, because in real life biology is too complex for us to approach otherwise. And the overall take-home message is that it is not easy to handle biological systems with tools borrowed from logic unless we understand what the logic of the system is.²

Selected associations: Anthropomorphism, Clever Hans, Declarative memory, Observational learning, Reduction

¹Nominalists deny the existence of universals. Universals are *generalizations of knowledge, abstract properties and relationships, that contrast with particulars, which are instantiated objects. Generally speaking, nominalists believe only in the existence of particulars, whereas their opponents, the realists, do believe in addition in universals (Armstrong 1989). Compare also 'token' vs. 'type' in *system. Nominalists and realists come in multiple versions, but a discussion of these variants in the present context would certainly defy Ockham's razor.

²Which brings us back to the question whether to fully understand we must be able to fully produce the *system; see *criterion, *observational learning.

3. A memory system in which new patterns are stored on top of previous ones.

The term had originated from Greek *palimpsestos*, 'scraped again' (*palin*, again, + *psestos*, scraped). It seems to have occurred first in the writings of the Roman poet Catullus (Hammond and Scullard 1970). When vellum was scarce, especially in the early middle ages, early manuscripts were erased and the writing material used again. As the removal of the original writing was seldom complete, valuable religious and classical texts have been recovered from such palimpsests (Lewis and Gibson 1900; Cuddon 1979; Shailor 1988). For example, the important mathematical text called *The method*, by Archimedes, was discovered in Constantinople as a tenth century manuscript on leaves of parchment over which Eastern Orthodox prayers had been added in the thirteenth century (Boyer 1989).

'Palimpsest' has been used as a *metaphor for brain and mind by Romantic writers. 'What else than a natural and mighty palimpsest is the human brain? ... Ever-lasting layers of ideas, images, feelings, have fallen upon your brain softly as light. Each succession has seemed to bury all that went before. And yet ... not one has been extinguished ... Yes, reader, countless are the mysterious hand-writing of grief or joy which have inscribed themselves successively upon the palimpsest of your brain' (De Quincey 1866). Postulated palimpsestic properties of biological memory systems were also contemplated by Freud (1925). Similarly, Gestalt psychologists have proposed that new memory records are inscribed on top of old ones (Koffka 1935).¹ 'Palimpsest' resurfaced in modern neurosciences with the introduction of *models of artificial neural networks (Nadal *et al.* 1986; Amit 1989; Amit and Fusi 1994). In subclasses of such model networks, which keep a permanent *capacity for learning, new patterns are stored on top of old ones that get progressively erased (*ibid.*).²

Palimpsestic memory systems may be classified into two major conceptual classes. In the first, the new memory is an autonomous representation that displaces and nullifies the old one(s). This is a 'winner-takes-all' situation. In the second, the new pattern is superimposed on the old one(s) to yield a representation that is different from both old and new (here too, with repeated learning memories may ultimately be diluted to practical extinction, but they always leave a mark on younger representations). This latter version of the concept retains more faithfully the original connotation of a palimpsest.

Ample theoretical and experimental data support the second aforementioned process in brain, i.e. new experience interacts with previous ones to generate

Palimpsest

1. A surface, such as vellum or parchment, that has been written on more than once, with the previous writing incompletely erased.

2. A text that reflects its history.

new *internal representations. For example, *percepts interact with endogenous brain activity at any given moment ('pre-representations'; Young 1979; Heidemann *et al.* 1984), activity that itself is expected to be at least partially experience dependent, to yield new patterns of brain activity (e.g. Arieli *et al.* 1996). If this



Fig. 53 A palimpsest fragment. A Hebrew script from the tenth/eleventh century, part of a Liturgical poem (*Piyut*), runs on a piece of coarse vellum across an older syriac text, a chapter of Deuteronomy from the tenth century (Lewis and Gibson 1900). The Hebrew letters faded until they have become of essentially the same hue as the older Syriac ones. In palimpsests like this one the different strata of the text are easily discerned. However, in some palimpsests the new text merges with the old one and occasionally a newer text emerges. This is the idea beyond 'palimpsest' in *models of memory.

indeed is the case, substantial implications emerge for both philosophical and practical issues such as the degree of objectivity of percepts and knowledge, the role of *a priori knowledge in learning, and the fidelity of memories (*false memories, *real-life memory). It also reflects on the question whether memories could indeed be utterly *forgotten.

Selected associations: A Priori, Cell assembly, Experimental extinction, False memory, Retrieval

¹For more on the Gestalt, see *binding, *insight.

²It is noteworthy that 'Palimpsest' found another modern use, in the critical theory of literature and culture, to denote the thesis that literary texts are rewritten versions of earlier texts, and hence writing is rewriting, e.g. Genette (1997).

Paradigm

1. An ideal instance of a concept.
2. An example that serves as a model.
3. A standard concept, method, or procedure used in a discipline.
4. A set of concepts, practices, findings, and beliefs that dominates a discipline and affects its activity, structure, and progress.

Paradeigma (Greek for *pattern*) was used by Plato in various meanings of 'example', including an ideal instance of a concept, a model and a standard (e.g. *Statesman* 278bsq.; Guthrie 1975). In the scientific literature, 'paradigm' is occasionally used to denote a standard concept, method, or procedure (definition 3, e.g. 'the *classical conditioning paradigm', 'the *conditioned taste aversion paradigm', etc.). It was, however, Kuhn (1962) who endowed 'paradigm' with its broader meaning and central position in the philosophy, sociology, and history of science (definition 4).

Kuhn treated the culture of science from a historical perspective. He differentiated five stages in the ontogeny of a scientific discipline: immaturity, normal science, crisis, revolution, and resolution. 'Immaturity' is characterized by fact gathering in the absence of an accepted conceptual and practical framework. 'Normal science' is 'research firmly based upon one or more past scientific achievements ... that some particular scientific community acknowledges for a time as supplying the foundation for its further practice' (Kuhn 1962).

Paradigm

These achievements form ‘paradigms’ (definition 4). Paradigms are constructs of thought (shared concepts and beliefs), methodology (standard methods and practices), and sociology (they underlie the behavioural code and *esprit des corps* of the discipline, as reflected in professional societies, journals, and meetings; *culture). Achievements that give rise to paradigms delineate the workings of the discipline, yet are sufficiently open ended to leave problems for resolution in the future. Crisis arises when anomalies pop-out in the worldview that is advocated by the paradigm, and success in solving problems and advancing the field slows down. The crisis ultimately leads to a revolution, in which a new paradigm starts to emerge. The new and old paradigms, according to Kuhn, are incommensurable, and the revolution is characterized by a struggle between the disciples of each. Finally, the struggle is resolved with the new paradigm prevailing—till the next cycle.

Kuhn’s analysis was very influential, itself approaching the status of a paradigm in the philosophy and history of science. Typical of Kuhnian paradigms, it encountered crisis and gave way to new accounts of scientific practice (Hacking 1981; Bechtel 1988), in which ‘paradigms’ were replaced by other concepts, such as ‘research programmes’ (Lakatos 1978) or ‘traditions’ (Laudan 1977). For the purpose of the present discussion, ‘programmes’ and ‘traditions’ could be described as families of theories with some shared characteristics, which, in contrast to Kuhnian paradigms, coexist to various extent throughout the ontogenesis of the discipline. Hence, in the philosophy of science, Kuhnian paradigms and revolutions are not so trendy anymore, but still, they retain some usefulness in contemplating the state of the art and the progress of a given discipline.

It is only fair to note that even if Kuhn’s account of the ontogeny of scientific disciplines were valid, the question would still remain whether the science of learning and memory has attained the status of ‘normal science’. The answer is not simple. Kuhn, similarly to many philosophers and historians of science, drew mostly from the analysis of physics, in which theories and paradigms are easier to delineate. Research on learning and memory combines multiple disciplines, ranging from psychology via neurobiology to computational science. In each of these disciplines, the level of ‘normality’ (in the Kuhnian sense) is different. Nevertheless, for the sake of argument, analysis of the field of learning and memory with Kuhnian tools is of substantial interest. It sharpens attitudes, illuminates the source of current trends, and provides perspectives on popular scientific as well as social practices.

So which are the paradigms of memory research? The discipline at large draws on some paradigms that are shared by other disciplines in the natural sciences. Because these paradigms are at a higher levels of “generalization, we can consider them as ‘metaparadigms’. Here are examples:

1. **Reductionism*. Well, this is surely a successful paradigm. The secret of using it smartly is to focus on those *levels of analysis that fit the discipline. This is not at all trivial in memory research (*internal representation, *learning; Dudai 1992).
2. *Modularity*. This paradigm considers biological systems as composed of modules, or elementary systems, either cross or within levels. Modularity serves reductionism. At the same time, it could lure us away from considering the system as an integrated whole. For the fingerprints of the modularity paradigm in the cognitive and the brain sciences, see *engram, *functional neuroimaging, *phrenology; also the critique in Fuster (2000a).
3. *The Panglossian paradigm*.¹ This paradigm posits that natural selection is an optimising agent, and therefore biological systems are neatly adapted to perform particular tasks (Gould and Lewontin 1979; Dennett 1983). The Panglossian paradigm guides us to search for an adaptationist explanation whenever we encounter an incomprehensible system. The truth might be that the system is as is because of built-in, accumulating internal constraints, irrespective of the assumed adaptation; or that the ongoing evolution of the system is still far from the optimum.

In addition to the above ‘metaparadigms’, other paradigms are more specific to memory research. In the history of psychology, several schools have approached the status of the dominant paradigm at their time (e.g. Weimer and Palermo 1973; Ghoshal and Barker 1985). Most notable were *introspective psychology*, that has characterized the emergence of the ‘new psychology’ in Germany a century ago (Boring 1950a), and the subsequent reaction to it, **behaviourism*. In current neuroscience, a few paradigms fuel the *zeitgeist. A major example is provided by the prevailing concept that *long-term memory is embodied in synaptic remodelling and growth*. This conceptual framework has definitely reached the status of a Kuhnian paradigm, influencing so much of the current research in molecular and cellular neurobiology (see *consolidation, *CREB, *development, *immediate early genes, *late response genes, *protein synthesis). The *classification of memory systems* into *declarative and nondeclarative (*taxonomy) is another

contemporary paradigm. And the assumption that **long-term potentiation (LTP) is memory* is yet another example, still a mini-paradigm, but ambitiously aiming higher.

Given the current paradigms of memory research, and adhering for the sake of argument to the Kuhnian terminology—will revolutions ensue? As noted above, when facts are difficult to explain in terms of the existing conceptual framework, be it a paradigm or a research programme or a tradition, they herald new concepts and ultimately change worldviews (e.g. Lightman and Gingerich 1991). It would be naive to assume that statements such as *memory=growth*, or *LTP=memory*, will not succumb to anomalies. Behaviourism did, to the complexity of language (Chomsky 1959) and of learning (Dickinson 1980). The exclusiveness of instantaneous associations in **associative learning*, if it was ever substantiated in the data, was diminished by the documentation of effective long-delay associations in nature (Garcia 1981). Even the hegemony of laboratory experiments, whose practitioners came to worship reaction times, avoidance boxes, and **mazes*, was shattered by the complexity of **real-life memory* (Neisser 1978). Interestingly, in all the above cases, the prevailing paradigm did not disappear, but rather lost some of its inflated status, while retaining its usefulness side by side with newer paradigms. The piecemeal evolutionary accounts of Lakatos (1978) and Laudan (1977) seem thus to be more realistic than the Kuhnian sharp survival of the fittest. This means that on the one hand, even paradigms that currently seem amazingly robust are not immortal, but on the other, their spirit will survive in their progeny.

Selected associations: Development, Bias, Culture, Reduction, Zeitgeist

¹Dr Pangloss ('entirely-language'), the teacher of Candide (Voltaire 1759), was the ultimate incurable optimist. He justified every disaster in the world by the **a priori* assumption that everything under the sun is for good cause. Pangloss was hanged, which, judged by his own philosophy, couldn't be but good.

'Percepts' are glimpses of the sensory world captured by the brain in real-time (definition 1; from *per-* + *capere*, 'to seize' in Latin). These short-lived representations serve as raw material for more advanced analysis of the sensory world. The brain then decides, within a few milliseconds, whether to pay **attention* and use the information for further processing, or simply forget about it. Research on perception is an extremely rich and dynamic discipline at the core of the neural and cognitive sciences (Hochberg 1998). It addresses the whole gamut of processes and mechanisms by which the nervous system extracts information from sensory input. In the context of this type of research, 'percept' is also referred to not as the initial internal representation of the stimulus, but as the intermediate or end-product of central analysis (definitions 2 and 3). Construed this way, 'percept' denotes a **memory*, as it outlives the stimulus. As noted below, the distinction between 'percept' and 'memory', specifically 'immediate' memory (**phase*), is not trivial. In discussions of learning and memory, however, there are merits to such a distinction. Furthermore, for the purpose of the present discussion, considering percept as dependent on awareness (definition 3), which is central to cognitive treatments of percept, is not obligatory. Hence the more restricted, **reductive* definition 1 is here preferred.

Information about the world arrives at our brain via sensory channels. The interaction of sensory energy with peripheral receptors at the front end of these specialized channels is termed 'sensation'. 'Perception' involves processes downstream of the peripheral receptors. Both the peripheral receptors and the central sensory units could be characterized using multiple **criteria*; two common ones are modality, i.e. the type of energy detected, and the 'receptive field'; i.e. that portion of the world from which that energy can affect the detector. Over the years, philosophers and psychologists have been debating and re-debating the relative role of the external and internal (brain) world in perception. What the frog's eye tells the frog's brain (Lettvin *et al.* 1959) may depend not only on what is in front of the eye, but also on what is at its back. The debate can be illustrated by contrasting theories of 'direct' vs. 'indirect' perception. Both types of theories agree on the basic good old philosophical tenet that 'perceiving is knowing' (Price 1950; Hall 1964; Burnyeat 1990). They disagree, however, on critical elements of this tenet. Adherents of 'direct' theories (alias 'ecological', 'stimulus-centred') suggest that the focus of perceiving is in the animal-environment interaction rather than in the animal, and perception is merely the selection and capture of information that is awaiting us outside there (Gibson 1979;

Percept

1. A short-lasting **internal representation of an on-line sensory *stimulus*.
2. An internal representation of a sensory stimulus.
3. The **conscious experience of sensed energy*.

Michaels and Carello 1981). In contrast, proponents of the ‘indirect’ theories (alias ‘information-processing’, ‘constructivist’) propose that in perception, sensory data interact with endogenous information and are subjected to neuronal computations before becoming meaningful and useful (Ullman 1980; Rollins 1998). The view taken in this book is the latter. Ample data indicate that sensory areas in the brain function as filters tuned to specific sets of features (Dosher and Sperling 1998; Nakayama 1998). The information flows in both bottom-up and top-down streams (Knierim and Van Essen 1992; Ullman 1996; Jones *et al.* 1997; Nakayama 1998), with the latter possibly involving interactions with endogenously generated pre-representations (*a priori) as well as with previously acquired representations. The process probably becomes accessible to consciousness only at brain stations far from the sensory periphery (e.g. Crick and Koch 1995). Ultimately it *binds into a coherent percept. Thus, sense data do not represent the whole physical object but only selected aspects of it, biased by the species’ and the individual’s experience.

The fine tuning of central sensory systems and, as a consequence, the perception of attributes of sensory stimuli, is altered during brain *development in the young and by experience in the adult. This experience-dependent modification in the ability to extract information from sensory stimuli is termed ‘perceptual learning’ (Hebb 1949; Sagi and Tanne 1994; Goldstone 1998). Perceptual learning is manifested in multiple alterations in perceptual competence, including discrimination, categorization, and the attentional valence attributed to sensory features. It could involve the formation of perceptual ‘sets’¹ and is implicated in a wide range of behaviours. In addition to the overall maturation of sensory abilities, these behaviours include, among others, filial and sexual *imprinting during sensitive periods early in life; re-adjustment of sensory capabilities in response to insult (*map, *plasticity); and the acquisition of sensory *skill. Fine discrimination of odours in wine tasters is but one refreshing example for the latter (Bende and Nordin 1997). Whereas the normal brain is destined to benefit from improved perception over time, certain pathologies do the opposite. ‘Agnosias’ lead to failure in perceptual processing and recognition in the absence of disorders of sensation or language (Peach 1986). Their investigation assists in identifying brain regions that are involved in specific aspects of normal perception.

‘Percept’ by definition 1 above is a transient internal representation. It refers to the cognitive present. What is ‘transient’ and ‘present’ in this context? And can one at all distinguish a percept from very short-term memory?

A reasonable *criterion is to rely on the estimate of the minimal time that is required by the brain to extract information from sensory input. The exact value is expected to vary according to the complexity of input, but still, converging evidence from both cellular and psychophysical investigations points to 20–30 ms as the elementary cognitive stroke (e.g. Rolls and Tovee 1994; Horowitz and Wolfe 1998; *binding, *cell assembly). Even the complete processing of a complex visual scene, including the immediate response to it, requires <150 ms (Thorpe *et al.* 1996). This is shorter than the commonly accepted life span of ‘sensory memory’ (0.25–2 s; Dosher and Sperling 1998). So do ‘percepts’, as defined above, live 20–200 ms before they either become memories or die out? Possibly, but not necessarily. Circuits encoding percepts may sustain the primordial representation longer than that. First, because of their inherent biophysical properties. Second, because the brain may have evolved to always allow some more time for decision to be taken before sensory data are discarded. For example, is the endurance of evoked activity detected in cortical ‘face’ cells (200–300 ms after the offset of a stimulus; Rolls and Tovee 1994) evidence for the representation of a percept, or of an immediate memory trace? In real-life, the transition from percept to very short-term memory is probably gradual. Attempts to dissociate the two by behavioural *assays were unsuccessful (Haber 1966; but see Neisser 1967). Advanced psychophysical and cellular methodologies (e.g. Horowitz and Wolfe 1998; Parker and Newsome 1998) may clarify the issue, set new criteria, or declare the problem solely semantic and therefore practically irrelevant.

Yet even if at the end of the day ‘percept’ as a phase that precedes memory remains hypothetical and elusive, it is still a notion worthwhile to retain. This is because it sharpens the conceptual differentiation among memory phases and subphases. ‘Percept’ as considered here refers to the ‘encoding’ but not the ‘registration’ function in *acquisition (see there). It is also the concrete agent of ‘stimulus-driven’ attention, capable of pushing the input into the road to the *engram; for the brain, a stimulus has no meaning unless it results in a percept. A percept could also serve as a ‘sign stimulus’, which activates an innate response programme (Lorenz 1981), in which case the registration of the input is not a must. And, finally, percepts could provide *cues for *retrieval. Percepts thus induce major ‘rites of passage’ in the life of a memory.

Selected associations: Binding, Cue, Internal representation, Phase, Stimulus

¹On what a ‘set’ is, see *learning set.

Performance

1. The generation of output by a *system.
2. The execution of a mental or motor act.
3. The execution of overt behaviour.
4. Achievement on a specific task.

In behaving animals, the process or the outcome of learning are measured by monitoring changes in performance. But learning and performance are not equivalent. Learned information may remain latent until the appropriate conditions emerge for its expression as a change in performance ('latent learning'; Tolman 1932). Earlier in the twentieth century, orthodox *behaviourists attempted to shy away from this common knowledge. They claimed that only overt behavioural acts (definition 3) are legitimate psychological data, whereas inferred implicit changes in the potential to behave are not. The distinction between performance and competence, however, is now taken for granted in memory research. It does complicate the life of the experimenter who studies learning and memory in the behaving organism. For how could one be sure whether an apparent failure on a memory test is due to faulty learning, feeble memory, or impaired performance under the test conditions? The impaired performance could be due to trivial causes, such as defective sensorimotor capabilities, but also to more elusive causes, such as lack of *retrieval cues, inappropriate *context, diverted *attention, subthreshold motivation, too little or too much arousal,¹ latent alterations in the ability of *stimuli to control behaviour, and more. The distinction among these types of causes requires smart test designs, which take into account factors that could hinder the expression of behaviour (for selected examples of pitfalls and how to circumvent them, see *experimental extinction, *state dependent learning, *transfer). In other cases, the brain itself may simply need more time to surrender its new knowledge (*insight).

The distinction between performance and competence should be a source of concern in dealing with *reduced preparations as well (definition 1). These preparations range from isolated ganglia (**Aplysia*) to brain slices and neuronal cultures (*long-term potentiation). Cellular analogues of learning, such as a lasting *synaptic facilitation, may remain dormant under certain conditions yet become apparent under others. This may due to inappropriate test conditions such as nonpermissive *ionic composition of the solution in which the brain slice is immersed, unfavourable

neuromodulatory state (*neurotransmitter), or impaired cellular metabolism (*nutrients). Similarly, even if we knew the representational code in a given neuronal circuit, and were in principle able to infer learning by noting the alteration in the *internal representation in that circuit, we might still fail to identify the change because of certain nonpermissive states of the system or the context. The differentiation between competence and performance may hence pop up at various *levels of analysis, from the behaving organism to its individual synapses.

In some cases competence is not aptly transformed into performance simply because the system can do well without exploiting its full *capacity. This is nicely demonstrated in language. We know many more words than we use in daily life. This is why educated adults tend to estimate their vocabulary at a figure that is only 1–10% of the actual value (Seashore and Eckerson 1940). Whereas the vocabulary used in routine daily activities ranges from a few hundreds to a few thousands words, depending on education and profession, and goes up to 8000–20 000 in literary works,² the number of distinct words in printed school English (excluding derivatives and compounds) is about 89 000, of which an average 6-year-old child commands already no less than 13 000 (Pinker 1994), and a high school graduate 27 000–53 000 (Nagy and Anderson 1984). This implies that tests to quantify skill should not only be permissive for the expression of this skill, but also properly designed to allow the expression of its capacity. Training and testing conditions that allow for the expression of maximal performance may, however, yield 'ceiling effects'. Testing under ceiling conditions is not appropriate for measuring delicate alterations in performance, such as caused by learning or *development, because it could mask the effect of the experimental treatment.

Performance has multiple roles in the different *phases in the life history of a memory. It is a key element in *instrumental conditioning, acquired via stimulus–response (S–R) contingencies.³ Repetitive performance is essential for training on *habits and skills; this, among others, underlies the use of simulators in training (Hammerton 1967; *transfer). And in solving complex problems, performance itself may actually be an essential step in the *algorithm: the subject (an organism or a computer) tries the problem, attempts a solution, which produces a new problem-solving strategy, which is then used to tackle the problem again, and so on. The overall approach involves a sequence of transformations from one attempted strategy to another, each emerging from the one that just preceded it. This is called 'learning by doing' (Anazi and

Simon 1979), a sort of on-the-job training. Performance is also, of course, the embodiment of retrieval. The distinction from competence notwithstanding, performance is the ultimate measure of learning both in the field and in the laboratory (Richardson-Klavehn and Bjork 1988; Martin and Bateson 1993). However, as performance involves activation of neural circuits and therefore *plasticity on the one hand, and adaptive interaction with a dynamic outside world on the other, performance in retrieval may also induce modification of the trace upon its use (re-*consolidation). Thus usually, performance P_i of a task is not an exact replica of performance P_{i-1} , because the performance itself actuates learning. Virtuous musicians should surely attest to that.

Much has been learned in recent years about *internal representations that underlie motor performance and learning, and about distinct brain regions that monitor the behavioural performance and its deviation from the desired output (Carter *et al.* 1998; Kawato 1999; *dopamine, *planning). Prevalent theories of motor control and motor learning propose that the brain generates, stores, refines with experience, and executes internal models of the world, that mimic the input/output characteristics of the specific motor act, and uses them on-line to calculate the desired motor commands (Jeannerod 1994; Kawato 1999). Imagery may engage such internal models without culminating in overt performance (Jeannerod and Decety 1995). Furthermore, there are reports that imagery can substitute for real action in motor training; under such conditions of 'learning by imaging', the distinction between overt and covert performance becomes even fainter (e.g. Yáñez *et al.* 1998).

At least in certain types of mental operations, performance is also believed to be instrumental in *understanding* the world. There is evidence that in some *perceptual and *recognition tasks, the brain construes the perceived behavioural act by activating internal representations that are capable of performing that same act. This possibility has been suggested specifically by the so-called 'motor theories' of vocal recognition. These theories, which apply to human speech, mammalian calls, and *birdsong, propose that speech sounds are perceived and distinguished by tacit knowledge of the vocal gestures used in their production (Liberman *et al.* 1967; Peterson and Jusczyk 1984; Williams and Nottebohm 1985). If this is the case, then the take-home message is that those who cannot perform cannot understand (for a similar conclusion see also *observational learning). This conclusion, however, should not be taken too orthodoxy and seriously; we can surely enjoy a melody even if we sing notoriously out of tune.

Selected associations: Habit, Insight, Mnemonics, Observational learning, Skill

¹The observation that appropriate performance requires an optimal level of arousal is called 'the Yerkes–Dodson Law' (Yerkes and Dodson 1908). As all the other 'laws' of behaviour, this is not a law but rather a pragmatic *generalization. The Yerkes–Dodson law should be kept in mind when an attempt is made to improve memory, either by behavioural methods (*mnemonics) or by drugs (*nootropics). Hence excessive training could result in a weaker memory (*spaced training), and taking stimulants before an exam may damage attention and performance. This was clearly realized by Maimonides (1180): 'the righteous way is the median measure'. The Yerkes–Dodson law is hence a special case of the 'Maimonides Law', itself a reformulation of the old wisdom that preaches for taking the golden path in life (*aurea mediocritas* in Latin).

²Shakespeare used 15 000 words, Milton 8000, but Italian Grand Opera enchanted audiences with 800 words only (Seashore and Eckerson 1940).

³But see Deese (1951) and Solomon and Turner (1962) for selected cases in which overt performance is not essential to obtain an instrumental response.

Persistence

1. Continual existence.

2. *The metaphysical 'persistence problem': Does the whole retain its original identity if all its parts are replaced over time?*

3. *The memory 'persistence problems': (a) How does biological memory persist over time in spite of cellular and molecular turnover? (b) How do items in memory persist in the brain over time in the absence of continual actualization?*

If we only abandon highly simplistic *metaphors of memory storage, such as 'cabinet files' or 'computer disks', 'persistence' (*per- + sistere*, Latin for 'to stand') becomes a prominent *enigma of memory research. As memory is the retention of acquired information over time, persistence is clearly its central attribute. Generally speaking, there is a family of 'persistence problems'. The *classic philosophical problem (definition 2 above) is also known in metaphysics as 'The Ship of Theseus': the ship of the mythical Greek hero was placed on display in Athens, and with time, parts of it were replaced, one by one, till none of the original remained. Is this still the same ship? (Plutarch, *Theseus* 1–2C AD/1914b; Kim and Sosa 1999). Metaphysics notwithstanding, this

discussion will focus primarily on the more pragmatic ‘persistence problems’, which relate directly to memory (definition 3a,b). First, how come that in spite of the notorious frailness of the individual components of the biological material in which the trace is registered, the *engram endures, sometimes for a lifetime? This is ‘the endurance issue’. Second, how do items in memory persist over those periods in which they are not expressed? This is ‘the dormancy issue’. Both issues seem to call for some engineering solutions. They also invoke, however, interesting conceptual and methodological issues. For example, although the ‘dormancy issue’ can be satisfied rather easily, its probable solution leads to the paradoxical conclusion that specific items in memory are not at all ‘stored’ in the common sense of the term.

Let’s turn to the ‘endurance issue’ first. Organisms are epitomes of the pre-Socratic saying ‘everything flows’ (*Panta Rei*, Guthrie 1962). Their constituents never experience a dull moment. Metabolic instability contributes to *plasticity and adaptation, hence to survival. Stability and completion, probably contrary to intuition, could promote atrophy: ‘How long/Do works endure? As long/As they are not completed./Since as long as they demand effort/They do not decay’ (Brecht 1929–33). In the mature organism, cells are constantly born and die (Alberts *et al.* 1994). Proteins within cells turnover within minutes to weeks, their actual life expectancy being determined by their type, location and history (Varshavsky 1992; Shi *et al.* 1996; Krupnick and Benovic 1998; Huh and Wentold 1999; Xu and Salpeter 1999). Furthermore, it is now evident that cells are born even in tissues that were traditionally considered to be stable throughout adult life; the brain is no exception (e.g. Kirn *et al.* 1994; Eriksson *et al.* 1998; Gould *et al.* 1999b). This situation raises the following questions.

1. *The molecular *level.* If an experience-dependent change is embodied in modified *synaptic components (e.g. **Aplysia*, *long-term potentiation), such as enzymes, *ion channels, and *receptors, which have a limited life span—how does the change outlast the limited life span of the proteins, and becomes immune to the consequences of molecular turnover? Without such resistance to the effect of turnover, no long-term memory would be possible. We should also worry about the persistence of post-translational modifications in protein molecules (*protein synthesis), because these modifications are unlikely to survive immediate re-modification by enzymes *in vivo* (e.g. Shuster *et al.* 1985). Multiple mechanistic solutions have been proposed to account for the immunity of use-dependent

neuronal changes to molecular turnover (Crick 1984b; Lisman 1985; Goelet *et al.* 1986; Buxbaum and Dudai 1989; Dudai 1989; Chain *et al.* 1999; Lisman and Fallon 1999). These proposals include molecular positive feedback loops, that, once activated, are shifted into a new stable state, and regenerate the molecular change again and again (*protein kinase); modulation of gene expression, that results in a new, stable expression pattern (*CREB, *immediate early genes, *protein synthesis); or a combination of the above.

2. *The synaptic to circuit levels.* If traces are subserved by synaptic connections, but these connections are continuously remodelled *in vivo*, how is the trace preserved (e.g. Bailey and Kandel 1993; Kleim *et al.* 1997)? At least in complex circuits, the problem is solvable by assuming distributed codes, in which no single node in the net is exclusive in representing a significant chunk of the message (*cell assembly, *homunculus, *model). The idea is thus that at any given moment, the trace is retained by a sufficiently large chunk of the circuit, so that it can tolerate elimination of part of the nodes. This property is termed ‘graceful degradation’.

Similarly, if newly-born neurons are incorporated into functional circuits in the adult brain (Kirn *et al.* 1994; Eriksson *et al.* 1998; Gould *et al.* 1999b; though see Rakic 2002), how does the perturbed circuitry sustain the old memory? Again, the conceptual difficulty is ameliorated by assuming a distributed code as above. Note that by explaining how hardware turnover does not undermine the persistence of the trace, we do not solve the metaphysical ‘Ship of Theseus’ identity problem. But at least we can explain how copies of the ship become available. That this is a partial answer is perfectly OK, because neuroscientists should definitely relegate some problems exclusively to philosophers.

And what about the ‘dormancy issue’? We have defined ‘*memory’ as the retention over time of experience-dependent *internal representations, and noted that representations are expected to be encoded in the spatiotemporal activity patterns of neuronal circuits. If this is the case, how is the memory retained in our brain when the representation is not actualized? Note that for the sake of argument, it does not really matter whether the representation is activated only in explicit *retrieval of the item in memory, which may occur very rarely, or also, probably more frequently, in the course of hypothetical, implicit ‘house-keeping’ routines in the brain.

The ‘dormancy issue’ can be rather easily resolved if we only switch the level of analysis and recall the difference between ‘*memory’ and neuronal and synaptic ‘storage’. What is retained over time is not the actual internal representation, but rather the capacity to

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generate it. The information is stored as ‘hardware’ alterations in the circuit that is capable of expressing that specific representation. For a memory to be retrieved, certain *cues are required to engage the circuit and generate the relevant activity pattern anew. In other words, memories are not retained ‘as is’, but reconstructed; what persists after learning is the change in the system that leads to their reconstruction in a certain way but not another; retrieval is not merely an expression of memory, but rather a condition for its mere existence. We can also conclude that the study of synapses and individual nerve cells is expected to generate information on the generic mechanisms of storage, whereas the study of active circuits suits better the search for the fingerprints of specific instances of memory.

Selected associations: Consolidation, Engram, False memory, Metaphor, Plasticity

Phase

- 1. Each of the distinct states in a *system or process.**
- 2. Stage of *development.**
- 3. Each of the distinct stages in a periodic process.**
- 4. Period.**

Phases (*phasis*, Greek for ‘appearance’) are distinct states in time and space. *Acquisition, *consolidation, retention, *retrieval, and *forgetting are all phases of memory. Some authors use the term ‘stage’ instead of phase to refer to these different periods of memory. ‘Phase’, however, is more suitable, because in addition to denoting a distinct state (definition 1), including in development (definition 2), it also connotes the recurrence of states (definition 3). This is important, because memory phases could recur. For example, items in memory shift back and forth between active (retrieved) and nonactive (stored) states (Lewis 1979; *persistence), and, upon retrieval, might even be reacquired and reconsolidated (Sara 2000; Nader *et al.* 2000). The expression (*performance), endurance, and susceptibility of the *engram to interference are common *criteria in the *taxonomy of memory phases. Our knowledge, however, about the number, nature, and transition of memory phases is a function not only of the particular memory system and memory task, but

also of the sophistication of the research *methods employed.

A particularly popular distinction of phases in a memory trace, once formed, is between ‘short-term’ memory (STM) and ‘long-term’ memory (LTM). That memory can be short or long lived, was probably noted by the first human who forgot the items on his daily hunting list but still remembered the way back to the cave. More formal distinctions emerged in experimental psychology. The results of both contemplation and experimentation gravitated toward *models of two to three memory phases. Here are a few examples. The German physiologist Exner concluded that ‘states of mind’ vanish, if not caught by *attention, within a few seconds, and dubbed these first few seconds in the life of a memory ‘elementary memory’ (cited in James 1890). James preferred the term ‘primary memory’, as opposed to ‘secondary memory’, or ‘memory proper’ which is ‘... the knowledge of a former state of mind after it has already dropped from consciousness’ (*ibid.*). Meumann (1913) advocated a three-phase distinction: immediate, temporary, and permanent. Hebb (1949), drawing from earlier data and concepts (Lorente de No 1938; Hilgard and Marquis 1940), returned to the basic two-phase type of models, and proposed a ‘dual trace’ hypothesis as well as mechanism: a reverberating, transient, unstable trace, that ‘carries the memory until the growth change is made’ and memory is stabilized in the long term. The introduction of the specific ‘short-term’ vs. ‘long-term’ terminology is accredited to Broadbent (1958; *attention), who spoke about ‘short-term’ and ‘long-term’ storage systems (see also Peterson and Peterson 1959).

The current terminology of elementary temporal memory phases refers to ‘sensory’, STM and LTM. Sensory memory of visual and auditory information is termed ‘iconic memory’ and ‘echoic memory’, respectively (Sperling 1960; Efron 1970). Sensory memory lasts for less than a second (Figure 54) to a few seconds at most. The duration of STM and LTM depends on whom you talk to. STM lasts for a few minutes for neurologists (Sacktor and Mayeux 1995), up to a few hours for cellular neurobiologists (Goelet *et al.* 1986; Dudai 1989, 1997b). LTM, according to this coarse classification, is for neurologists memory that lasts for more than a few minutes, and for neurobiologists, by convention, memory that lasts for more than 24 h. In what is regarded as a cellular analogue of learning, *long-term potentiation in a brain slice, the limits of ‘long term’ are pushed backwards to 1–3 h only. Similarly, consolidation of LTM could last anything from a few hours (*cellular consolidation’, which requires *protein

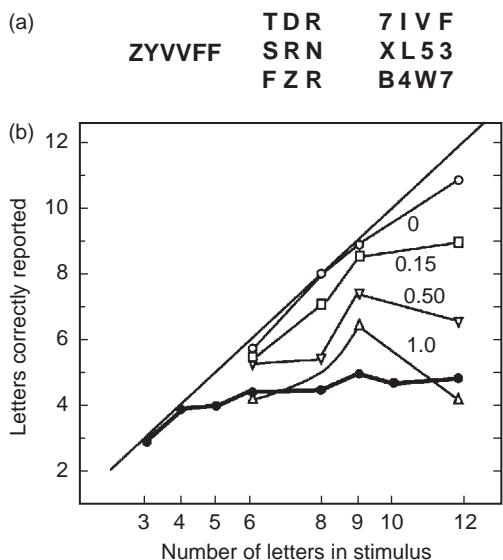


Fig. 54 The shortest memory phase. In a *classic experiment, Sperling (1960) presented a group of *subjects with nonsense *stimuli composed of letters (or letters and numbers) in various arrangements (a). The stimuli were each presented for 50 ms only. The subjects were requested to report all the items in each stimulus immediately afterwards. When the number of items was higher than four, the subjects never reported all the items correctly (heavy curve in b). The subjects were then presented again with stimuli consisting of letters in three symmetric rows (a, middle and left). They were told that a tone would come immediately after the stimulus, and that this tone would be either high, middle, or low. If high, only the upper row should be reported; if middle, only the middle row; if low, only the bottom row. Under this *cued, partial report mode, the amount of information reported was two to three times larger than in the whole report mode. The availability of this information declined within less than a second (b; the straight diagonal is the theoretical curve; the numbers on the other curves are the onset of the tone in seconds after the visual stimulus). This short-lived memory is called 'iconic'.

synthesis) to weeks or longer ('system consolidation', Dudai 1996; *hippocampus). Behavioural, *neurogenetic, pharmacological, and cellular analysis unveils additional, 'intermediate' memory phases, between 'short' and 'long' (Rosenzweig *et al.* 1993; Tully *et al.* 1994; Winder *et al.* 1998; Wüstenberg *et al.* 1998; Sutton *et al.* 2001). In *real-life, 'long' itself is evidently not an homogeneous phase, as some LTM are irretrievable already within a few days, whereas others linger for many years, up to a lifetime (e.g. EBT 1923).

Different memory systems (*taxonony) may have different types of temporal phases, probably moulded in evolution to comply with the specific functional

demands imposed on the particular system. For example, in mammals, *declarative memory is characterized by multiple LTM phases, ranging from weeks (hippocampal-dependent) to years (hippocampal independent), whereas nondeclarative memory appears to be consolidated faster (McClelland *et al.* 1995; Shadmehr and Brashers-Krug 1997a). Such heterogeneity probably stems from the different properties of the particular circuits that subserve the different memory systems, but not from different building blocks at the molecular *level.

Why are there short- and long-term phases of memory? And are these phases serial or parallel? The favoured answers to the first question are three: (a) transient STM phase(s) provide the organism with the ability to hold information indispensable for *ad hoc* tasks but superfluous in the long run (in this respect, 'short-term' fulfils the role of '*working memory'); (b) transient STM phase(s) provide the organism with a better opportunity to evaluate, prune, classify, and rearrange information before the decision is taken to store it 'permanently' (McClelland *et al.* 1995); (c) there are phases because biological memory is incapable of operating otherwise, due to the structural and functional constraints of the machinery.¹ As to the second question, namely are the short- and the long-term phases of memory serial or parallel, information from both cellular and system studies suggest that short- and longer-term memory could unfold in parallel; further, there are situations in which LTM is intact but STM is faulty (Shallice and Warrington 1970; McCarthy and Warrington 1990; Emptage and Carew 1993).

Finally, all learning and memory processes could themselves be regarded as a phases in the overall continuous process of the development of the organism. Recent findings in cellular and molecular biology support such view, which has been promoted well before promoters, *immediate early genes and transcription factors were even dreamt of: 'Growth and learning are one continuous process, to the earlier phases of which we give the one name, and to the later ... we give the other' (Holt 1931).

Selected associations: Acquisition, Consolidation, Retrieval, System, Taxonomy

¹The reader who is already familiar with *paradigms will recognize in possibilities *a* and *b* the Panglossian paradigm, and in *c* an alternative.

Phrenology

A school in psychology that held the following set of premises:

- (a) the mind is composed of distinct mental faculties;
- (b) each faculty resides in a specific brain organ;
- (c) individuals are innately predisposed to different proficiencies in different mental faculties;
- (d) the more developed the mental faculty, the larger the size of the brain organ;
- (e) the size of brain organs is manifested in the external configuration of the skull.

Phrenology (*phren*, Greek for ‘mind’, *-logos*, ‘reasoning’) was born toward the end of the eighteenth century. It is considered pseudoscience because of postulate *e* above. This postulate is ‘craniometry’—the belief that one can determine a mental profile from the shape of the skull. The point is that while craniometry is indeed a preposterous claim, the rest of phrenology’s assumptions do deserve proper attention. These are the modularity of mind (*a* above), the localization of function in the brain (*b*), the individual variability in innately predisposed potential (*c*), and the dependence of function on neural space (*d*). All these postulates are echoed in contemporary neuroscience. Assumption *a*, with or without the rest but in the absence of *e*, is ‘neophrenology’. Many neuroscientists speak ‘neophrenologish’ without even being aware of it.

The founder of phrenology was the prominent neuroanatomist Gall (Germany 1758–France 1828; Temkin 1947). Gall himself was not happy with the term ‘phrenology’, which was introduced by his co-worker, Spurzheim. But Gall never came up with a catchy term as an alternative. He developed his views of brain and mental function against the background of a variety of earlier theories. Quite a number of these theories considered mental function to be subserved by fluids (humours), in amazing disrespect to the tissue of the brain itself. Many also regarded the mind a unitary whole, unresponsive to physical dissection. Gall considered the available data, added his own observations, and spiced it all with the influence of the contemporary practice of ‘physiognomy’, the art of judging character and disposition from the features of face and body. Phrenology was the outcome. Gall’s ideas arouse opposition among some and enthusiasm among others.

An example of the first was the decisive response by Emperor Francis I, who banished Gall from Vienna: ‘This doctrine concerning the head, which is taken about with enthusiasm will perhaps cause a few to lose their heads and it leads also to materialism, therefore is opposed to the first principles of morals and religion’ (cited in Greenblatt 1995). An epitome of the more enthusiastic reaction was provided, years later, by the poet Walt Whitman, who, swept by admiration for the new science, subjected his own ‘splendid head’ (*sic.*) to the test of phrenology (Davies 1971).

Phrenology as it became known in the nineteenth century was mostly Spurzheim’s modification of Gall’s conceptual framework. Gall originally distinguished 27 faculties. These included, among others, multiple memory systems (*taxonony): memory for facts, memory for persons, and memory for words (Temkin 1947). Some of Galls’ proposed faculties pointed to unflattering facets of human nature: the instinct of killing, the desire to possess, pride, and vanity. Spurzheim, while expanding the list of faculties, got rid of the more annoying traits. He also emphasized the ability to improve ‘deficient’ faculties by training.

We will get a better appreciation of phrenology if we evaluate its premises in the context of present knowledge:

1. *The modularity of mind.* The basic assumption here is that the mind is a collection of different kinds of mental faculties. This view is also known as ‘faculty psychology’ (Fodor 1983). In principle, a ‘module’ may refer to a general type of mental function such as *attention, *perception, or memory, irrespective of the specific mental content or behavioural task. It could alternatively refer to a specific behavioural programme, e.g. *imprinting, or a specific mental *skill, e.g. language, musicality, or sociability, each of which requires attention, perception, memory, etc. The original phrenological maps listed mostly specific aptitudes rather than general mental processes that cut across skills (Temkin 1947). This view is shared by modern versions of the modularity of mind (Rozin 1976; Fodor 1983; Gardner 1993). The mere existence of mental modules could make sense from the point of view of the evolution, as different phylogenetic pressures might have had advanced distinct mental capacities, to offer specific solutions to specific survival needs. It has furthermore been suggested that the progress in evolution toward more intelligent organisms involves enhanced interaction among different modules (Rozin 1976; see also ‘central systems’ in Fodor 1983). Neuropsychological analysis of brain-damaged patients with highly circumscribed behavioural deficits has been used as

evidence for the existence of highly specific cognitive modules (Damasio 1990; Baynes *et al.* 1998). However, the relevance of the breakdown unveiled by pathology to the normal divisions of the mind, as well as its relevance to the modules/central processors distinction, awaits clarification. Another central question is to what degree are different modules innate (Karmiloff-Smith 1994; Spelke 1994; Markson and Bloom 1997; Paterson *et al.* 1999).

2. The localization of function. Whereas the modularity of mind supposes *mental organs*, the localization of function in brain assumes *neural organs*. The latter assumption is 'organology'. Note that modularity of mind does not entail organology. It is legitimate to

assume mental modules while displaying complete indifference to their physical substrates. It is also possible to envisage a model in which the whole brain is induced, either spontaneously or by external *stimuli, to produce distinct mental modules at need. However, given the modularity of mind, some organology becomes a logical possibility. Phrenology prompted systematic attempts to localize brain function, including *engrams, by relying on the effect of disease and injury (Brazier 1988; Finger 1994; *method). We are now experiencing a new wave of this search, this time using *functional neuroimaging. The pitfall that the 'new organologists' (Marshall 1980) must avoid is the tendency to adhere to the descriptive levels,

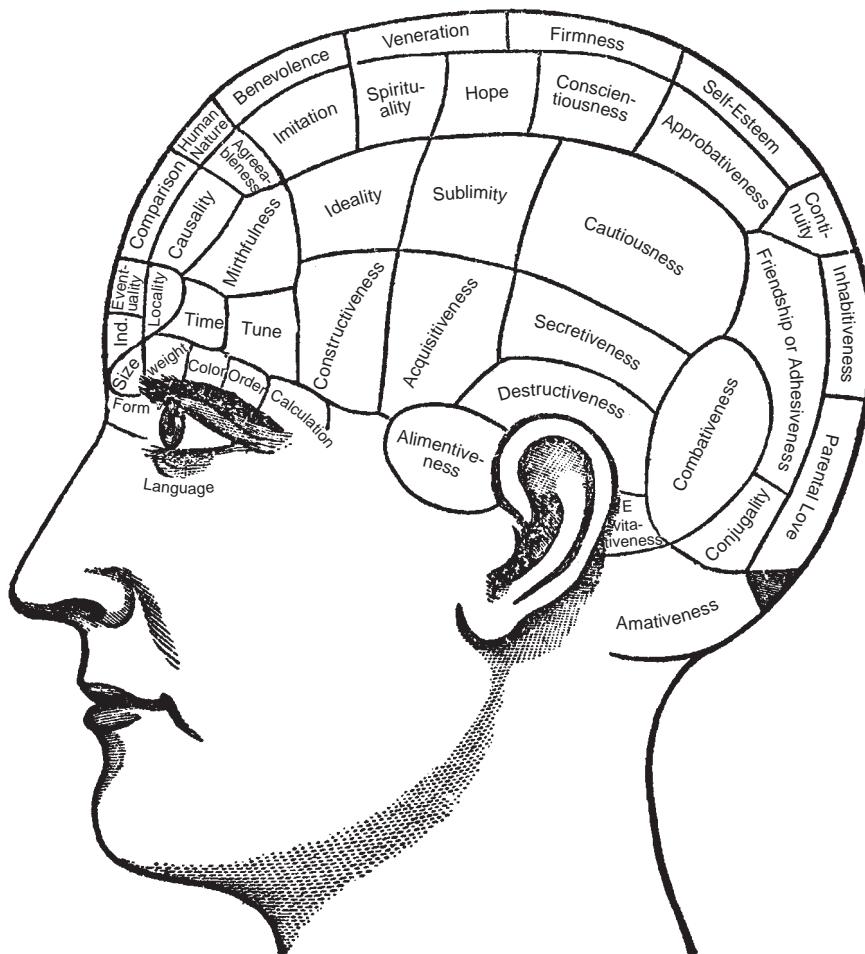


Fig. 55 A phrenological map, delineating the location of 'mental organs'. Multiple versions of such maps have been issued throughout the nineteenth century. They usually depicted memory not as a unitary faculty but as multiple *systems (e.g. memory for words, memory for facts, memory for persons), or as an implied component of other faculties (e.g. language). (Reproduced from Davies 1971.)

Phrenology

rather than create a *model that will account for what the different organs and circuits compute and represent. Also, much as the localization of function is an attempt to dissect the brain into parts, it should not be forgotten that *in situ* these parts function together. The brain is not an homogeneous porridge, but also not a random collection of individual organs.

3. Individual variability in the innate potential. Genes influence human behaviour (e.g. McClearn *et al.* 1997; *a priori, *neurogenetics). But each distinct behavioural trait depends on many genes, most of which are pleiotropic (i.e. contribute to more than one phenotype). We also know that the structure and function of cognitive modules depend much on how the brain interacts with the environment (Sadato *et al.* 1996; Paterson *et al.* 1999; *development). Our current view on how much is nature and how much nurture depends on which trait is analysed and how one construes the data (Rose 1995a; Gelernter *et al.* 1997; Leboyer *et al.* 1998; Noble *et al.* 1998; Flint 1999).

4. The dependence of function on neural space. The idea that brain space is correlated with *performance is not considered far-fetched any more (e.g. *birdsong). Consider, for example, the recent report that professional taxi drivers, who earn their living from navigation in urban streets, have a larger *hippocampus, a brain area critical for spatial memory (Maguire *et al.* 2000). But of course, nobody claims that such an alteration creates bumps on the skull.

5. Craniometry. Neither the shape of the skull, nor the overall size of the healthy brain, are indicative of mental power (Gould 1981). Gall himself objected to being called a craniologist, claiming that the focus of his research is the brain, not the skull. Therefore, despite the failure of his mental diagnostic methods, he would have probably been proud of neophrenology.

Selected associations: Engram, Homo sapiens, Red herring, Zeitgeist

3. The generation, modification, or selection by the brain of *internal representations of future actions and their anticipated consequences.

'It is a poor sort of memory that only works backwards', said the White Queen to Alice (Carroll 1865). But mocking at the memory of the visitor to Wonderland was rather unjustified. For even without pushing modern physics to its limits, we do have a kind of 'memory of the future' (Fuster 1992). This is planning.¹ This capability should not be belittled: in spite of its alleged reputation, even Destiny, speaking through the Delphic oracle, only rarely dared to give clear predictions of the future (Fontenrose 1978).

'Planning' originally referred to the design of ground plans for the purpose of planting, itself a word derived from *planta*, Latin for 'sole of the foot'. Definition 1 is the generic one; Definition 2 assumes volition.² This is what people commonly have in mind in considering planning. The distinction between definitions 1 and 2 touches philosophical issues that exceed the scope of this brief discussion; suffice it to note that definition 2 applies to living organisms (myths and deities notwithstanding), yet in the future will fit smart robots as well. Definition 3 rephrases definition 1 while focusing on the *reduced concept of internal representations, which is central to discussion of *learning and *memory in this book.

Planning could be manifested in a gamut of markedly different behaviours, ranging from fast motor actions to long-term strategic plots. It is therefore methodologically useful to classify it (*taxonomy), using *criteria such as the behavioural domain, complexity, timetable of the anticipated action, flexibility, and the trigger for the plan.

1. Behavioural domain. An elementary dichotomy distinguishes motor planning, referring to motor acts and their anticipated consequences, from cognitive planning, referring to cognitive narratives and their mental, behavioural, and social consequences. Multiple taxonomies are possible within the behavioural domain *dimension. Related dimensions are the complexity of the planned goal, and the explicitness of planning (*declarative memory).

2. Time to attain the goal. From what has been said above it becomes apparent that different planning acts could refer to very different temporal spans, ranging from seconds on the one hand to years on the other. Compare, for example, a tennis player planning a tricky serve vs. a college student planning a career. In considering the shortest time spans, two issues are noteworthy. One is the automaticity of the plan. This will be further discussed in 3 below. The other is the transformation from the present to the future. As the

Planning

- 1. The design of a *method or programme for achieving a goal.**
- 2. The volitional organization ahead of time of goal-oriented behaviour.**

cognitive present in not infinitesimally small, plans of brief motor acts raise the question what is 'present' and what is 'future'. Based on psychophysical and physiological data, 'present time' appears to be in the order of ~100 ms (this estimate is task dependent; e.g. Thorpe *et al.* 1996; Helenius *et al.* 1998; *percept). In motor tasks such as orienting and reaching, neuronal activity is detected in the brain several hundreds of milliseconds prior to the actual execution of the act (Georgopoulos *et al.* 1989). This could therefore be construed as a candidate neuronal correlate of *bona fide* elementary planning (Georgopoulos 1994; Andersen *et al.* 1997; Flanagan and Wing 1997). Within this narrow temporal window, there is ample time to modify the plan by intervening with the activity of the circuit during the planning phase (Groh *et al.* 1997; *method).

3. Innateness and flexibility. But how much of a short-lived motor plan is really a plan, rather than the deterministic unfolding of an automatic response? Even the most sophisticated, imaginative cognitive plans are expected to depend to some degree on **a priori* constraints on our perceptual and cognitive faculties, which lead to automaticity of certain elements in the behaviour. Yet clearly, some plans are more constrained by innate predispositions than others. It is phylogenetically advantageous to limit the anticipated alternative outcomes of fast motor plans that are essential for survival, by relying on innately encoded internal representations that can be selected within fraction of a second. The most elementary brief motor plans could be said to differ from elementary reflexive responses in that the former include a component of active selection and decision making by the **system* (definition 2), whereas the latter are solely deterministic reaction. The reflexive response could still be fine-tuned by experience, but the action pattern is a given once triggered. This distinction between 'reflexive' and 'nonreflexive' is convenient yet shaky; what appears as a 'voluntary' planned act might still be an intricate reflex shaped by complex input (Luria 1962).

4. Trigger. Plans ranging from very simple to rather complex ones (e.g. ambushing a prey) could be triggered by a single 'release **stimulus*' (Lorenz 1981). In contrast, complex cognitive plans may be initiated by **retrieved* or endogenously generated representations.

In spite of their immense heterogeneity, in all mental plans the internal representations are expected to include a representation of a hierarchical set of sequential actions and of the anticipated outcome (Miller *et al.* 1960). These organized sets of actions, termed 'schemas' (Bartlett 1932), draw from past experience—be it encoded in innate or learned responses or both. In other

words, although plans refer to the future, they always draw from either the species' or the individual's past.

Naturally, the investigation of planning in laboratory setting is limited to tasks that are completed within a few minutes or a few hours at most. Systems that are particularly useful for the cellular and system analysis of elementary planning in the **monkey brain* involve limb, head, or eye movement (e.g. Georgopoulos 1994; Thach 1996; Andersen *et al.* 1997; Flanagan and Wing 1997; Zhang and Barash 2000). These studies focus, depending on the specific task, on the role of motor and posterior parietal **cerebral cortex*, as well as the **cerebellum*. Relevant to this area of research is also the investigation of the role of neuromodulatory systems (**neurotransmitter*, **dopamine*) in the selection among alternative response patterns.

In the study of planning in humans, the tests commonly involve puzzles that could be solved by mentally testing sequences of moves ahead of time, such as the Tower of London task (Shallice 1982; Figure 56). In this task, three beads, one red, one green, and one blue, have to be moved in a minimal number of steps from the initial configuration on three sticks of unequal length to the designated goal position. The problems vary in complexity, from two to five moves. More recent versions of the task involve the manipulation of coloured shapes on a computer screen (e.g. Dagher *et al.* 1999). Other types of tasks that tap into human planning involve simulation of **real-life* situations, such as financial planning (Goel *et al.* 1997). All in all, the combined data from neuropsychological and **functional neuroimaging* studies in patients with circumscribed brain lesions and in normal volunteers, implicate frontal cortical areas in the multiple aspects of cognitive planning (Luria 1962; Shallice 1982, 1988; Fuster 1995a; Goel *et al.* 1997; Owen 1997; Bechara *et al.* 1998; Dagher *et al.* 1999; Figure 56; for an example of **modelling* of planning in cortex, see Dehaene and Changeux 1997). This cortex is 'where the past and future meet' (Fuster 1995) to integrate past experiences, both declarative and nondeclarative (Bechara *et al.* 1997), in planning ahead.

Selected associations: A Priori, Algorithm, Dimension, Prospective memory, Working memory

¹A related type of memory of the future is **prospective memory*, which is discussed separately.

²Volition refers in this context to autonomous decision making by a **system* regardless of its state of **conscious awareness*. Hence 'planning' according to definition 2 could either be **declarative* or *nondeclarative*.

Planning

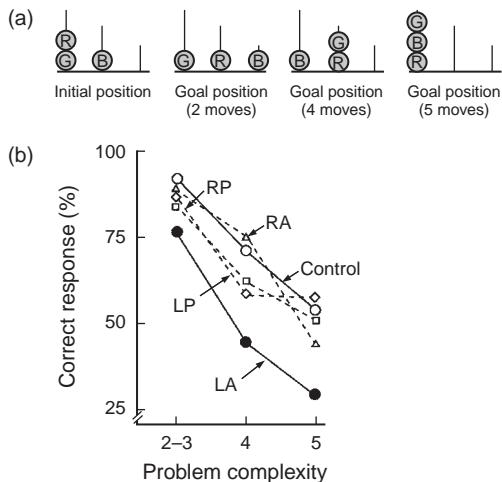


Fig. 56 The Tower of London task is used to test planning because it is possible to solve it by mentally testing sequences of moves ahead of time, before actually executing them. (a) In the original version (Shallice 1982), three beads, one red, one green, and one blue, have to be moved from the initial configuration on three sticks of unequal length to the designated goal position in a minimal number of steps. The problems vary in their complexity, from two moves to five moves. More recent versions of the task involve the manipulation of coloured shapes on the computer screen rather than beads and sticks (e.g. Dagher *et al.* 1999). (b) The *performance on the task of *control, healthy volunteers and of brain lesioned patients, plotted as the percentage correct on the first attempt to solve the problem vs. the complexity of the problem. LA, left anterior brain lesion; LP, left posterior lesion; RA, right anterior lesion; RP, right posterior lesion. The patients with left anterior brain lesions, involving the left frontal lobe, were dramatically impaired. (Adapted from Shallice 1982).

Plasticity

1. The ability to undergo modification without immediate relaxation or disintegration.
2. A lasting shift in the set point of a *homeostatic *system.

Plasticity is probably the most widely used term in modern neurobiology, clearly not to be recommended as an effective keyword in literature searches in this field. In its rudimentary form, the notion of plasticity as a vehicle for memory appears already in pre-scientific times: Socrates depicted memory as an impression on wax tablet, too hard in slow learners and oversoft in the forgetful ones (Plato, *Theaetetus*). It is likely that this and similar *metaphors were used much earlier. In the scientific discipline of memory research, 'plasticity' was

formally born at least twice. James (1890) brought it up in his *classic chapter on *habit: 'Plasticity... means the possession of a structure weak enough to yield to an influence, but strong enough not to yield all at once... Organic matter, especially nervous tissue, seems endowed with a very extraordinary degree of plasticity of this sort... the phenomena of habit in living beings are due to the plasticity of the organic materials of which their bodies are composed'. Half a century later, Konorski (1948) listed plasticity as one of the two metaprinciples that underlie the operation of the central nervous system. These principles are excitability (later renamed 'reactivity', Konorski 1967), which is the capacity to be activated by stimulation of receptive organs, and plasticity, the capacity to change reactive properties as a result of successive activation.

At about the same time, Hebb (1949) proposed how use-dependent *synaptic growth can subserve learning (*algorithm, *cell assembly), and Monne (1949) suggested that *protein synthesis allows for lasting neural remodelling in the formation of the *engram.¹ These proposals are tenets of neurobiology to date. The current zeitgeist is that *stimulus-induced regulation of *intracellular signal transduction cascades, which culminates in the modulation of gene expression (*immediate early genes) and hence in *de novo* protein synthesis, embodies use-dependent neuronal plasticity; and that much of this action takes place in the synapse. The relation of all this to memory is encapsulated in the *synaptic plasticity and memory hypothesis*: 'Activity-dependent synaptic plasticity is induced at appropriate synapses during memory formation, and is both necessary and sufficient for the information storage underlying the type of memory mediated by the brain area in which that plasticity is observed' (Martin *et al.* 2000).

This zeitgeist deserves a caveat or two. But they will follow later. First, it is useful to consider briefly neural plasticity at multiple *levels of function and analysis. These are the theory level, the algorithmic level, and the implementational, or hardware level.

1. *The theory level.* In the theoretical world of all-possible organisms, it is not a given that adult individuals will show neural plasticity.² That in real-life plasticity is the rule rather than the exception, is commonly attributed to the selective pressures of biological evolution. This means that the gain of adult plasticity outweighs the loss. The gain is clear: the ability to fine-tune the *a priori genetic adaptations, and hence survive in an even larger spectrum of mutable habitats. To this one could add the capacity to utilize only part of the potential gene products at one time, and also to amend injured cells and tissues. The loss is the metabolic

price paid for the production of the plasticity machinery, and the risk that plasticity will go astray, resulting in malignancy or degeneration (indeed some authors consider *dementia to be a catastrophe of plasticity, e.g. Mesulam 1999). Another type of explanation, though, is that adult organisms are plastic because of built-in properties of biological material, and not because plasticity was selected for *per se*.³ This could be due to the ephemeral nature of the stuff of cells, plasticity being the by-product of the ability to replace continuously cellular components and correct mistakes in their production; or to opportunistic capitalization by evolution on processes that permit multicellular organisms to grow postnatally.

The above considerations refer to the overall principle of 'adapt your behaviour to the world'. How is this achieved? The system follows a few computational rules, which refer to the probability of co-occurrence of events. It is methodologically legitimate to describe these rules as though they have a teleological rationale: if events tend to *coincide in time or place, then they are related, one can predict the other, and their *internal representations deserve to be *associated. If an event follows action, then this event has a significant probability to be caused by the action, and again, this apparent causality deserves to be encoded.⁴ These rules guide *classical conditioning and *instrumental conditioning, respectively, yet are relevant to other learning situations as well.

2. The algorithmic level. The synaptic postulate of Hebb (1949), noted above, which proposes that synaptic connections are *reinforced by coincident activity of pre- and postsynaptic terminals, is the one most discussed in the literature on neural and behavioural plasticity [*algorithm, *long-term potentiation (LTP)]. Additional algorithms at the circuit and system levels are illustrated in *algorithm, *dopamine, *instrumental learning.

3. The hardware level. How are the neural algorithms implemented? This is done by multiple types of cellular devices, which include *receptors, *ion channels, *neurotransmitter release machinery, *intracellular signal transduction cascades, *protein kinases, cytoskeletal elements, *immediate and *late response gene products.⁵ Among these are *coincidence detectors that operate on a variety of time-scales, and growth regulators. Each of these molecules is itself plastic. Pioneering work in identifying molecules of neural plasticity and their relevance to simple memory has been done on **Aplysia* (Kandel 1976; Kandel and Schwartz 1982). Other systems, capable of *LTP, *habituation, *sensitization, and *classical conditioning, are also used extensively.

A recurrent issue in the field of neural plasticity is whether the same cellular machinery that subserves development also subserves learning and memory. Some authors emphasize the similarity (e.g. Martin and Kandel 1996), others the differences (e.g. Constantine-Paton and Cline 1998). It is noteworthy that developmental plasticity, in contradiction to long-held dogma, continues to function in the nervous system throughout life (*birdsong, *hippocampus; interestingly, simple physical activity could activate it; van Praag *et al.* 1999). Even if it does stop, it manages to affect markedly the *capacity of later use-dependent plasticity in the adult (e.g. Martin *et al.* 1991; Carvell and Simons 1996; Rosenzweig and Bennett 1996; Sylva 1997; Crair *et al.* 1998). Another point to remember is that components of the plasticity machinery in neurons are shared by non-neuronal tissues throughout development and in adulthood. This reinforces the notion, mentioned above, that plasticity is a universal biological property; it also supports, by the way, the conviction that cellular plasticity alone will not explain *memory.

The fact that the molecular biology of learning has become predominantly the molecular biology of synaptic plasticity, is an inevitable consequence of the *reductive approach to learning. The remarkable success in deciphering the mechanisms of synaptic plasticity should not, however, distract us from noting some caveats. First, it now becomes evident that the focus on the synapse has led to unjustified neglect of cell-wide processes and mechanisms (Frey and Morris 1997; Casadio *et al.* 1999; Dudai and Morris 2000). Second, the role of glia cells is still an *enigma, and breakthroughs should be expected on this frontier (Araque *et al.* 1999; Ullian *et al.* 2001). And third, most importantly, the crucial issue is whether neural plasticity, be it synaptic or cell-wide or both, is both *necessary* and *sufficient* (*criterion) for learning and memory. Ample evidence, much of which is cited in this book, indicates that neural plasticity is necessary for learning and memory; but a careful survey of the literature shows that few data currently support the notion that synaptic plasticity is sufficient for learning and memory to take place (Martin *et al.* 2000). To prove sufficiency, one should be able to induce artificially controlled plasticity in identified synapses that implement the specific, targeted internal representations. This is not easy, as it requires identification of circuits that encode specific internal representations, and of synapses that are critically important in these circuits. Examples of attempts to follow this line of research are mentioned in *method. Note that even if at the end of the day experiments of this type will indeed show that use-dependent

Plasticity

synaptic plasticity is sufficient to register a specific memory, it will still remain to be determined how learning and memory processes are initiated *in vivo*; is it a bottom-up process, from the synaptic to higher levels, or is it a top-down process, in which higher-level activity initiates the plastic change in the appropriate synapses.

Selected associations: Development, Metaplasticity, Persistence, Reduction, Synapse

¹Both Hebb (1949) and Monne (1949) drew, naturally, upon the work of others. The role of synaptic growth in learning has been discussed earlier (e.g. Cason 1925; *development). The precedents of Hebb's synaptic postulate are discussed in *algorithm. The proposal in Monne's paper was based on the pioneering work of contemporary research groups in cellular and chemical biology (e.g. Hamberger and Hyden 1945).

²In this discussion, plasticity (definitions 1 and 2), unless otherwise indicated, refers to neural plasticity. But most early authors, such as James (1890) and Semon (1904), aptly emphasized that plasticity, whether called by that name or not, is a universal property of the biological material.

³This argument fits the anti-Panglossian paradigm, see *paradigm.

⁴No assumptions are being made here concerning *conscious awareness of this potential causality, or the validity of the assumed causality. See also Macphail (1996) and Heyes and Huber (2000).

⁵This is an appropriate point to note that many authors distinguish functional from structural plasticity. The truth is that 'functional' plasticity also involves modification in some hardware component(s) of the system, hence is structural. It is all a matter of the level of *reduction. What those who speak about structural plasticity mean, is morphological plasticity: those structural changes in the tissues that are detectable down to the level of electron microscopy (see example in *development, Figure 25, p. 81).

(Storms 1958; see also Wohlgemuth 1913; Williams 1953). An experiment by Storms (1958) illustrates what was meant. Storms asked a group of students to study a list of words, *A*, which elicit high-frequency associations, such as 'eagle' (which typically elicits 'bird') or 'hill' ('mountain').¹ He then presented the students with another list of words, *B*, which included the words that are high-frequency responses to the words in *A*, but themselves do not ordinarily elicit words in *A*. For example, although 'eagle' elicits the response 'bird', the converse is not usually the case. Storms found that the production of words in *A* as responses to words in *B* was significantly higher when list *A* was encountered just previously. Cofer (1960) termed this use-dependent augmentation of associative strength as 'priming of associations'.

Over the years the use of the term 'priming' has been extended to include additional protocols and meanings. The current major *taxonomies of priming are based on two types of interrelated distinctions: 'direct' vs. 'indirect', and 'perceptual' vs. 'conceptual' (Richardson-Klavehn and Bjork 1988; Roediger and McDermott 1993). In direct priming, also termed '*repetition priming*', the item presented in the training ('study') *phase is identical to, or is composed of fragments of, the item to be produced in the test phase. In indirect priming, also termed '*associative priming*', the item presented in the study phase is associated with the item to be produced in the test but not identical with it. Direct priming is mostly 'perceptual'; it is modality specific and relatively independent of the meaning (semantics) of the item. It may last for many weeks. Indirect priming, which persists for much shorter periods, is mostly 'conceptual' or 'semantic'; it is dependent on the meaning of the item, and relatively independent of the sensory modality.

Repetition priming is where the frequency, speed, or accuracy of response is facilitated as a consequence of prior exposure to a particular stimulus (Tulving and Schacter 1990; Ochsner *et al.* 1994; Wiggs and Martin 1998). The most commonly used repetition priming *assays include 'perceptual identification', 'word completion', and 'lexical decision' tasks (Schacter 1987; Roediger and McDermott 1993). On a typical *perceptual identification* task (Jacoby and Dallas 1981), the subject is exposed on the study phase to series of words. Each word is flashed on the screen for a fraction of a second only. In the test phase, series or lists of words, including both the previously presented and 'new' words, are presented and the subject is requested to identify them. Priming is reflected in the increase in the accuracy or in the speed of identification of the

Priming

- 1. The non-*conscious modulation of the processing, *retrieval or production of a mental item by prior exposure to specific information on that item or on items associated with it.**
- 2. The presentation of a *stimulus or the induction of a change that prepares the *system for functioning.**

'Priming' in the current memory literature almost always refers to a specific protocol or type of memory (definition 1) rather than to the more general concept (definition 2). This contemporary use was introduced by Cofer (1960), on the basis of earlier observations

previously presented words compared to the ‘new’ words. On the *word completion* task (Roediger *et al.* 1992), the subject is presented in the test with either word stems (e.g. AIR...), or word fragments (e.g. _R_ _I _ G), and instructed to complete them with the first word that comes to mind; priming is manifested as the preference for words that have been presented on the study phase (e.g. ‘AIRCRAFT’, ‘PRIMING’). On the *lexical decision* task (Meyer and Schvaneveldt 1971), the subject is required to state whether or not a particular letter string is a legal word, for example, ARDUBOK, BELABOR, GARGOZOM (the middle one is a word, the two others are pseudowords, unless psychologists or molecular biologists have invented something since this has been written). Priming in this case is reflected in the decreased latency to make the decision on the second presentation of the letter string relative to the first. The examples above refer to visual presentation of verbal material; similar tasks could be performed with other sensory modalities and nonverbal material.

Commonly used *associative priming* assays include word associations, category production, and general knowledge priming tasks. On the *word association* task (Storms 1958; Shimamura and Squire 1984), a word presented in the study session results in preference for an associated word, e.g. stem–flower; the study by Storm (1958), mentioned above, is but an example. On the *category production* task (Srinivas and Roediger 1990; Gabrieli *et al.* 1995), the subject is presented with items from a certain category (e.g. animals), and later asked to produce as many as possible category exemplars (e.g. ‘lion’, ‘elephant’); priming is manifested by a *bias toward production of the previously studied category exemplars. On the *general knowledge* task (Blaxton 1989; Vaidya *et al.* 1996), presentation of a word will enhance the production of an answer to trivia questions related to that word; for example, presentation of the word ‘Jerusalem’ in the study phase, will facilitate the production of the correct answer to the question ‘What is the capital of Israel?’

Priming is a hot topic in research on human memory. There are four main reasons for this popularity. First, priming using verbal material is useful in the analysis of the perception, processing, and production of language. Second, priming, similarly to *transfer, provides a window to the processes and mechanisms of retrieval and to their dependence on the conditions and processes of encoding in *acquisition. Third, priming, a non*declarative memory, illuminates distinctions among memory systems (*taxonomy; Squire *et al.* 1993). And fourth, priming protocols are used to tap residual memory in *amnestic patients. It was noted

almost a century ago that past information in ‘global’ amnesia could sometimes be recovered if the patient is provided with clues to that information (see in Williams 1953). It is now evident that perceptual priming, and possibly some capabilities of conceptual priming, are preserved in amnesics (Warrington and Weiskrantz 1968; Backer Cave and Squire 1992; Schacter and Buckner 1998; for conceptual priming that is impaired in amnesics, see Vaidya *et al.* 1996). As ‘global’ amnesia is known to occur as a consequence of damage to structures in the medial temporal lobe and the diencephalon, it follows that perceptual priming is not critically dependent upon the integrity of these areas. The introduction of noninvasive *functional neuroimaging has expended tremendously the ability to identify brain regions that subserve priming (Schacter and Buckner 1998; Henson *et al.* 2000; Yasuno *et al.* 2000). In a nutshell, perceptual priming is correlated with reduced neuronal activation in modality specific neo*cortex, especially in higher-level processing areas. Conceptual priming is correlated with a similar change in multiple neocortical areas, including the prefrontal cortex. At the cellular level, repetition priming is thought to be correlated with a *decrease* in neuronal response in cortex with repeated stimulus presentation (‘repetition suppression’, Desimone 1996).² However, the possibility that in some circuits repetition priming involves experience-dependent synaptic *facilitation*, e.g. *long-term potentiation, should not be neglected (Milner 1997; for a candidate mechanism, see Frey and Morris 1997).

It is important to re-emphasize that ‘priming’ covers heterogeneous processes, which are expected to be subserved by multiple circuits and mechanisms in the brain.³ The common denominator to all these processes is the nonconscious use-dependent facilitation of the processing and retrieval of an item.⁴ *Sensitization also facilitates future processing, retrieval, and *performance, but is nonspecific, whereas priming depends on the specificity of the item(s) presented in the study phase. In some of its properties, such as the independence of *conscious awareness, priming resembles *habit and *skill. In others, it resembles declarative memory: it provides the brain with specific, discriminative, and precise information about events in the world. Tulving (1983) speculated that in performing priming experiments, we tap into memory capabilities that had emerged in phylogenesis after procedural memory systems but before declarative memory, and have played an important part in the life of early hominids (**Homo*). Were those ancestors of ours knowledgeable about the world but not consciously aware of it the way

Prospective memory

we are? Were they a bit like global amnesics? Even if the role of priming early in the evolution of our species remains a mystery, analysis of the distinction between brain systems that subserve priming and those that subserve declarative knowledge might provide us with clues to the identity of brain circuits that subserve consciousness.

Selected associations: Acquisition, Retrieval, Skill, Taxonomy, Transfer

¹For another *classic example of the use of word associations in unveiling intriguing properties of memory, see *false memory.

²This finding is also discussed in the context of *habituation.

³This raises the question whether priming is a memory system, or a property that cuts across different memory systems. The *zeitgeist is to classify it as a memory system (*taxonony), but it is unlikely that repetition and conceptual priming are subserved by the same system. This classification problem is not unique to priming: take, for example, *classical conditioning. It is considered a system of procedural memory, but trace conditioning is declarative, whereas delay conditioning is not. The take-home message is that taxonomies should be taken seriously only as much as they promote new concepts and research.

⁴Those cases in which the prior exposure results in inhibition of processing, are termed 'negative priming'.

remember till they are either completed or intentionally aborted.¹

Although the memory for intentions and future actions was occasionally tapped already in the early days of experimental human psychology (Colegrove 1898), its systematic analysis has gained momentum only in the past two decades (Brandimonte *et al.* 1996; Dalla Barba 2000; for a provocative critique, see Crowder 1996). There were several reasons for this delay. First, science is often notorious for neglecting important issues, the science of memory being no exception (Neisser 1978). Second, we may be intuitively *biased by the *paradigm that memory is about the past, not the future. Third, prospective memory might be more difficult to control and interpret than retrospective memory in experimental settings; more than in many retrospective tasks, performance on prospective memory tasks involves non-*mnemonic functions that confound the analysis of the mnemonic components of the task (e.g. Dobbs and Reeves 1996).

Consider, for example, the aforementioned manuscript-review assignment, which is now done. At first I had to encode the intention to perform the prospective task, as well as its specific content. (Interestingly, if I were *a priori inclined not to perform the review but rather rethink it only, the memory of the prospective task might have been weaker, see Koriat *et al.* 1990; also 'levels of processing' and 'transfer appropriate processing' in *acquisition, *retrieval.) Following the acquisition *phase, I had to monitor over time the time-to-performance, occasionally rehearsing and refreshing the intention and possibly the content of the intended action. At the appropriate time and *context, I had to retrieve the *internal representations of the intention and the content; perform the task while monitoring the output and matching it with the representation of the goal; and, finally, remove the completed assignment from my cognitive to-do list. All this involved idiosyncratic strategies of allotting and monitoring cognitive resources, executive functions (*working memory), *attention, motivation, tenacity, and more. Furthermore, the job has been accomplished in a multiple tasking situation, i.e. while performing many other behaviours that are not related to the review of the paper.

Whereas the evaluation of a scientific manuscript could be delayed for days, even weeks, prospective memory tests that are used in the laboratory cover only minutes or hours. Two simple tasks could serve as examples (Cockburn 1995). The first is a 'time-based' task. The *subject sits in front of a table with a clock on it and a booklet of sentences. He or she are asked to work through the booklet, putting a tick by those

Prospective memory

The memory of intentions and things to do.

The term 'prospective memory' was introduced by Meacham (Meacham and Singer 1977). It contrasts with 'retrospective memory', which is the memory for past events and experiences. A scientific *culture trivia will illustrate the distinction. I just got a request from a neuroscience journal to review a manuscript. I glanced through it and decided to read it again thoroughly over the weekend, conclude then whether to recommend acceptance—or rejection, because it may not be sufficiently novel (*scoophobia), and send my recommendation to the editor via email, with the completed evaluation form in snailmail as a backup. The fact that I got the paper for review, my knowledge of the specific scientific discipline, and the realization that similar results have been reported earlier by another group, all are retrospective memory. But the intention to read the manuscript over the weekend and send my evaluation immediately afterwards is prospective memory. It is on my mind, but it has not yet been done; those are future actions, which I have to remember and remember to

sentences that are true (e.g. 'apples are edibles') and a cross by those that are false (e.g. 'vans read books'). The instructions are to write the start time, answer as many questions as possible in 10 min, stop even if the booklet is not completed, and write the time. The second prospective task is 'event based'. The subject is instructed to work through a booklet containing rows of two- or three-digit numbers per page, cross out the smallest number in each row, and sign the name at the end of the last page after completing the task. Both protocols involve a prospective task (stopping and writing the time after 10 min in the first task, signing the name after completing the job in the second), superimposed on other cognitive tasks. Note that short-lived prospective tasks that are not superimposed on other ongoing tasks, are probably subserved by on-line retention of the internal representation of the intended action over the *delay; this is a typical working memory situation. In *bona fide* prospective memory, the internal representation of the intention is held off-line over the delay, to be retrieved only intermittently and ultimately during the execution of the task. Occasionally, human neuropsychologists who extend the notion of 'working memory' to ongoing tasks that last many days, consider even long-delayed prospective memory as a type of working memory.

Semantics notwithstanding, clearly, remembering to do things plays an important part in our daily life. We use this type of memory extensively at home, at work, in social contexts, and, equally important, while shopping (e.g. Shapiro and Krishnan 1999). Forgetting what we wanted to do may lead to anything from a slight embarrassment to deep distress (*dementia). Interestingly, although many aged individuals would swear that they have prospective memory problems (*metamemory), in controlled laboratory experiments, age-dependent prospective memory impairments are rather elusive (Maylor 1996). This could be due to the presence of useful *habits, and to accumulated experience, that guides the subject to take advantage of optimal strategies to obtain the goal. By the way, slight prospective memory deficits are not so difficult to overcome; no drugs are required (*nootropics), only user-friendly personal digital assistants (PDAs).

The neuropsychology of prospective memory is not as yet developed as that of retrospective memory. All prospective tasks involve retrospective memory. As *amnesics and *demented patients are highly impaired in retrospective memory, identification of brain areas that are specifically involved in the prospective but not the retrospective memory in such patients is difficult. The search is still on for that unfortunate brain damage that erases prospective but not retrospective memory

(e.g. Cockburn 1995). Instead of studying the effect of lesions, one could use the correlative *method, and map brain activity in normal individuals performing prospective memory tasks (*functional neuroimaging). So far, one brain area, itself heterogeneous, is suspected to play an important, although not exclusive, part in prospective memory. This is the frontal *cerebral cortex (Okuda *et al.* 1998; Fuster 2000b; but see Brunfaut *et al.* 2000). This will not surprise those readers that have already read about *planning or *working memory.

Do animals have prospective memory? The frontal cortex of other mammals is less developed than ours. Still, if we consider frontal cortex to subserve prospective memory, then these species do have a primitive version of the necessary neuronal gear. Of course, dog owners do not need all this boring scientific argumentation to know for sure that their dog wakes up in the morning having a very clear idea of what should be done throughout the day. Sometimes this dogish memory of things to do seems even stronger than that of the human master. It would be nice, though, to design a smart experiment to verify (*assay) that prospective memory is involved. How boring would the world become if such experiment ends up in *reducing the dog's behaviour into only consecutive, on-line stimulus-response chains (*behaviourism, *instrumental conditioning). Let's hope that this is not the case.

Selected associations: Declarative memory, Metamemory, Planning, Working memory

¹These future actions may involve *planning, but planning and prospective memory are not identical. Planning involves organized scheme(s) of operation for attaining a goal, whereas prospective memory refers also to unstructured intentions and to isolated to-do items.

Protein kinase

A ubiquitous type of enzyme that modifies proteins and regulates their function by catalyzing the addition of a phosphate group.

In biochemical language, protein kinases (PKs) transfer the terminal phosphoryl group of the compound adenosine triphosphate (ATP) to an amino acid in the target protein. It is estimated that as much as 3% of all the genes code for PKs (Hunter 1994; Venter *et al.* 2001).

Protein kinase

After proteins are produced on the ribosomal machinery in the cell by translation from their corresponding messenger RNA (mRNA, *protein synthesis), they are still subjected to a variety of post-translational modifications, which regulate their function. These post-translational modifications can switch cellular activity from one state to another. PKs are the most ubiquitous agents of post-translational modification in all tissues. The superfamily of PKs is classified into a number of families (Hanks and Hunter 1995). A major meta*criterion in this classification is the target amino acid: serine/threonine, or tyrosine. Most phosphorylation sites on proteins involve serine and threonine residues, and only about 0.1% involve tyrosine ('dual specificity' kinases phosphorylate both serine/threonine and tyrosine). PKs phosphorylate other proteins, but in many cases can also undergo autophosphorylation and regulate their own activity. The multiple families of serine/threonine kinases include PKs regulated by cyclic nucleotides, e.g. cyclic adenosine monophosphate (cAMP)-dependent PK (PKA); diacylglycerol-activated/phospholipid-dependent PKs (PKC), e.g. *calcium-dependent PKCs; calcium/calmodulin dependent PKs, e.g. multifunctional calcium/calmodulin dependent PK (CaMK); and mitogen-activated PKs (MAPKs). Other subfamilies of serine/threonine kinases are also known. Protein tyrosine kinases are conventionally classified into *receptor tyrosine kinases, which are associated with the cell membrane, and nonreceptor tyrosine kinases. Each of these protein tyrosine kinase families is further classified into subfamilies.

The biochemistry and molecular biology of PKs is complex. In the context of memory mechanisms, some generalizations and examples can however be made. PKs respond, either directly or indirectly, to extracellular *stimuli. This means that they fit to serve as components of the molecular *acquisition or *retrieval machinery in neurons (see also *ion channel, *reduction). PKs can switch the cell from one functional state to another, and some types regulate differentiation and growth. This implies that they fit to serve as triggers for *consolidation, memory *phase shifts and long-term memory. Some types of PKs can be converted into a *persistently active form that is autonomous of the activating signal. This implies that these PKs can serve as molecular information storage devices in neurons, and retain activity dependent information over time. A few examples will illustrate the aforementioned generalizations.

1. **PKA.** Here the most detailed data so far are from **Aplysia*, although data from other invertebrates

(e.g. Müller 2000) and from mammals (e.g. Abel *et al.* 1997) are also abundant. In the circuits that encode defensive reflexes in the sea hare, facilitatory interneurons that mediate the sensitizing stimulus release serotonin and other neuromodulators that bind to *receptors on the sensory neurons. These receptors activate the enzyme adenylyl cyclase, generating the second messenger cAMP (*intracellular signal transduction cascade). PKA is composed of two types of subunits, catalytic (C) and regulatory (R) (Figure 57). In the holoenzyme (i.e. C+R), R masks the enzymatic active site on C. When cAMP binds to R, it dissociates it from C and activates the latter. C phosphorylates substrate proteins in the *synapse, culminating in changes in ionic conductances, *neurotransmitter release, and an overall enhanced efficacy of the sensory-to-motor synapse. This results in synaptic facilitation, which is taken to be the cellular correlate of behavioural *sensitization in *simple systems. In the above process, PKA, as part of the cAMP signal transduction cascade, fulfils multiple roles. It is part of an acquisition machinery that creates the short-term trace (probably by phosphorylation of selected types of *ionic channels); it is also a component of the consolidation machinery that

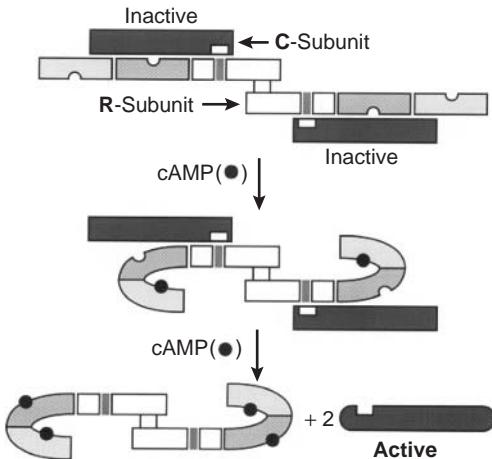


Fig. 57 A simplified scheme of the structure and function of the cAMP-dependent PK (PKA). The enzymatic complex is composed of two types of proteinic subunits, catalytic (C) and regulatory (R). R masks the enzymatic active site on C (upper configuration in the scheme). Binding of the intracellular messenger cAMP to R, dissociates R from C (middle configuration), and renders the latter free to phosphorylate its substrate proteins in the cell (bottom configuration). Cellular processes that degrade R or lower its affinity to C could hence lead to the accumulation of an autonomous, persistently active C. This could sustain use-dependent changes in the synapse for many hours (Buxbaum and Dudai 1989; Chain *et al.* 1999).

stabilizes the long-term trace (see also *CREB). PKA has also been suggested as a candidate information-storage device in the neuron. One of the *immediate early genes induced in consolidation codes for the enzyme ubiquitin hydrolase, which enhances specific proteolysis (breakdown of proteins). A major target of ubiquitin hydrolase is the R subunit of PKA. In the absence of R, C becomes persistently active and autonomous. This mechanism can sustain experience-dependent changes in the synapse for at least 24 h (Chain *et al.* 1999; for other mechanisms whereby the alteration in the R/C ratio can lead to persistent activation of PKA, see Buxbaum and Dudai 1989).

Studies of *classical conditioning in the *honeybee provide another illustration of the postulated role of PKA in triggering the consolidation of neuronal information in the context of learning. Conditioning of the bee to extend its tongue (proboscis) in response to an odour that is associated with sucrose solution, is correlated with activation of PKA in the antennal lobes, the functional analogues of the mammalian olfactory bulbs (Müller 2000). Only multiple-trial conditioning, which induces long-term memory, but not single-trial conditioning, which induces only short-term memory, leads to prolonged activation of the kinase. Inhibition of the PKA during training blocks long-term memory. Mimicry of the prolonged PKA activation, by a biochemical trick that increases the level of cAMP in the antennal lobes, when combined with a single conditioning trial, is sufficient to induce long-term memory. Hence in this study the *methods of observation, intervention, and mimicry combine to provide evidence that the activity of PKA is correlated *in vivo* with the induction of long-term memory, is necessary for long-term memory, and is sufficient to trigger the long-term registration of the sensory information in memory.

2. CaMKII. This kinase, highly concentrated in synapses, is implicated in multiple facets of neuronal *plasticity and growth (Braun and Schulman 1995). CaMKII is capable of autophosphorylation, which reduces its dependency on calcium, and produces an autonomous kinase. The enzyme can thus be considered as a molecular switch that becomes persistently activated following a transient calcium burst, i.e. a cellular information storage device (Saitoh and Schwartz 1985). In *long-term potentiation (LTP), CaMKII phosphorylates and enhances the responsiveness and the trafficking into the synapse of AMPA *glutamatergic receptors (Barria *et al.* 1997; Hayashi *et al.* 2000), and regulates AMPA receptor synthesis (Nayak *et al.* 1998). Shifts in the availability of the

autonomous enzyme alter the responsiveness of synapses. An increased level of autonomous CaMKII was found to favour long-term depression over LTP, providing an appealing mechanism for regulating *metaplasticity (Chapman *et al.* 1995; Mayford *et al.* 1995). And mice expressing a mutant, autonomous CaMKII were found to be defective in certain types of LTP, and incapable of forming stable place *maps in the *hippocampus (Rotenberg *et al.* 1996).

3. MAPKs. The function of the MAPKs involves sequential activation of several cytoplasmic kinases, resulting in transmission of regulatory signals from the cell surface to the nucleus (Seger and Krebs 1995). MAPKs are involved in response to growth factors, and have been shown to be required for the formation of long-term memory (Martin *et al.* 1997b; Berman *et al.* 1998). In this process MAPK functions in concert with PKA (Kornhauser and Greenberg 1997; Martin *et al.* 1997b).

4. Tyrosine kinases. These are involved in many facets of regulation of differentiation and growth (Schlessinger and Ullrich 1992). Ample evidence attests to their role in synaptic plasticity and learning. For example, mutation in a nonreceptor tyrosine kinase, *fyn*, impaired LTP, *maze learning, yet also hippocampal development (Grant *et al.* 1992). In the behaving rat, tyrosine phosphorylation of the glutamatergic NMDA receptor was shown to correlate with LTP (Rosenblum *et al.* 1996) as well as with taste learning (Rosenblum *et al.* 1997).

By no means are the above examples exhaustive. Many other PKs are implicated in plasticity, learning, and memory, for example, members of the PKC family (e.g. Thomas *et al.* 1994). Judging by their multiple, ubiquitous roles in cellular function, and by the extensive cross-talk of networks of PKs in the cell (*coincidence detector), the involvement of PKs in multiple phases of learning and memory is expected to be the rule rather than the exception. Protein phosphatases should also not be forgotten (Mulkey *et al.* 1993; Winder *et al.* 1998). Whatever goes up also comes down, and phosphatases are enzymes that undo what the kinases do. Protein phosphatases may inhibit memory formation in the first seconds or minutes in the life of an *engram, and, furthermore, erase cellular traces of immediate- and short-term memories. They should definitely provide interesting targets for modern analogues of the legendary *lotus.

Selected associations: CREB, Consolidation, Intracellular signal transduction cascades, Plasticity, Reduction

Protein synthesis

The process by which cells manufacture protein molecules from amino acids on the basis of the genetic information that is encoded in the DNA.

The genetic code is decoded in all living cells in two major *phases. First it is transcribed from the DNA into a specific messenger RNA (mRNA) molecule. This process is termed ‘transcription’. The code is then read from the mRNA molecule to produce the copy of the corresponding protein. This process, which takes place in a complex cellular factory called ribosome, is termed ‘translation’. In practice, a group of ribosomes (‘polyribosome’) performs the task on each mRNA. There are many complex steps in protein synthesis (Alberts *et al.* 1994), but most of the details need not concern us here. Rather, we will concentrate on those aspects of protein synthesis that have become a major focus of research in the biology of learning and memory.

It has all started with the notion that the brain develops with experience, and that, similarly to all *developmental processes, this involves growth. This is an old idea, which has become a tenet of modern neurobiology (Hebb 1949; *zeitgeist). Growth means, among others, synthesis of proteins, which are the major constituents of all living cells. It became evident that experience is indeed accompanied by alteration in protein synthesis in the nervous system (Hamberger and Hyden 1945). Eventually, the proposal was explicitly made that the formation of new memory traces depend on new protein synthesis (Monne 1949; Katz and Halstead 1950). The experimental proof followed (RNA synthesis—Dingman and Sporn 1961; protein synthesis—Flexner *et al.* 1963; Agranoff and Klinger 1964).

Over the years, two types of *methods have been used to demonstrate the role of protein synthesis in memory. The first method involved intervention with the metabolism of the brain, by the use of antibiotics that inhibit RNA or protein synthesis (inference of function from the dysfunction, *method). After the initial successes (Flexner *et al.* 1963; Agranoff and Klinger 1964), scores of laboratories became enthusiastically immersed in the new paradigm, injecting protein synthesis inhibitors into the brain of behaving animals ranging from goldfish to rodents. In spite of occasional worries about the exact target of the antibiotics (e.g. Kyriakis *et al.* 1994), the overwhelming conclusion was that protein synthesis during or up to a few hours after training, but not afterwards, is required for the *consolidation of long-term memory, but not for its *acquisition, short-term

retention, or *retrieval once the long-term memory had been formed (Davis and Squire 1984; Dudai 1989; Rose 1995b).

In the early days of the protein-synthesis-inhibition-of-memory experiments, the inhibitors were injected into wide areas of the brain, the whole brain, or even the whole body. This created a problem, because the experimenters could not prove that the effect is on neurons, and that the targets have anything to do with the specific memorized task. This difficulty was resolved only in the mid-80s. During that period, new preparations were developed, in which identified memory-subserving neurons are studied in isolation (**Aplysia*), and cellular analogues of learning are analysed in brain tissue (*long-term potentiation). Another wave of protein-synthesis-inhibition-of-memory studies soon followed. These experiments finally proved that the initial conclusions about the role of RNA and protein synthesis in consolidation were basically correct (e.g. Montarolo *et al.* 1986, Linden 1996). The new preparations also permitted the effective use of a complementary approach, based on correlation rather than perturbation: identification of neuronal gene products that are induced by experience (*immediate early genes, *late response genes).

The combination of the two aforesaid approaches has led to the following textbook cellular *model of long-term memory: *stimuli that exceed a certain threshold or *coincide in appropriate combinations, operate on the relevant *receptors in the target synapses, and activate *intracellular signal transduction cascades. The latter activate constitutive transcription factors (TFs), and induce the transcription of additional TFs as well as other types of immediate early genes.¹ The TFs trigger phases of gene expression, culminating in the induction of expression of late response genes. The products of the induced genes ultimately induce and embody persistent alterations in the synapses and neurons that encode the memory. Further, whereas neuronal alterations that are based on post-translational modifications are constrained by the limited life span of the modified protein molecule (which is commonly anywhere between a few minutes to a few weeks), the modulation of gene expression could render the alterations immune to the molecular turnover of individual protein molecules. The mechanisms of transcriptional regulation by extracellular signals in neurons are basically similar to those that operate in non-neuronal cells (Hill and Treisman 1995). This suggests, by the way, that the specificity of the *engram should be searched for at higher *levels of organization of the brain (*reduction).

The textbook model is, as usual, too simplistic. The complications are of two types. One type relates to the role of the newly synthesized proteins in the context of memory: Is it permissive, or causal? Do these proteins play a direct role in modifying the use-dependent *internal representation? This issue surfaces in several discussions in this book (e.g. *CREB, *homeostasis, *late response genes); it will not be further elaborated here. The other type of issue refers to the specificity of the process and to cellular economy. Isn't the modulation of cell-wide gene expression by only one or a few synapses remarkably nonparsimonious? And how would synaptic specificity be preserved, if at all?

The solution may lie in the intricacies of a multiphasic mechanism, which is both synapse-specific and cell-wide (Figure 58) (Dudai and Morris 2000). It appears that the activated synapse is somehow 'tagged', possibly by post-translational modification of synaptic protein(s), or by reorganization of such proteins (Katz and Halstead 1950; Dudai 1989; Frey and Morris 1997; Martin *et al.* 1997a). This results in a new local synaptic configuration. It could also attract proteins from other parts of the cell. In addition, the stimulus activates constitutive transcription factors, such as CREB, and induces immediate early gene expression, some of which encode inducible transcription factors, others different types of proteins, including enzymes, cytoskeletal elements, and growth factors. The synapse itself contains the full translation apparatus and is capable of synthesizing proteins on location, from mRNA which is delivered from the nucleus (Steward and Levy 1982; Rao and Steward 1991; Weller and Greenough 1993; Martin *et al.* 1997a; Steward *et al.* 1998; Huber *et al.* 2000). These locally synthesized proteins strengthen the tagging of the synapse, and/or serve as retrograde messages, which travel to the cell body and inform the nucleus about the change (Casadio *et al.* 1999). This results in modulation of gene expression in the nucleus, and in the production of new mRNAs and proteins, that are funnelled to the tagged synapse. All in all, the process is hence assumed to involve intimate co-ordination between the synapse and the nucleus, which probably optimizes the exploitation of the metabolic resources of the neuron and the specificity of the long-term synaptic change (Dudai and Morris 2000).

We still have a long way to go before we fully understand the mechanisms and roles of synaptic tagging and step-wise synaptic consolidation. We are bound for surprises on the way. For example, it has been reported that the wave of protein synthesis that is triggered by a salient event in one synapse, is capable of affecting the registration of activity in adjacent synapses as well. This

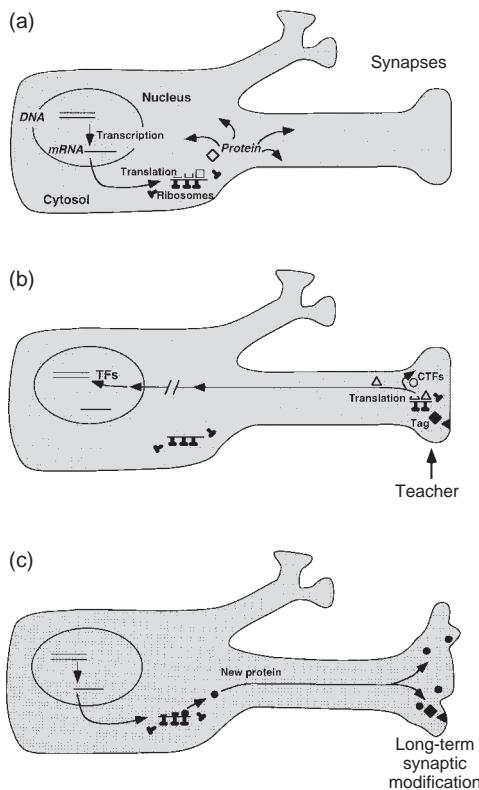


Fig. 58 A highly simplified *model of the role of protein synthesis in the production of long-term synaptic modifications that are assumed to subserve the *acquisition and *consolidation and contribute to the *persistence of long-term memory. (a) Protein synthesis involves transcription in the nucleus and translation on ribosomes in the cytosol (the inner cellular space outside the nucleus). (b) A teaching stimulus ('teacher'), which is sufficiently salient to induce long-term memory, activates membrane receptors and their downstream *intracellular signal transduction cascades. This results in the activation of constitutive transcription factors (CTFs), such as *CREB, and in the induction of the expression of *immediate early genes, which encode inducible transcription factors as well as a variety of other proteins. Immediately after the stimulation, the activated *synapse is tagged in a way that differentiates it from the nonstimulated synapses. The teaching stimulus also induces local protein synthesis in the synapse (the ribosomes in the synapse are not shown in (a) for simplicity). The proteins that are synthesized on location might contribute to the tagging of the activated synapse. They might also comprise or generate a retrograde signal, which travels to the nucleus. The expression of certain genes in the informed nucleus is now modulated by sets of TFs. (c) The newly synthesized proteins travel from the cell body to the activated, tagged synapse, and contribute to its lasting modification. Protein synthesis hence fulfils multiple roles at multiple sites and times after the training, and is controlled by both the activated synapse and the cell body and nucleus.

Rat

means that synapses are tuned to the history of each other (Frey and Morris 1997). This could subserve the cellular encoding of *context, *generalization, even *priming. Whether the synaptic phenomenology indeed contributes to the behavioural phenomena of context encoding, generalization or priming, is currently an intriguing yet unresolved issue.

Selected associations: Consolidation, CREB, Development, Immediate early genes, Late response genes

¹On what transcription factors are, and on the distinction between constitutive and inducible TFs, see in *immediate early genes.

Rat

A small mammal of the genus *Rattus*, family *Muridea*, order *Rodentia* (rodents).

The contribution of the rat to the behavioural and brain sciences is second only to that of humans, the main difference being that the contribution of the latter is frequently more voluntary. It has all started with the invasion of Europe by the brown rat (*Rattus norvegicus*). The brown rat arrived from Asia at the beginning of the eighteenth century, almost 400 years after its cousin, *Rattus rattus* (the black or grey rat), spread the devastating Black Death throughout the Continent. The brown rat was very successful in the new niche. The human response was to engage in extensive rat trapping, and to establish rat baiting as a popular sport. The twist in the story came when albino mutants of the brown rat were noted, isolated, and kept for entertainment. The albino rat proved to be much more tameable than the wild type. The relative docility of this mutant provided it with the opportunity for eternal fame; by 1850s, it has already been used in metabolic and genetic experiments in France. England and Germany followed right thereafter. As a matter of fact, this was the first species to be domesticated for scientific purposes (Lockard 1968; Lindsey 1979). In the 1890s, a Swiss scientist who emigrated to the USA imported the albino rat to the University of Chicago.¹ At about the same time, a short-lived attempt was made to use the grey rat at Clark University (Munn 1950), but the white soon replaced the grey in Clark as well. The standardized stocks and inbred strains of laboratory rats used today were developed from the albino as well as from crosses between the albino and wild type (Lindsey 1979).

The championship of the psychology lab did not come easy to the rat. Chicks, cats, and dogs were all at

one time or another effective rivals for the attention of researchers (Boakes 1984; *classical conditioning, *imprinting, *instrumental conditioning). The laboratory rat was small, cheap, easily bred and cared for, and, most importantly, smart. At Clark University, it became the subject of the first *maze experiments (Small 1901; Miles 1930). The combination of mazes and rats emerged as a real winner, shaping experimental psychology for generations to come. Rat learning *paradigms became so dominant that at a certain stage, toward the mid-twentieth century, experimental psychologists, especially in North America, became convinced that rat behaviour can faithfully *model human behaviour. Furthermore, they entertained the idea that the rat mind holds many of the clues to human psyche. '... Most of the formal underlying laws of intelligence motivation and instability can still be studied in rats ... more easily than in men ... (rats) do not go on binges the night before one has planned the experiment; they do not kill each other off in wars; they do not invent engines of destruction, and, if they did, they would not be so dumb about controlling such engines; they do not go in for either class conflicts or race conflicts; they avoid politics, economics and papers on psychology' (Tolman 1945). Whereas avoidance of politics and of papers on psychology does have some merit, the enthusiasm appears today a bit exaggerated.

The advantages of the rat for the science of memory are numerous. Some of these advantages pertain directly to the rat's ability to learn quickly in tasks which are convenient for use in the laboratory. It is especially shrewd in spatial, olfactory, and taste learning (Tolman 1948; Slotnick 1994; Biegler and Morris 1996; Schul *et al.* 1996). Other advantages of the rat relate to its size (not too big, not too small). But probably most important at this stage is the immense body of knowledge that has accumulated over the years on the rat's neuroanatomy, neuropharmacology, neurophysiology, and behaviour. This combination turns the rat into a prime choice for the cross-*level study of certain types of mammalian learning.

The rat, however, has at least two types of disadvantage. First, clearly, in some cognitive tasks, such as *delay tasks, which are of great importance to the understanding of primate *recognition and *recall, the rat is no rival to more advanced species such as the *monkey (Hunter 1913; Keller and Hill 1936; Steckler *et al.* 1998a,b). It is also debated whether it can form genuine *learning sets, a popular *criterion for rudimentary concept formation (Reid and Morris 1992; Slotnick 1994). Second, the molecular genetics of the rat is undeveloped. Transgenics were reported

(e.g. Waller *et al.* 1996), but no knockout technology is yet available at the time of writing. This deprives the rat of one of the most powerful tools of molecular neurobiology (*neurogenetics). So far, in this arena, the *mouse outperforms the rat, and if the latter doesn't catch up, which is rather unlikely, it will lose its hegemony in the world of mazes and puzzle boxes.

Selected associations: Maze, Model, Subject, Zeitgeist

¹Whether all the albino rats later used in research in the USA indeed originated from this import is uncertain (Lindsey 1979).

Real-life memory

Memory acquired, used, and investigated in natural settings.

It may come as a surprise to postdocs running mice in water *mazes, poking molluscan neurons in a dish, or flashing computerized test icons in front of bored students—but memory does have a life outside the laboratory. It is this potential detachment from reality, particularly in dealing with human memory, that has prompted Neisser (1978) to deliver in the first International Conference on Practical Aspects of Memory a signal presentation, entitled ‘Memory: what are the important questions?’. Neisser claimed, more or less, that the bulk of experimental research on human memory, since its first days some one hundred years earlier (Ebbinghaus 1885), meant very little as much as memory in real life is concerned. He further went on to argue that ‘if X is an interesting or socially significant aspect of memory, then psychologists have hardly ever studied X’ (*ibid.*). Neisser’s scholarly provocation stirred emotional polemics (e.g. Banaji and Crowder 1989; Conway 1991; Loftus 1991), itself a potentially interesting topic for research on everyday memory (Roediger 1991). It also epitomized, and contributed to, a deflection in the direction of human memory research.

It is difficult to underestimate the importance of the first controlled paradigms for quantifying human memory (Ebbinghaus 1885). Without them, memory research would have not been promoted to the rank of a respectable, quantitative, and reproducible science. In parallel, the mainstream research on animal learning, while looking for reproducible methods and quantifiable variables, has also become increasingly dependent on artificial laboratory *paradigms (*classical and

*instrumental conditioning). Many of these paradigms expose the experimental animal to settings and demands far remote from the ecological niches and from the problems that these niches pose (Boakes 1984). The effectiveness and popularity of these animal learning paradigms have tempted prominent investigators to adapt them to human use (e.g. Woodworth and Scholsberg 1954), and even to go as far as to declare that most, if not all, the riddles of human memory will ultimately be solved by understanding the behaviour of the *rat (Munn 1950). There were, of course, early attempts to investigate human memory in its natural settings (e.g. Galton 1879; Colegrove 1898; Thorndike and Woodworth 1901a,b; *capacity, *transfer). Furthermore, over the years the mainstream ‘laboratory approach’ to memory research was not without its ardent opponents, who claimed that most of the studies miss the social and ecological context, function, and complexity of memory in real life (Bartlett 1932). However, the challenge did not gain much momentum until the 1970s.

Real-life memory research was at first formulated as an opposition, devoid of a formal consensus on its precise definition (Klatzky 1991). It is known by multiple names, which refer to the same or similar notions: ‘everyday memory’ (‘an awkward phrase’, Neisser 1991); ‘ecological memory’ (Bruce 1985); and ‘real-world memory’ (Cohen 1996). In essence, the majority of the traditional research on memory throughout the first half of the twentieth century has focused on the structure and the ‘syntax’ of memory, i.e. how the system operates and what are the formal relations between *stimuli and actions (*algorithm, *model). Furthermore, this research was dominated by the role of the investigator, who in many respects shaped the behaviour of the *subject in artificial settings by choosing the problems, the constraints, and the *reinforced response. In contrast, real-life memory research concentrates on the subject in its natural environment, on phenomena relevant to daily life, and on familiar types of stimuli and responses. It emphasizes better the ‘semantics’ of the learned behaviour, i.e. its content, function, context, and meaning. Here is a selection of ‘real life’ questions: How accurate are our autobiographical reminiscences? Should we trust eyewitnesses? What shall we do to remember better which name belongs to which face? How do we keep a mental record of what we *plan to do later in the day (*prospective memory)? How do experts differ from novices in their everyday *skill? Or, closer to academic life, how much do we remember after attending a classroom lecture (not too much, and unfortunately or not,

Real-life memory

jokes rather than facts are remembered best; Kintch and Bates 1977).

Criticism of research on real-life memory focuses on what is considered by the critics as lack of *controllability, rigorousness, and reproducibility of the *methods and the generalizability of the conclusions (Banaji and Crowder 1989). But the reduced control of extraneous variables is the price many investigators are ready to pay in exchange for the ability to tackle naturalistic, complex behaviours, and unveil new memory phenomena (Baddley 1981; Klatzky 1991). Explicitly or implicitly, the modern real-life memory movement did exert a significant impact on human memory research.¹ The development of novel techniques that permit on-line analysis of the conscious brain in normal subjects has in parallel extended and enriched the repertoire of methodologies available in the investigation of human memory (e.g. virtual reality, *functional neuroimaging). As a consequence, many *bona fide* real-life phenomena are currently being dealt with at the forefront of human memory research, both inside and outside the laboratory (Cohen 1996; Goel *et al.* 1997; Maguire *et al.* 1997).

Selected associations: Context, False memory, Flashbulb memory, Observational learning, Prospective memory

¹The parallel in the field of animal learning is the ethological approach (Tinbergen 1969; Lorenz 1981). For a review, see Camhi (1984); for more recent variants, see Eichenbaum (1996) and Chiel and Beer (1997); also *birdsong, *imprinting.

because retrieval is a universal process, which must occur to actualize any type of learned information, even the simplest ones such as *habituation and *sensitization, whereas recall corresponds to retrieval only under the conditions specified in definition 1. Recall as a process is inferred to underlie the recall faculty. Recall as a test involves the generation by the *subject of the internal representation of a fact or event according to instructions, in the absence of the corresponding on-line sensory information, for example, reproduce in mind a remote autobiographical episode while sitting in the laboratory. But recall could also be involved in tasks that are not intentionally meant to tap into it. For example, in a *recognition test, a subject instructed to identify an on-line sensory *stimulus probably uses recall of off-line information to evaluate the meaning of this target.

A few additional words on variants of recall. When recall is tested in the absence of intentional *cues, it is called 'free recall'. When cues are provided, it is called 'cued recall' or 'prompted recall'. Each of these terms can be used, as far as it is remembered that there is probably no recall without cues—only that in prompted recall these cues are provided by the experimenter, whereas in free recall they are generated by the subject. When recall is initiated by instructions or by focused intention, it is focused or intentional recall, whereas if it is the spin-off of a stream of *associations, it is incidental recall. When the recall yields what is judged to be the complete target, it is complete or total recall. But in many cases recall is only partial. Two examples of partial recall are provided by the 'feeling of knowing' (FOK) and the 'tip of the tongue' (TOT) phenomena. In FOK the subject judges that the target is in memory despite a failure to retrieve it at present time (Hart 1965); in TOT, the subject judges as if verbal information resides on the tip of the tongue (*metaphor) despite the failure to express it (Brown and McNeill 1966; *metamemory).¹ An attempt to recall an item in memory may at first prove futile but later succeed without further learning. This is called 'reminiscence', i.e. the recall of previously unrecalled items (Ballard 1913; Payne 1987). Under certain conditions, the overall recall performance of the subject on a certain type of test and material may improve with repeated recall trials; this is termed 'hyperamnesia' (Erdelyi and Becker 1974; Payne 1987).

Starting from the early days of experimental psychology (e.g. MacDougall 1904; Hollingworth 1913), many attempts have been made to explain how recall works, and what distinguishes it from recognition. It should be said at the outset that this focus on the distinction of recall from recognition may be a bit misleading,

Recall

- 1. The reactivation or reconstruction of the *internal representation of a target item in the absence of this item.**
- 2. The brain process(es) by which this occurs.**
- 3. Recall test: A test situation by which this is measured.**

Recall is a type of memory (definition 1), brain process (definition 2), and test situation (definition 3). It is important to distinguish between the three. Recall as a memory faculty is the phenomenon that most people have in mind when they refer to 'remembrance' or 'recollection'. It is 'memory par excellence' (Bergson 1908). Some authors, especially in the older literature, equate recall with *retrieval. This should be avoided,

because it suggests that the two phenomena or processes are decisively different, which may not be true. In a nutshell, there are two main types of recall 'theories', or *models. One type refers to recall and recognition as lying on a continuum of retrieval (Tulving 1976). The main difference between recall and recognition, according to this view, is the nature and availability of *retrieval cues*: supplied in recognition, self-generated in recall (see above). The other type of models distinguishes basic differences between recognition and recall. These models propose that recall operates in *two phases*, or stages (Bahrick 1970; Kintsch 1970). The first phase is the search, *generation*, or retrieval phase. The second phase is the identification, or decision, or *recognition* phase, once the target has been retrieved.²

Two points about the two-stage models of recall are noteworthy. One, recognition also involves retrieval. Therefore, distinguishing one phase of recall as the retrieval phase, as opposed to recognition, disregards the universality of retrieval as the process necessary to actualize stored information. Second, it is tempting to assume that if recognition is a subprocess in recall, recognition will be easier than recall. Intuitively it makes sense: how easy it is to recognize a face, how difficult is it to recall the name that belongs to that face (McWeeny *et al.* 1987). Yet it can be shown that under certain conditions items are recalled but not recognized (Bahrick and Bahrick 1964; Tulving and Thomson 1973). For example, consider the following experiment (Tulving and Thomson 1973): subjects were presented with an input list of pairs of words, one a target word, such as *baby*, the other a weak semantic associate that was intended to be used as a *cue for the target word, e.g. *grasp*. Afterwards, the subjects were presented with strong semantic associates of the target words, e.g. *infant*, and asked to generate a list of associated words. The subjects were then asked to mark all the words in the generated list that they recognized as having occurred in the input list. Finally, the subjects were presented with the original input list cues and asked to recall the target words. Under these conditions, the prompted recall was superior to the recognition of words from the input list. This seems incompatible with recall being a generation-plus-recognition process. The recognition failure was explained by the authors by invoking the 'encoding-specificity principle'. This principle (*acquisition, *retrieval) states that memory performance is best when the cues present at retrieval match those present in acquisition. The encoding of the target words in the input list was in the presence of the input list cues, and influenced by the subjects' expectation that they will be tested with these cues. In the later

part of the experiment, which involved the recognition task, the retrieval attempt was made using different cues and in a different *context. The encoding specificity principle predicts that this will hamper the retrieval, hence recognition, of the target words. Another interpretation of the data is that the recognition failure resulted from the formation of two different traces in the different parts of the experiment, rather than from differences in the retrieval efficacy of the same trace (Baddeley 1982). The two different traces could have resulted from the interaction of each target word with two different semantic contexts, shaped by the weak and the strong semantic associates, respectively. If correct, this means that the 'item to be recognized' was not actually identical to the 'item to be recalled', rendering the comparison of the efficacy of recognition and recall in this experiment questionable.

Can animals recall? We find it easy to understand recall because we frequently recall and because we can ask other individuals to declare their own recall experience. But how do we know whether a dog is musing spontaneously, or at least is cued to muse, about things past? In referring to recall, there is an implicit assumption that it does not refer to very short-lived memory, say of a few seconds only. If this assumption is abandoned, then trace conditioning (*classical conditioning) and *working memory involve cued recall functions, and clearly, they can be performed by nonhuman species. Furthermore, animals do seem capable of high-order stimulus–stimulus associations (Dickinson 1980; Mackintosh 1983), so why not consider these as resulting in stimulus-independent retrieval, hence recall? Nonhuman species might also be capable of *conscious awareness of the recall act (Clark and Squire 1998, *declarative memory). A reasonable conclusion is that recall is a spectrum of functions, differing in their dependence on available cues, and their explicitness, and other species are capable of rudimentary forms of recall (see also discussion in *episodic memory).

Which brain circuits subserve recall? The analysis of defective recall in *amnesics indicates that, similarly to recognition, recall depends during the acquisition and *consolidation phases of the memory on the integrity of the *hippocampal formation and other mediotemporal structures (Haist *et al.* 1992). *Functional neuroimaging of normal subjects confirms that the hippocampus is indeed involved in explicit recall (e.g. Maguire *et al.* 1997). With time, however, the memory to be recalled becomes practically independent of the hippocampal formation, and remains in the *cerebral cortex (e.g. Teng and Squire 1999). There is evidence that recalling a target

Recall

in its absence activates areas in the sensory cortex that were originally involved in *perception of the target (e.g. Kosslyn *et al.* 1995; Zatorre *et al.* 1996; Wheeler *et al.* 2000). And finally, to recall a target, monitor the operation and verify it, the prefrontal cortex is needed (Jetter *et al.* 1986; Buckner and Koustaal 1998; Fletcher *et al.* 1998; Tomita *et al.* 1999; Maril *et al.* 2001). This brings us back to the issue as to whether nonhuman species can recall: those species that have a reasonably developed prefrontal cortex, such as other primates, can probably recall, but less efficiently than **Homo sapiens*, who happens to have a more sophisticated prefrontal cortex.

Selected associations: Amnesia, Confabulation, Recognition, Retrieval, State-dependent learning

¹FOK and TOT apply to *recognition as well.

²The notion of recall involves search and identification can be traced to much earlier literature: it is hinted already in Augustine (400: *classic).

and Gibertson 1999; Mombartes 1999). The receptive apparatus in sensory receptor cells is not prime candidate for fulfilling memory functions. This is because, being at the front end of the sensory channel, its alteration affects the input globally, whereas most learning is expected to involve a discriminative alteration in response to the input. We shall therefore concentrate on receptor proteins in the brain, particularly on those receptors that reside on *synaptic membranes and bind *neurotransmitters, neuromodulators, and growth factors. Such receptors subserve intercellular communication and could mediate or encode lasting modifications in circuit properties.

The term ‘receptor’ is used in pharmacology in a broader sense than in cellular neurobiology, and refers to any type of drug–target in living tissue (Ariens and Beld 1977; definition 1). The notion that drugs and poisons mimic or block physiological function by interacting with specific sites in the organism is at least over a century old. Langley (1905), studying the effects of the cholinergic (*acetylcholine) toxins nicotine and curare, was the first to term these sites ‘receptive substances’. The decisive proof that receptors are specialized proteins was provided by studies of the nicotinic acetylcholine receptor from the electric organ of electric fish. This receptor was isolated, reconstituted, and its gene was ultimately cloned (Numa *et al.* 1983; Changeux *et al.* 1984; for a personal view on the early history of the field, see Nachmansohn 1959). In its time, the cloning of the nicotinic receptor was a remarkable feat. Less than 20 years later, cloning receptor genes is a routine.

Before proceeding, a few semantic points should be clarified. Receptor proteins contain multiple functional components, which could reside in dissociable subunits. One type of component is the ‘binding site’, which recognizes and binds specific molecules (‘ligands’, from ‘bound’ in Latin). Most receptors have multiple binding sites, commonly for different types of ligands. Another component is the ‘effector’, that part that performs the response function. This could be, for example, an *ion channel pore, or an active site of an enzyme (and see below). Some authors refer only to the binding site as a *bona fide* ‘receptor’ (Cooper *et al.* 1996). Receptors without an effector are sometimes called ‘acceptors’, and could, for example, play a part in regulating the level of specific ligands in the cell. Specific ligands could either activate the receptor, in which case they are termed ‘agonists’, or block it, in which case they are ‘antagonists’. Ligands could also modulate the binding and action of other agonists. Finally, typically, a receptor protein is named after what is considered to be its major endogenous agonist,

Receptor

- 1. A molecule or molecular complex that binds other types of molecules in a specific, saturable manner.**
- 2. A protein that responds to the binding of specific types of molecules by triggering a distinct type of change in cellular activity.**
- 3. A specialized cell or organ at the front end of a sensory channel, capable of responding to specific types of sensory *stimuli by modulating its output to the nervous system.**

‘Receptor’ is from *recipio*, ‘to receive’ in Latin. The families of receptors that concern us here are molecular (definition 1), specifically, proteins that respond to molecular stimuli by triggering cellular response (definition 2). Many types of these receptors reside on the surface membrane of the cell. Other types of molecular receptors are on the membrane of intracellular organelles or in the cytoplasm. We will focus on the cell-surface types. Receptor molecules also exist on and in sensory receptors cells (definition 3), where they respond to either chemical or physical stimuli, depending on the sensory modality that the organ or the cell transduces (Hudspeth 1989; Lagnado and Baylor 1992; GarciaAnoveros and Corey 1997; Harness

e.g. **glutamatergic*, **dopaminergic*. Similarly, the name of a receptor subtype refers to an endogenous ligand or to a drug or poison that displays selectivity for that subtype (e.g. a cholinergic *muscarinic* receptor). Sometimes, another structural or functional attribute is used for naming, e.g. a '*metabotropic*' family of glutamate receptors (from 'metabolism'). In yet other cases, for the lack of a better alternative, arbitrary notations are employed, such as $1-n$, $\alpha-\nu$, etc. (e.g. Milligan *et al.* 1994). As the number of identified receptor types and variants keeps growing, notations tend to become cumbersome. The completion of the Human Genome project is expected to lead to a revision that will make the naming of receptor families more rational and convenient.

Cell-surface receptor proteins could be classified by their effector type. The three major effector types are ion channels, G proteins, and enzymes. Ion channel receptors are ligand-gated ion channels, for example, the nicotinic acetylcholine receptor is a Na^+ channel, and the *N*-methyl-D-aspartate (NMDA) receptor primarily a **calcium* channel.¹ G-protein-coupled receptors belong to a superfamily of membrane proteins that contain seven hydrophobic transmembrane domains, and function by activating members of a family of regulatory protein called GTP-binding protein (abbreviated G protein; Gutkind 1998; **intracellular signal transduction*). The G protein, depending on its specific type, activates or inhibits the activity of other target proteins, such as enzymes, ion channels—or yet other receptors. Examples for G-protein-coupled receptors are muscarinic (**acetylcholine*), dopaminergic, and metabotropic glutamatergic receptors. Finally, enzyme-linked receptors function as enzymes or are intimately associated with an enzyme. Examples are receptor **protein kinases* (Numa *et al.* 1983; Marshall 1995). *In situ*, receptor proteins do not live in isolation; they interact dynamically with other membrane, cytoskeletal and cytoplasmatic elements to form macromolecular complexes, which together control specific facets of cellular state (Kim and Huganir 1999).

Generally speaking, synaptic receptors fit to fulfil the role of elementary hardware components in biological 'learning machines' (Dudai 1994a). They could serve as:

1. **Acquisition devices*. Synaptic messages encoding stimulus information trigger a change in the target nerve cell by first activating receptor proteins. These receptors could therefore be regarded as 'cellular acquisition devices', implementing decoding and registration functions. Examples are various types of glutamatergic receptors that mediate excitatory transmission in the mammalian brain.

2. *Transducers of *context*. In the acquisition **phase* the receptor could mediate information about the conditioned stimulus, about the **reinforcer* (e.g. Shimizu *et al.* 2000), or about other, contextual **dimensions of the input*.² For example, receptors for acetylcholine in the mammalian brain transduce information on the novelty or saliency of stimuli (e.g. Naor and Dudai 1996). **Noradrenergic* and dopaminergic receptors probably fulfil similar types of roles. An illustration of the role of receptors in encoding context at the cellular **level* is provided by their ability to modulate stimulus-induced long-term alterations in synaptic efficacy (e.g. Kirkwood *et al.* 1999, also **long-term potentiation*).
3. **Coincidence detectors*. Receptor proteins could associate incoming stimuli. A popular example is the glutamatergic NMDA receptor, a molecular AND gate that integrates information encoded by glutamate and by membrane depolarization. Another example is provided by the role of serotonergic or peptidergic receptors³ in the conditioning of defensive reflexes in **Aplysia*. In this case, the transmitter, which carries information about the unconditioned stimulus, activates a receptor-coupled enzyme, adenylyl cyclase. For optimal activation, however, the enzyme also requires calcium, which carries information about the conditioned stimulus. This dually activated receptor was reported to display the order and temporal-specificity constraints that are characteristic of **classical conditioning* (Yovell and Abrams 1992).
4. *Information storage devices*. Use-dependent alterations in the sensitivity or availability of receptor molecules could encode long-lasting modifications in synaptic activity, and hence subserve the **persistence* of the **engram* over time (Changeux *et al.* 1984; Lynch and Baudry 1984). The idea is that even in the absence of other experience-dependent lasting synaptic modifications, increased availability or facilitated kinetics of a receptor is read-out by the retrieval input as a facilitated synaptic state. The proposed role of the AMPA-type glutamate receptor in long-term potentiation is a prominent example (Nayak *et al.* 1998; Shi *et al.* 1999).

In fulfilling the above roles, the specificity and effectiveness of the receptor-mediated information could be contributed by the sender (the ligand), the receiver (the receptor), or, most probably, by both. Candidate dimensions of specificity include the spatial (point of origin), temporal (rate and frequency), and intensity of the incoming stimulus, the location and concentration of the receptor on the cell surface, and the combinatorial

Receptor

activation of the receptor and its downstream intracellular signal transduction cascade(s) together with other types of receptors and cascades (e.g. Gutkind 1998; Madhani and Fink 1998).

The multiple roles of synaptic receptors in learning, memory, and retrieval marks them as promising targets for new memory-enhancing drugs (*dementia, *nootropics). For example, agonists of AMPA-type glutamate receptors have already been tested on humans and reported to improve memory (Ingvar *et al.* 1997).

Selected associations: Acquisition, Coincidence detector, Ion channel, Neurotransmitter, Stimulus

¹Ligand-gated is contrasted with 'voltage-gated' channels (see *ion channel). Ligand-gated receptor channels are sometimes referred to also as 'chemically gated'. It makes sense to reserve the term 'ligand gated' to channels that are regulated by an extracellular ligand such as a neurotransmitter, and use the term 'chemically gated' to refer to channels that are regulated by either extracellular or intracellular compounds.

²The types of roles fulfilled by receptors in acquisition, including encoding of context, could also be fulfilled in *retrieval.

³'Serotonergic' is a receptor for the neurotransmitter serotonin, and 'peptidergic' is a receptor for peptides that function as neurotransmitters, neuromodulators and hormones.

measure only familiarity, or recency among equally familiar targets.

The aforementioned types of knowledge are reflected in an influential *model of recognition, called the *dual-process* model (Juola *et al.* 1971; Mandler 1980; Jacoby 1991; Yonelinas 1999). As the name implies, this model depicts recognition as being subserved by two qualitatively different processes. One process is the judgement of *familiarity*; it is generally considered to be automatic and fast.¹ The other process is termed *recollection*, or search, or retrieval.² It is considered to be intentional and slower, and refers to the retrieval of information about the target and its context. This complements the familiarity decision, and identifies specific attributes of the target and the context. The familiarity process is also labelled *K* (for '*know*') and the recollection process *R* (for '*remember*'). The terms 'recollection', 'remember', and 'know' connote *conscious awareness, and indeed, the use of these terms in the context of recognition stems from human memory research, where remembering and knowing is *declarative (e.g. Tulving 1985b). One can, however, adapt the dual process model to animal studies where conscious awareness is not assumed. An interesting spin-off of the dual-process model is the blurring of distinction between recall and recognition. Prominent models of recall propose two stages, the second of which is recognition (see there). A combination of the two-stage model of recall and the dual-process model of recognition, depicts recall as involving a search phase in which the target is generated, followed by familiarity judgement and recollection. But recollection itself could involve activation or reconstruction of *internal representations in the absence of the target, which is *bona fide* recall. This situation reinforces the notion that both recall and recognition are processes along the continuum of *retrieval (Tulving 1983). These situations differ in the information sought in each case (about the context in recognition, about the target in recall; Hollingworth 1913), and in the retrieval cues (provided by the experimenter or the environment in recognition, self-generated in recall). The clearest distinction between recognition and recall is therefore in the test situation, not necessarily in the type of processes employed by the subject to perform the task.³

Whereas whether animals are capable of genuine recall is open to debate, ample evidence proves that they can surely recognize (e.g. *classical conditioning, *instrumental conditioning, *delay task). Two points are noteworthy. First, is the recognition of only detection of familiarity, or also identification of the specific attributes and context of the target, as we humans recognize? The answer is likely to depend on the species

Recognition

1. The judgement of previous occurrence.
2. The brain process(es) by which this is achieved.
3. **Recognition test:** A test situation in which the *subject judges the familiarity or recency of a *stimulus.

Similarly to *recall, recognition (*re-cognoscere*, Latin for to get to know again) refers to a type of memory (definition 1, Mandler 1980), a brain process (definition 2), and a memory test (definition 3). To judge that something has occurred previously may mean different things, ranging from the detection of familiarity or recency to the identification of the specific attributes of the target in its proper *context. Imagine entering a classroom and detecting a new student in the front row. Her face looks familiar, but you have no idea who she is. In this case recognition means detection of familiarity only. But now suppose you enter the classroom and realize that the person in the front row is Ann, whom you first met last month at the Faculty club. This is also recognition, but this time, it involves much more knowledge. Many recognition tests in the laboratory

and the task, but in any case requires the proper attention in construing the data. Second, in those tests in which recognition is judged by a decreased response to a familiar stimulus, the possibility that the *performance represents *habituation should not be ignored.⁴ These caveats notwithstanding, there are clearly tasks in which animals can recognize better than humans, due to superior sensory sensitivity, discriminability, and possibly categorization in the domain of the relevant sensory modality. A beautiful *classic example is provided by Argos, Odyssey's dog: the old dog is the first to recognize Odyssey upon his much belated return to Ithaca, probably by his scent, whereas the nurse Eurykleia needs much more time and the scar on her master's leg as a retrieval cue (Homer, *Odyssey, Books XVII, XIX*). There are, of course, tasks in which the recognition capacity of the human brain is impressive (Dudai 1997a). For example, in one study subjects learned to recognize no less than 10 000 pictures and the author concluded that even a million are possible (Standing 1973).

What are the brain substrates of recognition? This question can be broken into the following subquestions: (a) What is the flowchart diagram of the circuits that subserve recognition? (b) What is the role of each of the stations in these circuits in the different postulated subprocesses of recognition? and (c) What are the cellular and molecular mechanisms that subserve these roles in each of the stations? The experimental *systems used in this type of research range from recognition tasks, mostly visual, in humans and in the *monkey, to recognition tasks involving the chemical and other senses in rodents (e.g. Mishkin and Murray 1994; Nakamura and Kubota 1996; Schacter *et al.* 1996c; Reed and Squire 1997; Tanaka 1997; Tulving and Markowitsch 1997; Aguirre and Farah 1998; Berman *et al.* 1998, 2000; Brown and Xiang 1998; Murray and Mishkin 1998; Parker and Gaffan 1998; Steckler *et al.* 1998a,b; Suzuki and Eichenbaum 2000; von Zerssen *et al.* 2001). The *methods involved are selective lesions in experimental animals and analysis of brain damage in *amnesics, cellular physiology and molecular biology in laboratory animals, and in recent years, *functional neuroimaging of human subjects. To this one should add psychophysics and modelling, that contribute to the understanding of the *algorithms involved (e.g. Wallis and Bulthoff 1999). But before saying a few words on some general conclusions of this research, it helps to ask what is it that we expect the system to contain. Well, it must contain, as any other memory system, circuits that store the information and are able to retrieve it. But there is an additional component that is a must for recognition: a comparator, that matches the target with stored internal

representation, and detects familiarity/novelty. A brain-stem–thalamocortical loop was suggested to subserve this function in taste recognition (Berman *et al.* 2000); other circuits, including corticocortical ones, could fit as well in other systems.

The storage and retrieval circuits that subserve recognition are in general similar to those that subserve recall (Haist *et al.* 1992; Zola-Morgan and Squire 1993), and include the *limbic archicortex, paleocortex, neocortex, and neuromodulatory systems that regulate *acquisition, *consolidation, and retrieval, including monitoring (*cerebral cortex, *hippocampus, *metamemory, *retrieval). The identity of the areas and their subdivisions and their relative contribution depend on the task type and particulars, e.g. sensory modality involved, or whether the task is spatial or not. Within these systems, there are species-adapted specializations that allow recognition of specific features in the world, such as letters and digits in humans (Polk and Farah 1998), faces in mammals (Gross *et al.* 1972; Kendrick and Baldwin 1987; Desimone 1991; Golby *et al.* 2001), or species-specific melodies in birds (*bird-song). Furthermore, different components have been proposed to subserve differentially the two postulated subprocesses of recognition. Hence it was proposed that a neuronal system centred on the perirhinal cortex contributes preferentially to the familiarity judgement, whereas the system centred on the hippocampal formation contributes preferentially to recollection (Brown and Xiang 1998; see also Eldridge *et al.* 2000). Similarly, there is evidence that in word recognition, the left pre-frontal, left parietal, and posterior cingulate regions contribute to recollection more than to familiarity judgement (Henson *et al.* 1999). Within cortical circuits that subserve recognition, discrete types of cellular responses are discerned, including a characteristic suppression of the neuronal response to a stimulus once it becomes familiar (Desimone 1996; Brown and Xiang 1998; *priming⁵). Recognition learning may also take advantage of the presence in the cortex of specific molecular 'novelty switches', which are activated only by unfamiliar but not by familiar stimuli, and whose activation triggers *intracellular signal transduction cascades, culminating in use-dependent long-term *plastic changes in the circuit that ultimately encodes the familiarity (Berman *et al.* 1998, 2000).

Selected associations: Delay task, Habituation, Imprinting, Recall, Surprise

¹The detection of familiarity could be examined in the context of system detection theory (e.g. Yonelinas 1999). This theory (Wickens 1984) is applicable to situations in which there are two or more states

Red herring

of the world that cannot be easily discriminated, and whose discrimination involves two response categories, yes or no, e.g. familiar or unfamiliar. This discrimination is not absolute, but rather based on a number of factors, including the discriminability of input signals and the *criteria used by the *system, themselves shaped by the price paid for false decisions. These factors depend on experience and *context. The signal detection theory was originally developed to deal with the detection of sonar and radar signals in the Second World War. It is a prominent example of the application of engineering and information processing theories to human psychology; a related example is the application of such theories to *attention.

²It is important to note that the use of the term retrieval in the dual-process theory of recognition refers to a limited aspect of retrieval (see also *recall). Retrieval in general is a universal *phase of memory, without which no stored information can be actualized. Detection of familiarity, by definition, involves retrieval as well, in this case of the old *internal representations that are compared with the new ones. It is, however, the convention in the discussion of the dual-process models of recognition to use the term 'retrieval' (or 'recollection', or 'search') to refer specifically to the retrieval of information about the identity of the recognized item.

³Again, the distinction between recognition and recall becomes even fuzzier when recognition pertains to the judgement of previous occurrence of mental images, propositions, and concepts in the train of thought, rather than of sensory *stimuli only. Hence when one recognizes a thought as contemplated previously, it involves recall and recognition intimately combined.

⁴The relationship of habituation to recognition is not trivial. A *reductionist view considers habituation as rudimentary recognition, because the nervous system functions differently if the stimulus has occurred previously. However, the simplest reflex habituation does not involve matching of stored representations with the percept of the on-line stimulus (e.g. **Aplysia*). Complex habituation, such as that of the mammalian orienting reflex (*sensitization), may already involve such matching to detect novelty (Sokolov 1963b).

⁵Although in the cortex cellular response in recognition may resemble that seen in repetition *priming, priming is not the source of familiarity in recognition (Stark and Squire 2000).

(*scoopophobia). The diversionary data or concepts could pose a real treat to academic careers. Indeed one may toy with the arithmetic of the red herring phenomenon: the magnitude of damage is likely to be proportional to the significance of the research topic, the time elapsed since the diversion, the ego-driven stubbornness of the investigator, and the number of scientists that managed to become enticed by the misleading clue.

Red herrings come in multiple sizes. Tiny herrings are daily encounters in research laboratories, and are frequently identified rapidly as *artefacts and 'disturbances' (e.g. Lynch 1985). They are disguised as imaginary bands on electrophoretic gels, speckles on blots, blips on oscilloscopes, distortions in histological preparations, or erratic software. Experienced investigators are quick to sort out the herrings from the real big fish, and alert the scientific community to the potential problem (e.g. Moser *et al.* 1994). Furthermore, talented scientists somehow find their way between the exceptional and the expected; in encountering surprising findings, such individuals may insist that what others see as a red herring, is actually not, and ultimately they win.

Medium-size herrings are those that affect a person's career over extended periods but do not necessarily divert the activities of the research community at large. This may happen, for example, in eccentric projects, which are not quick to attract many followers. Imagine a hypothetical scientist sitting in a hypothetical laboratory, aiming to elucidate the function of a hypothetical metabolic pathway. That person erroneously becomes convinced (because of a sampling error, dim light, or too much beer) that a hypothetical rare fly carries a new variant of an enzyme that catalyses a redundant metabolic pathway, and for which 72 variants had already been discovered in other species. As after, that same person devotes a frustrated career to the search for the nonexistent isozyme. Sad, indeed, but the impact on the scientific community is bound to be small, if at all.

Some research programmes that now look rather eccentric were not regarded as such at their time; see, for example, the case of *Clever Hans. In some respects, the horse Hans was a red herring on the path of experimental psychology. In that specific case, the exposure of the interpretational and conceptual mistake had a beneficial effect on subsequent research (Sebeok and Rosenthal 1981), because it led to the identification of sources of errors, for example, of the demand characteristics type (Orne 1962, *bias). Giant herrings, of the order of magnitude of the Clever Hans phenomenon, may stir stormy waves in the scientific community. A more recent example is that of memory transfer. In the early sixties, several laboratories devoted

Red herring

Something that diverts attention from the real issue or purpose.

A bundle of smelly smoked (red) herrings drawn across a fox's trail confuses the hounds (Cowie *et al.* 1985). Discovering that a *metaphorical red herring had been hiding in one's path is a scientist's nightmare, although not discovering it if it is there is even worse. It possibly tends to materialize more frequently on the fringe of hectic, fast-advancing disciplines that attract risk-takers

substantial resources in an attempt to replicate the results of the so-called memory transfer experiments. The original reports have claimed that specific memories can be transferred from one individual to another, either via cannibalism (in the flatworm *Planaria*) or in brain extracts (in rats). For a while the possibility existed that many research groups, excited by the striking breakthrough, would embark upon a lengthy journey into a blind ally. As the idea of specific memory transfer is so catchy, the methods and data were soon scrutinized and ultimately the approach was abandoned (Harrity *et al.* 1964; Byrne *et al.* 1966).

The 64 000 herrings question is whether right now we coexist with hidden fat red herrings, that lure scores of labs off-track. One can never be sure. Is there a red herring element in the link of massive modulation of neuronal *protein synthesis and gene expression with memory? (*consolidation, *immediate early genes, *late response genes.) And is *long-term potentiation, a fascinating cellular phenomenon *per se*, actually diverting us away from the ultimate goal of memory research, namely the mechanisms of experience-dependent alterations in *internal representation? Thus are heretic notions, no doubt, but orthodox believers may not be especially good in detecting conceptual mines. We should accept that red herrings are cohabitants of the scientific *culture, and that the success in detecting them is based on the combination of luck, open-mindedness, intuition, humbleness, and most of all, experience. At least the latter competence can be acquired. A good lab should therefore alert its graduates to the smell of red herrings. Familiarity with the history of the discipline, and with the failures as well as the success stories, is useful in achieving that goal.

Selected associations: Clever Hans, Culture, Phrenology

example, from orthodox *behaviourists. Clearly, biology at large has accomplished some of its most impressive triumphs so far by adhering to the radical reductionist approach, epitomized in state-of-the-art molecular and cellular biology, genetic engineering (*neurogenetics), and the Genome project. Whether ardent reductionism also fits all the needs of memory research is, however, still a debatable question.

In science and the philosophy of science, 'reduction' (*reducere*, Latin for 'to bring back') is employed in different connotations (Nagel 1979; Mayr 1982; Dudai 1989). In its most common use, it refers to the mere process of analysing a complex phenomenon by dissecting it into elementary components. This is '**constitutive reductionism**' (definition 1, 'description'). In the context of our discussion, it means that one attempts to identify brain, neuronal, or molecular correlates (*criterion) of learning and memory. This type of reductionist approach is accepted by all neurobiologists and practised by the majority of them; ethologists and behavioural psychologists can still excuse themselves from preaching the reductionistic *zeitgeist. In the course of practising constitutive reductionism, neurobiologists take 'reductive steps'. These are shifts in the level of analysis from the level of a *system as a whole to the level of its components. For example, a shift in the analysis from that of molar electrical activity in *cortex to that of individual cortical neurons, or from single neurons to individual molecules in the *synaptic membrane, is a reductive step. In addition, constitutive reductionism almost always involves 'simplifying steps'. These are procedures taken to facilitate experimental analysis, without altering intentionally the level of analysis. For example, proceeding in the analysis of single neuron activity from *in situ* to a brain slice (e.g. *hippocampus), or removing part of the tissue and hence decreasing the number of cells in a ganglion (e.g. *Aplysia), while still maintaining the cellular level of analysis, is a 'simplifying step'. This *methodology is best epitomized by Johnson (1751), who noticed that 'Divide and conquer is a principle equally just in science as in policy'. A 'simplifying step' may also mean switching to a simpler organism or circuit that display the phenomenon, process, or mechanism in question (*model, *simple system).

More rigorous than constitutive reductionism is '**explanatory reductionism**' (definition 1, 'explanation'). It assumes that, ultimately, the knowledge of the components will explain properties of the system as a whole. This means, in our case, that having once understood the properties of neurons and molecules, one should be able to show how these properties are

Reduction

1. **The description or explanation of higher-*level phenomena in terms of lower-level phenomena.**
2. **The formulation of a theory in terms of a more inclusive or basic theory.**

'Reductionism' is a tenet of modern neuroscience. Only its version and explicitness vary among subdisciplines and their practitioners. Neuroscientists attempt to explain mental faculties by brain faculties, hence mental phenomena by biology. In that they are different, for

necessary and sufficient to explain learning and memory. Most neurobiologists practise constitutive reductionism in the hope of achieving explanatory reductionism. Others doubt whether in the neurosciences, satisfactory explanatory reductionism is always feasible.

Most demanding is '*theory reductionism*', i.e. reducing a theory, including all its concepts and laws, into another, more inclusive or basic theory (definition 2; e.g. Nagel 1979). This would mean that, having a biological theory (such as a future theory of brain function), one would be able to reduce it without residue into a physical theory. Profound doubts are often expressed whether this is appropriate and feasible (for a modern *classic, see Fodor 1974). '*Theory reductionism*' requires that 'bridge laws', or 'correspondence rules', be established to enable shifts from the terminology of one theory to the other. A limited concept of 'correspondence rules' is also useful in the less stringent, descriptive, or explanatory reductionist approaches, because it focuses attention on the need to formulate systematic relationships between findings at one level to those at another. For a selection of the literature on explanatory and theory reduction in the neuroscience, see Putnam (1973), Searle (1990), Schaffner (1993), Churchland and Churchland (1998), Crick and Koch (1998), and Fodor (1998). For issues related to other facets of reductionism in biology, which reflect on neurobiology and especially on *development and neurogenetics, see Hull (1981), Sober (1994), and Kirschner *et al.* (2000). And for a bit more on the philosophy involved, see Brentano (1874) and Kim and Sosa (1999).

Within the context of the present discussion, two issues deserve special attention. The first is what do we expect the relationships to be between properties, processes, and events at a lower level to those at a higher level, and vice versa. It is safe to assume that even conservative psychologists will agree that mental events somehow relate to physical events. But what does the relationship mean? For example, the two may correspond to each other property by property, and ultimately unique mental states would correspond one by one to unique brain states. If this is true, then having identified a certain physicochemical brain state in sufficient detail, we will be in a position to deduce from a set of physiological data what the *subject *recalls. This argument applies to multiple levels of brain function: knowing the molecular details will be expected to tell us precisely what a cell encodes, monitoring the electrical activity of a *cell assembly will be expected to tell us exactly what the assembly represents, etc.¹ An alterna-

tive possibility is that a given mental/behavioural state is encoded by different molecular and physiological states. This would mean that indeed, a particular mental/behavioural state corresponds to some physical events in the brain, but the former does not necessarily correspond to a unique configuration of the latter. This view might induce chagrin in many practising neurobiologists who attempt to read into defined codes, representations, and computations. The problem is not merely philosophical. When we devote our career to determining with great pains the activity of *signal-transduction cascades within neurons, or of circuits within brain regions, do we expect to be able, at the end of the day, to conclude from the lower-level data what the overall higher-level meaning is, and at what level of accuracy? Do we have an 'uncertainty principle' operating at the level of neuronal representations? Also, is knowing more lower-level details always means knowing more about the higher-level functional state of the system (Alberts and Miake-Lye 1992; Barkai and Leibler 1997; Sanes and Lichtman 1999; Kirschner *et al.* 2000)?

The second issue, related to the first one, is how far should one attempt to reduce a system without losing the characteristic properties that had provided the incentive for the research programme in the first place. In other words, how much of the system properties are 'emergent', i.e. appear only at a higher level of organization or function, because of some interactive or integrative properties (Pepper 1926; Meehl and Sellars 1956)? Why not aim at reducing the description of brains to the language of the elementary particles of matter? Most reasonable people will ridicule such a proposal, yet there is nothing in it that contradicts ardent reductionism. If not elementary particles, why not atoms? Or molecular motifs? When do reductionistic aspirations cease to amuse and become a serious scientific goal?² It seems that in the case of memory research, the clue lies in the definition of *memory. Once we agree that memory is retention over time of *internal representations, we should look for the level at which behaviourally meaningful representations are encoded. Lower levels (lower than cellular) will provide us with valuable information on mechanisms that subserve memory, but are unlikely *per se* to identify what a specific memory is. Memory research, as in any other branch of biological research, thus requires pragmatic, 'focused reductionism' (Dudai 1992). Otherwise, we may find ourselves in a situation so enchantingly illustrated by Geertz (1983): "There is an Indian story... about an Englishman who, having been told that the world rested on a platform which rested on the back of an elephant which rested in turn on the back of a turtle,

asked... what did the turtle rest on? 'Another turtle'. And that turtle? 'Ah, Sahib, after that it's turtles all the way down.'

Selected associations: Criterion, Level, Method, Paradigm, Zeitgeist

¹This argumentation is intentionally restricted to the pragmatic point of view of the experimenter. What is argued here is only whether there is one-to-one, or one-to-many, or many-to-many correspondence between the particular neuronal state and the particular behavioural or mental state. Nothing is claimed about the quality or type identity of the corresponding states, e.g. whether some events are of a 'physical type' and others of a different, 'mental type' (e.g. Block and Fodor 1972). Further, the correspondence may reflect correlation, supervenience, or causality (*criterion).

²This is actually still another manifestation of the classic 'Sorites paradox', which is presented in *insight.

the *subject's action; in the nervous system all events, including actions, translate into stimuli. Hence stimuli in general could have both eliciting and reinforcing functions, and the experienced experimenter makes good use of both.

On the history of the concept: two main approaches are distinguished in the *pre-scientific* thinking. One is the totalitarian, 'exogenous' approach, characteristic of certain religions and regimes. It states that conforming to the rules is bound to bring reward by deity or king, whereas opposing the rules will result in inevitable punishment. The other, 'endogenous' attitude attempts to identify drives that shape human behaviour independently of external authority. The most popular example is 'hedonism', the philosophical doctrine holding that only what is pleasant is intrinsically good; it is epitomized in the words of Diogenes Laertius (3C AD): 'All living creatures from the moment of birth take delight in pleasure and resist pain from natural causes independent of reason' (Long 1986).

The *scientific* treatment of reinforcers and reinforcements drew in its early days from two conceptual sources. One, philosophical contemplation of the attributes that foster the association of mental events, such as similarity, contrast, and contiguity. This philosophy can be traced back to Aristotle, but the main influence in the early days of experimental psychology was that of British Associationism (*associative learning). The other influential conceptual source was Darwinian evolutionism (Wilcoxon 1969; Boakes 1984). Evolution, so goes the Darwinian view, is moulded by natural selection of adaptive traits among the pool of genetically generated variations. Spencer, Bain, and Baldwin were the first to adapt this selectionist view to the theory of learning (*ibid.*; Cason 1932).² In a nutshell, the idea was that the adaptive processes of the ontogenesis of the individual's behaviour parallel the processes of phylogenesis, in that pleasurable states are selected among other states of the organism, whereas noxious states are selected against. This view has culminated in Thorndike's 'law of effect', a *generalization concerning causality and feedback, which posits that behavioural responses that lead to gratification are reinforced by their effect and repeated whereas those that result in discomfort recur less and less (Thorndike 1911; *instrumental conditioning).

The law of effect was remarkably influential in the theory of reinforcement, although within different conceptual frameworks. A prominent development was the consideration of reinforcement in stimulus terms in the elaborate Skinnerian system of operant conditioning (Skinner 1938; Ferster and Skinner 1957).

Reinforcer

A *stimulus that alters the probability or intensity of response.

'Reinforcer' (*fortis*, 'strong' in Latin), which is an *agent* or *event*, and 'reinforcement', which is the *process* that this agent is assumed to trigger and sustain, are among the most loaded terms in the behavioural literature. This is not because the concepts involved are necessarily more complex than certain other behavioural concepts, but because frequently their discussion connotes particular theoretical constructs, some of which have gravitated toward the status of a religious sect with all the convictions and emotions involved (*paradigm, *zeitgeist). The reinforcer, via the postulated reinforcement, can *shape* behaviour, and also *maintain* the response level once achieved; if the reinforcer is removed, the behaviour risks *extinction. The reinforcer itself is traditionally not considered to *produce* learning, only to augment response, which promotes *associations. Examples for reinforced learning are provided in many contexts in this book (e.g. Figures pp. 70, 76, 129, 131; *instrumental conditioning). Whether this dissociation between the reinforcing and 'teaching' actions of stimuli, respectively, holds water at *reduced *levels of description, is debatable (e.g. Shimizu *et al.* 2000; Berman and Dudai 2001).¹ 'Stimulus' in the above definition refers to stimuli presented intentionally to the *subject, or to incidental stimuli, or to stimuli that result from the exogenous and endogenous effects of

Reinforcer

Skinner's approach supported the 'empirical law of effect', which is similar to the original law but devoid of the theoretical assumptions about internal states, which orthodox *behaviourists shy away from. Another influential theory considered reinforcement in terms of drive reduction. Drives are hypothetical endogenous processes that impel an individual to act on the world or react to it. The drive reductionists proposed that reinforcements satisfy because they reduce drives. In other words, reinforcers promote *homeostasis. The 'law of primary reinforcement', coined by Hull (1943), epitomizes the idea: 'Whenever a reaction takes place in temporal contiguity with an afferent receptor impulse resulting from the impact upon a receptor of a stimulus energy, and this conjunction is followed closely by the diminution in a need (and the associated diminution in the drive and in the drive receptor discharge), there will result an increment in the tendency for that stimulus on subsequent occasions to evoke that reaction' (*ibid*; Hull's symbolic notations were omitted from the quote for simplicity) (see also: Miller and Dollard 1941; Birney and Teevan 1961; Wilcoxon 1969).

The reader should not be misled, however, to think that all the theories of reinforcement were related to the concept of effect. Many prominent thinkers considered the strengthening of response in the absence of the action–effect assumptions. The best example is Pavlov (1927). He used 'reinforcement' to account for the action of the unconditioned stimulus in *classical conditioning, which has nothing to do with the idea of action–effect.³

Over the years, additional theoretical approaches to the problem of reinforcement have emerged. A notable example is the proposal that reinforcement is primarily a function of the value of the response, not of the stimulus, and this response value is greater if the opportunity to perform the behaviour is smaller (Premack 1965). For example, water is an effective reinforcer for a thirsty rat because it reinforces a highly valued behaviour, drinking. Responses more valued by the organism reinforce those that are less valued. This also implies that the reinforcement value is relative. The thirsty rat will increase activity in a running wheel if this is followed by delivery of water; but a water-satiated, running-deprived rat will increase its drinking if this gets it access to running (Premack 1962). Some modern approaches to reinforcement abandon the simple cause-and-effect feedback loop of the effect theories, and take into account complex system properties of brains and organisms, drawing from system theory, cognition, and ecology (Timberlake 1993).

A major chapter in the analysis of reinforcers and reinforcement began with the first systematic attempt to identify brain circuits of reward and punishment. In a *classic series of experiments it was shown that rats could become engaged in intensive self-stimulation via chronically implanted brain electrodes, provided these electrodes are inserted into specific sites in the brain, such as the septal area and the medial forebrain bundle (Olds and Milner 1954; Olds 1969; *dopamine).⁴ This gave a boost not only to science fiction, but also to the cartography of the brain in terms of circuits that encode the *internal representation of reinforcers and compute reinforcements (Livingston 1967; Robbins and Everitt 1996; *limbic system).

Applied reinforcers and postulated reinforcements vary greatly by the type of experimental *system, *assay and protocol. It is, however, methodologically useful to consider some *generalizations. The *dimensions listed below refer to selected attributes of the reinforcing event, or of inferred reinforcement processes, or of experimental manipulations used to apply the reinforcer in order to exercise the reinforcement. All these factors are often mixed practically in the design and execution of the experiment.

1. *Valence*. A reinforcer, the addition of which strengthens the response, is termed a 'positive reinforcer'. A reinforcer, the removal of which strengthens the response, is termed a 'negative reinforcer'. A candidate reinforcer that leaves the response unaltered is a 'neutral reinforcer'. Many authors use the term positive reinforcer synonymously with 'reward'. This is basically OK, although reward may be delivered without affecting behaviour, as any parent knows, whereas a positive reinforcer by definition affects behaviour. It is not OK, however, to exchange negative reinforcer with 'punishment'. Indeed, both refer to aversive stimuli. But whether an aversive stimulus is a negative reinforcer or punishment depends on the stimulus–response contingencies. Hence an electric shock is a negative reinforcer if its removal is contingent on the response, a removal that is certainly not punishment, but is a punishment if its application is contingent on the response. This is the appropriate point to add that the valence of reinforcers is not always apparent at the time of the experiment. There are situations in which the subject appears to be reinforced in spite of the absence of an apparent reinforcer (e.g. latent *learning, *observational learning). In these cases it makes sense to talk about a 'latent reinforcer'. In the theory of learning there are views that learning is impossible if there is no reinforcer whatsoever; therefore, if there is no apparent reinforcer, there must be a latent one.

2. Magnitude. This refers to quality, or quantity, or both. Reinforcers differ in their quality; some types of stimuli are more effective in a given situation than others, e.g. food vs. toys to a hungry subject (Jarvik 1953; Garcia *et al.* 1968). Reinforcers could also differ in quantity, in terms of intensity or schedule of delivery.

3. Hierarchy. A reinforcer that has *a priori reinforcing properties to an individual of the species, is a 'primary reinforcer'. A reinforcer whose reinforcing properties are due to association with a primary reinforcer is a 'secondary reinforcer', or, depending on the order of association, 'higher-order reinforcer' (compare with higher-order conditioning in *classical conditioning).

4. Schedule. The schedule in which reinforcer/reinforcement is delivered is crucial to the behavioural outcome. Generally speaking, reinforcement could be delivered continuously, so that every response is reinforced, or intermittently, so that some responses are reinforced and some are not. Contrary to the intuition of newcomers to the discipline, intermittent reinforcement is often more effective than continuous reinforcement; we have already encountered this in *experimental extinction (the so-called 'PREE effect'; see there). Four main types of schedules are common in intermittent reinforcement: (a) **fixed ratio**, in which a response is reinforced upon completion of a fixed number of responses; (b) **variable ratio**, in which the reinforcement is scheduled according to a random series of response/reinforcement ratios; (c) **fixed interval**, in which the first response occurring after a given interval of time measured from the preceding reinforcement is reinforced; and (d) **variable interval**, in which reinforcements are scheduled according to a random series of intervals (Ferster and Skinner 1957; on the special case of delayed reinforcement and its behavioural consequences, see also Renner 1964).

5. Level. At the behavioural level, reinforcers are sensory input. At the circuit level, they are input from other circuits in the brain, or chemical messages such as hormones from other parts of the body. At the cellular and *synaptic level, reinforcers are encoded in *neurotransmitters, neuromodulators, ion currents, and other chemical or electrical messages.

It is currently possible to consider the neural encoding of reinforcers, and the computation of reinforcement, in terms of identified circuits, synapses, and molecules (e.g. Robbins and Everitt 1996; Schultz *et al.* 1997; Picciotto *et al.* 1998; Menzel *et al.* 1999; Corbit and Balleine 2000; Shimizu *et al.* 2000). Key brain structures involve *limbic–corticostratal–pallidal circuitry (Robbins and Everitt 1996) and diffused neuromodulatory systems (Schultz *et al.* 1997). This accumulated knowledge

contributes to the theory of brain and behaviour, and to the understanding and treatment of pathological conditions in which abused reinforcements result in bad *habits (Picciotto *et al.* 1998; Robbins and Everitt 1999). We should also become tuned to the possibility that soon there will be a need to apply this knowledge to the effective and safe training of smart robots (Saksida *et al.* 1997).

Selected associations: Algorithm, Instrumental conditioning, Model, Neurotransmitter, Stimulus

¹Teaching as used here can refer to instructive, adjustive, or selective actions, as explained under *stimulus.

²As in other entries in this book, unless otherwise indicated, theory does not mean a formal physical theory, but rather a conceptual framework for further hypotheses and experiments (see in *algorithm).

³Note that in this case the reinforcer does enter into the association. The use of the reinforcer/reinforcement terminology in the context of classical conditioning is considered by some authorities as obsolete.

⁴The original observation was fortuitous: James Olds noted that a rat keeps returning to the place on the table top where it had been when an electrical stimulus was applied to its brain via a chronically implanted electrode. This has led to experiments in which rats were trained to press a lever to self-deliver the stimulus. For more on the history of this important chapter in the neurobiology of reinforcement, drive, motivation, and learning, as well as on the *real-life events beyond the *culture of science, see Milner (1989).

Retrieval

1. The actualization of learned information.
2. The access, selection, reactivation, or reconstruction of stored *internal representations.
3. The brain state required to attempt or attain 1 and 2 above.

Until fairly recently, retrieval was an uncharted terrain in the neurobiology of memory. This was particularly striking when compared with the rich contribution of experimental psychology and modelling to the phenomenology and theory of retrieval (Semon 1904; Shiffrin and Artkinson 1969; Anderson 1983; Tulving 1983). This situation was also in sharp contrast to the signal role of retrieval in behavioural *assays of memory, for, at the end of the test, even if the intention is to study *acquisition, *consolidation, or retention of memory, it is retrieval that is tested. Hence many brain scientists study retrieval without even being aware of it. In a way, they are in the same

Retrieval

position as Mr Jourdain, Molière's bourgeois gentleman (Molière 1670), who suddenly realized ('insight') that he was speaking prose for 40 years without ever knowing it.

Definition 1 is molar, and pertains to both the phenomenon and the process of retrieval. Definitions 2 and 3 refer to the subprocesses and the brain state, respectively, that underlie 'retrieval' as defined in 1. Definition 3 includes also those situations in which the attempt to retrieve a particular item fails, or is only partially successful (e.g. Hart 1965; Brown and McNeill 1966).

The following points highlight selected attributes of retrieval:

1. At the behavioural *level, a *memory unretrieved is undetected*.¹ It is actually possible to go a step further and claim that there is no such thing as a behaviourally-meaningful *engram in a nonretrieved state (Tulving 1991; *persistence).²
2. Similarly to other memory *phases, retrieval refers to a *heterogeneous group of processes* that share a function. The computational theories, *algorithms and circuits that subserve retrieval of simple *reflexive memories are clearly different from those that subserve the actualization of abstract thoughts. Some operational principles and elementary building blocks of the molecular and cellular hardware may, however, be universal.
3. Success in retrieval depends on the *availability of appropriate *cues*. These cues are either external or self-generated. Cues are instrumental in retrieval even if unidentified by the *subject or the experimenter. Cues that are part of the response (e.g. a digit in a multidigit number) prompt gradual reconstruction of the memory; the product is termed 'redintegrative memory' (from 'reintegrative'; Horowitz and Prysulak 1969).
4. Retrieval is more effective when attempted in the presence of cues that were present in acquisition (*context, *state-dependent memory). This idea is reflected in the 'encoding specificity principle', which refers to the overall *relations between acquisition and retrieval*: retrieval occurs if and only if properties of the trace are sufficiently similar to the properties of the information available in retrieval (Tulving 1983). In other words, for the *system to retrieve, it must resonate with the input. A related idea is that retrieval is more effective when the subject processes the information in retrieval in the same way that it was processed in acquisition; this is termed 'transfer appropriate processing' (Morris *et al.* 1977). For example, in verbal tests,

semantic processing of verbal material in learning favours success in retrieval using semantic but not phonological processing, and vice versa. Whereas 'encoding specificity' emphasizes the information encoded, 'transfer appropriate processing' emphasizes the processing of that information by the subject.

5. Retrieval is not merely a passive readout of information, it is also an experience; therefore, once retrieved, *the engram is unlikely to remain exactly the same*. This is evident from studies at the behavioural, brain system, cellular, and molecular levels (Bartlett 1932; Schacter *et al.* 1998; Sara 2000; *false memory; see also below).

How does retrieval work in the nervous system? A simple case is illustrated by *classical conditioning of the withdrawal reflex in *Aplysia*. A simplified *model of learning in this system involves use-dependent facilitation of sensory-to-motor *synapses. This is expressed as the enhanced release of *neurotransmitter in response to the sensory stimulus. The facilitation is embodied in chemical changes in the presynaptic terminal. Retrieval is the readout of the new state of the synapse by the action potentials that encode the conditioned stimulus (CS) in the sensory neurons. The cue for retrieval is the CS. The neurons that retrieve are those that learn and retain at least part of the trace.³ The conditions at acquisition influence retrieval, because whether the animal was already *habituated or naive determines the nature and extent of the subsequent cellular modifications in the sensory synapse, hence the synaptic state encountered by the action potentials that encode the CS in retrieval (Byrne and Kandel 1996). And, finally, retrieval, being an experience in the same neuron that retains the memory, might disrupt *homeostasis and induce new *plastic changes.

Most of what we now know about neuronal mechanisms of retrieval, however, owes to systems that are far more complex than *Aplysia*. *Functional neuroimaging, combined with smart design of behavioural tests, has made it possible to identify neuronal players in the retrieval of explicit (*declarative) memory in humans. Before the introduction of functional neuro-imaging, data on the involvement of specific brain structures in retrieval in humans were based predominantly on clinical cases (Shallice 1988; Schacter *et al.* 1996b). As brain lesions, once formed, are permanent, and could affect the formation or 'storage' of the memory trace, whereas retrieval is restricted to a brief time window of memory expression, conclusions about retrieval that are based solely on the effect of static pathology are problematic

to start with. In contrast, functional neuroimaging could dissociate the neuronal events of retrieval from those of earlier memory phases (e.g. Buckner *et al.* 1995; Nyberg *et al.* 1996; Buckner and Koutstaal 1998; Fletcher *et al.* 1998; Wagner *et al.* 1998a,b; Schacter and Wagner 1999; Lepage *et al.* 2000; Rugg and Wilding 2000). This is currently one of the most dynamic fields in memory research, and the picture keeps changing. A tentative model of explicit retrieval in the mammalian brain can nevertheless be portrayed.

It is methodologically convenient, and probably correct, to describe the brain system that subserves retrieval as composed of two main types of components: item-specific and item-invariant. The item-specific component subserves the actual recovery of the particular memory item. This process is referred to as 'ecphory' (Greek for 'to be made known'). The term was coined by Semon (1904), the same person who brought us 'engram', and later retrieved by Tulving (1983). Ecphory involves circuits that 'store' (*metaphor) memories (Markowitsch 1995, Schacter *et al.* 1996a; Schacter and Wagner 1999; Eldridge *et al.* 2000; Nyberg *et al.* 2000; Wheeler *et al.* 2000). In the case of declarative memory, these circuits are distributed over areas in the *cerebral neocortex, and connect with paleocortical and subcortical structures (*amnesia, *hippocampus, *limbic system).⁴ In addition, there is an item-invariant system, which searches for items in memory, allocates the mental resources, controls the process, and verifies the outcome. This system is said to put the brain into a retrieval 'state', 'mode', or 'set'.⁵

Where is this retrieval-mode system located? It has been demonstrated by a number of groups that prefrontal cortex is differentially activated in retrieval (Buckner *et al.* 1995; Schacter *et al.* 1996a; Rugg *et al.* 1996; Buckner and Koutstaal 1998; Fletcher *et al.* 1998; Wagner *et al.* 1998; Lepage *et al.* 2000). The prefrontal cortex subserves multiple executive functions in the brain (*planning, *working memory), and is therefore a likely candidate for setting the stage for ecphory. There is hemispheric asymmetry in the retrieval-related activity of prefrontal cortex. This finding has led to a model, the hemispheric encoding/retrieval asymmetry (HERA), which proposes that the left prefrontal cortex is differentially involved in retrieval of semantic information and in encoding novel aspects of the retrieved information into *episodic memory, whereas the right prefrontal cortex is involved in retrieval of episodic memory (Nyberg *et al.* 1996). The possibility was further raised that the hemispheric asymmetry observed in retrieval in the prefrontal cortex is contributed by the memory retrieval mode, but not by the

ecphory (Lepage *et al.* 2000). Prefrontal areas probably contribute differentially to retrieval mode functions, as well as to the *metamemory processes that monitor and verify retrieval; but again, the picture is incomplete (Schacter and Wagner 1999; Rugg and Wilding 2000).

The main picture of the layout and function of retrieval system(s) in the human brain, including the executive role played by the prefrontal cortex, are supported by lesion studies and cellular physiology in the *monkey (Hasegawa *et al.* 1998; Tomita *et al.* 1999). The investigation of the mechanisms of retrieval at more reduced levels of analysis depends much on the use of additional species. These include rodents (Moser and Moser 1998a; Riedel *et al.* 1999; Maren and Holt 2000; Nader *et al.* 2000; Sara 2000; Berman and Dudai 2001), *Drosophila (Dubnau *et al.* 2001), and *Aplysia* (see above).

An intriguing proposal, hinted already above, is that retrieval, being an experience, is followed by a new *phase of *consolidation (Spear and Mueller 1984; Sara 2000). Even more provocative is the suggestion that in some systems and conditions the original trace, or at least a part of it, could become markedly labile for a while, after its retrieval (Nader *et al.* 2000). The 'reconsolidation' hypothesis, if validated, could guide the development of new drugs and behavioural methods to alter specific items in memory. This might be used to erase unwanted memories (Dudai 2000), or enhance desired ones. Until such treatments are identified, down-to-earth tricks could be tried to improve retrieval. Well, on the one hand, retrieval appears to be enhanced by glucose (Manning *et al.* 1998; *nutrients); on the other, stress and corticosteroids impair retrieval (De Quervain *et al.* 1998; *lotus). A good dessert in relaxed company might hence provide a reasonable alternative to medical intervention.

Selected associations: Performance, Persistence, Phase, Recall, Recognition

¹Lewis (1979) proposed to call unretrieved memories 'inactive', and retrieved as well as short-term memories 'active' (*taxonomy). This terminology, however, did not catch on.

²Retrieval is not obligatory evidence for memory at *reduced levels of analysis. Hence one could identify *persistent memory-related *plastic changes at the molecular, cellular, or circuit level in the absence of actualization of the internal representation. Still, for the engram to acquire its representational meaning, it must be retrieved.

³It is possible, though, that other parts of the nervous system of *Aplysia*, which are not involved in acquisition or consolidation of the information, evoke or control retrieval.

⁴The role of the hippocampus in retrieval of declarative memories is limited in time (Teng and Squire 1999; Haist *et al.* 2001; *consolidation).

⁵For more on the general notion of 'set', see *learning set.

Scoopophobia

The *fear of being scooped.

Scoopophobia (sometimes manifested as prioritymania) is a common occupational hazard in contemporary science. The term stems from 'scoop', which literally means to gather or collect swiftly, and *metaphorically, to top or outmanoeuvre a competitor in acquiring and publishing an important news story (it all originated in *schoope*, Old Dutch for 'bucket'). Scoopophobia is a very focused phobia: the victim does not fear scoops in general, only those of the competitors. The first signs could become apparent already in Graduate School ('early onset'), but more commonly in postdoctoral training or immediately afterwards ('late onset', but not senile). It is a chronic malady, with a pre-tenure acute phase and subsequent recurrent exacerbations, that could linger well into postretirement. Among the presenting symptoms: manic preoccupation with one's own findings, delusions that include an amazing belief that these findings are indeed the most important in the world ever, and frequent, mostly out-of-place statements about having achieved monthly (and in severe cases weekly) outstanding breakthroughs in research. Treatments based on attempts to augment one's modesty almost always fail. The prognosis is gloomy. Unfortunately, truly afflicted individuals (not the hypochondriacs or those who play the scoopophobe to impress their peers) seldom calm down. Even rarer are the cases in which the patient freezes and stops working (bipolar scoopophobia). Most scoopophobics enter intermittent frenetic states, in which they increase their publication output to a level that precludes even them themselves from reading all the papers that they publish. Their main achievement in such states is occasional induction of an attack of scoopophobia in a true or imaginary competitor. The disease is potentially contagious, as some students tend to contract it from their mentors. It may hence become an endemic epidemic.

Serious and distressing as it is (to victims, family, and friends), scoopophobia is actually only a symptom of the mechanisms and pressures of the scientific *culture. The aetiology of the syndrome is composite. A primary precipitating factor is the sheer competitive drive universally favoured by academic promotion committees. But this does not account for the whole story. The explosion of information in modern science can occasionally turn even a calm person into a paranoiac. It sometimes seems as though so many people are hectically plotting to do exactly the same experiment that

you yourself are planning to do at this very moment. The kinetics and volume of the scientific literature only augments this perceived threat. A simple number game illustrates the case: a search for the terms 'learning OR memory' in the citation indexes (Web-of-ScienceSM 2000), yields 3172 publications of a total of 847 708 papers for the year 1989, and 17 199 of 1 176 391 papers in 1999. This means 62 papers per week in 1989, 340 per week in 1999, i.e. a more than fivefold increase in the absolute number and an almost fourfold increase in the proportion of total scientific papers within a decade. Indeed, some of these papers could be easily neglected, but others, and in addition some that do not spell out 'learning' or 'memory' in their title, keywords, or abstract, are important. The conclusions: first, it is impossible to keep abreast of *all* the developments in one's discipline; second, the number of research groups that conduct research in learning and memory is amazingly large, and is on the rise.

An issue that comes immediately to mind is redundancy and its role in research. The mere use of the term 'redundancy' does some injustice to the phenomenon in the *context of science. Literally, 'redundancy' means unnecessary repetition. But usually redundancy in research is not genuine superfluity; different scientific programmes may be similar, but are seldom exactly the same in all their details and conclusions. Though for the individual researcher this similarity is sufficient to cause ego damage, for the scientific discipline it is an essential part of the game, because by virtue of the open, distributed nature of the scientific work, concepts, theories, and data are subjected to the scrutiny of repetitions and modifications. They are then either refuted, or corroborated, or modified, or simply neglected, navigating the discipline into new cycles of research (*culture; *paradigm). Hence the rules of the profession require the individual researcher to accept a certain degree of altruism: although not rewarding for the individual, redundancy is critical for the scientific community at large.

Redundancy can be either simultaneous, i.e. two or more groups start to do the same thing independently at the same time, or consequential, i.e. some groups follow the pioneering work of other groups. Most cases are of the second type. There is undoubtedly an intimate interaction between surges in consequential redundancy and the *zeitgeist. Examples in memory research include sudden interest in topics as diverse as the role of protein synthesis in *consolidation, protein phosphorylation (*protein kinase) in *synaptic plasticity, *long-term potentiation, *neurogenetics, the use of the water *maze as a memory *assay, or the search

and analysis of *false memory. (Statistics illustrating the kinetics of publication on topics that had become trendy are provided in *long-term potentiation, *zeitgeist.) Not all important experimental systems in memory research had triggered major waves of publications on the same topic by other labs. For example, although the discovery of memory mutants in **Drosophila* arose much interest, not many labs followed. Similarly, although **Aplysia* has no doubt contributed tremendously to our understanding of the cellular bases of *plasticity, the level of redundancy generated in other labs was relatively modest. Any attempt to analyse the reason for this in terms of scientific *culture, far exceeds the scope of our current discussion. So is also the question what causes some important findings to emerge truly in parallel in independent labs (Ogburn and Thomas 1922; Merton 1961, 1963).

Can one become immune to scoopophobia? An amateurish little survey suggests to me that some of those who have initiated new fields of inquiry in the neurosciences are more resistant to scoopophobia. Hence genuine self-confidence can obviously help, almost by-definition. (For a historical sampler of prioritymania among scientific giants, see Merton 1957.) Disregard for scoopophobia does not ensure that the fearless individual will be well remembered and cited. Actually, E.O. Wilson (cited in Weiner 1999) remarked that 'Progress in a scientific discipline can be measured by how quickly its founders are forgotten'. Another defence mechanism is the ostrich solution, namely, not to read the literature. Some of my best friends follow this practice. It might provide temporary, illusory relief, but also waste time and money and bounce back as a boomerang of unpleasant *surprise. Not reading the literature might have been a privilege of the old days in neuroscience; for example, Loewi (1936), who did the first experiment to prove that the *neurotransmitter *acetylcholine is secreted *in vivo*, was unaware of the earlier suggestion published by Elliott (1904) that chemicals mediate messages between neurons. Would familiarity with Elliott's paper have altered the course of Loewi's experiments? Was it better for Loewi not to know? It is difficult to see how all this could have happened nowadays, with the publications/meetings/web explosion.

In some cases, unfortunately too few, the identification of simultaneous discoveries culminates in an agreement between the competing laboratories to publish back to back (e.g. Rosenblum *et al.* 1996; Rostas *et al.* 1996). In others it results in endless fights on priority. Advice to newcomers to a scientific discipline are rarely effective. But one might at least

try (Cajal 1916; Cornford 1922). A somewhat useful (yet admittedly naïve) way to cope with scoopophobia, live in peace with inevitable competition, appreciate how science advances, and keep a modest level of modesty, is to *recall the saying of the Jewish sage, Rabbi Tarfon: 'Not yours is the work to complete, neither is yours the freedom to idle' (*Mishnah, Avot B15*). It surely epitomizes the blessed infiniteness of research, on which scoops are only ephemeral minute vibrations.

Selected associations: Culture, Homo sapiens, Paradigm, Surprise

Sensitization

Augmentation of the responsiveness to *stimuli following the presentation of a salient stimulus.

Sensitization is a type of non-*associative learning. The sensitizing stimulus is usually strong or noxious. Sensitization contrasts with another type of nonassociative learning, *habituation, in which there is a *generalized diminution of response following the presentation of a weak or monotonous stimulus. If the response is already habituated, the effect of the sensitizing experience is termed 'dishabituation'. Thus, whether the *subject is said to undergo sensitization or dishabituation, depends on what we know about its history.

Sensitization is a lingering manifestation of arousal. Another manifestation of arousal is the 'investigatory' or 'orienting reflex', which is an immediate, complex somatic and sensory response to an unexpected stimulus (Pavlov 1927; Sokolov 1963b; *attention). Sensitization complements the behavioural adaptation to the *surprising situation by transiently decreasing the threshold to further stimuli. The phylogenetic value of sensitization is rather straightforward: 'An earthworm that has just avoided being eaten by a blackbird that has taken a peck at it, is indeed well advised to respond with a considerably lowered threshold to similar stimuli, because it is almost certain that the bird will still be nearby for the next few seconds' (Lorenz 1981).

The ability of a salient stimulus to alter the subsequent response to other stimuli was systematically investigated already by Pavlov. He reported that after *experimental extinction of a *classically conditioned response, a strong or novel stimulus temporarily restored the original response (Pavlov 1927). Later,

Sensitization

Grether (1938) reported that unpaired presentation of unconditioned and conditioned stimuli could result in conditioned response. This was termed 'pseudoconditioning'. Whereas pseudoconditioning can be described as nonassociative classical conditioning, sensitization can be described as nonassociative α conditioning.¹

The widespread occurrence and the many expressions of sensitization throughout the phylogenetic spectrum makes it unlikely that a single mechanism will explain it all. Indeed, the investigation of a variety of vertebrates and invertebrates preparations unveils diverse circuit and cellular mechanisms (e.g. Egger

1978; Russo and Ison 1979; Davis *et al.* 1982; Hawkins *et al.* 1998). Dishabituation and sensitization, which at a certain stage were suspected to be two manifestations of the same phenomenon, were later found not to be so on the bases of differences in the behavioural parameters, in the *development of the response with age, and in the neuronal mechanisms (Rankin and Carew 1988; Byrne and Kandel 1996; Hawkins *et al.* 1998).

Among the preparations used to study elementary types of sensitization, a prominent place is reserved to a *simple system, the sea hare, *Aplysia*. In *Aplysia*, sensitization of the defensive withdrawal reflexes, achieved

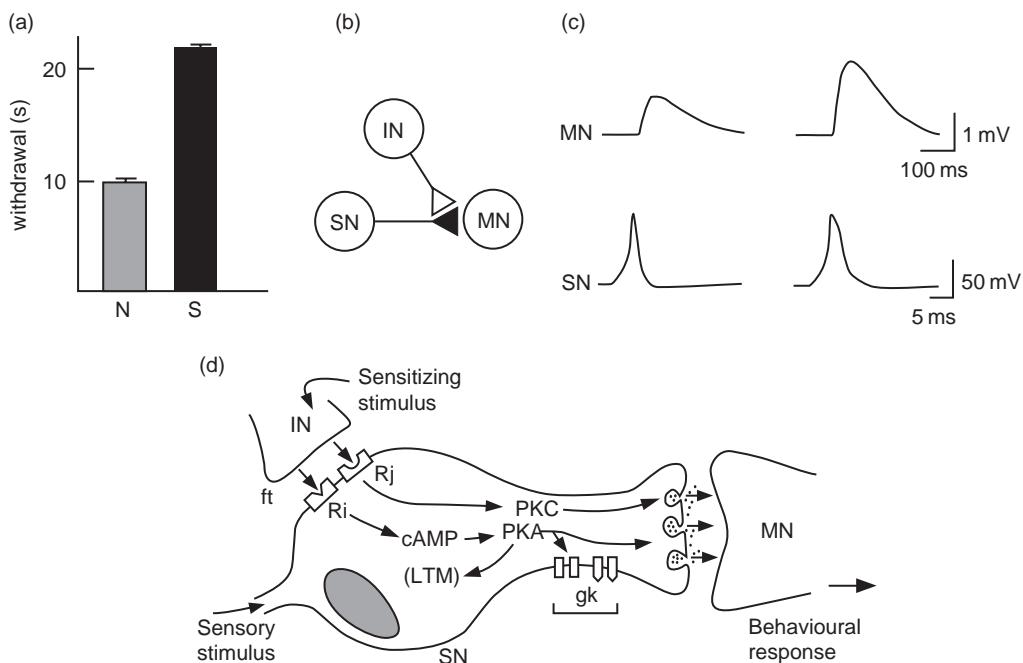


Fig. 59 A simplified scheme depicting the sensitization of the gill and siphon withdrawal reflex in *Aplysia* at various *levels of analysis. (a) The behavioural response (see also page 16). N, 'naive' *Aplysia*, withdrawing the gill and siphon in response to a mild touch to the skin; S, the augmented response of subjects sensitized by a shock to the tail. (b) The elementary module of the central circuit that subserves the behaviour. IN, interneuron; MN, motor neuron; SN, sensory neuron. (c) Synaptic facilitation, the correlate and cellular analogue of behavioural sensitization in this system. The lower curve in each case is the action potential (spike) in SN, and the upper curve is the excitatory postsynaptic potential (EPSP) in the follower MN (left-hand curves, pre-training, right-hand curves, post-training). The broadened spike in SN after sensitization training ultimately results in an enhanced response to subsequent action potentials, and therefore in enhanced transmitter released on to the MN. This contributes to the augmentation over time of the behavioural response. (d) Elements of the molecular machinery that underlies short-term synaptic facilitation. The sensitizing stimulus releases facilitatory transmitter(s) (ft) from the IN on to the SN. These modulatory substances, e.g. serotonin, activate several types of receptors (R_i, R_j) on the SN membrane. The receptors in turn activate *intracellular signal transduction cascades. One type of receptor activates the *protein kinase C cascade, which results in enhancement of transmitter release. Another type of receptor activates the cyclic adenosine monophosphate (cAMP) cascade, leading to phosphorylation of potassium channels (g_k), which results in spike broadening and enhanced excitability in response to subsequent stimuli to the SN. The cAMP cascade could also trigger memory *consolidation that involves modulation of gene expression and culminates in the long-term memory of sensitization (LTM; see *CREB). In reality, the relative contributions of multiple signal transduction cascades, enhanced excitability and enhanced transmitter release, depend on the history of the SN as well as on the time after the sensitizing experience. Use-dependent alterations in other components of the circuit are not shown for simplicity. (Modified from Abrams, 1985, and Byrne and Kandel, 1996.)

by applying a noxious stimulus to the skin, is based on multiple time- and *context-dependent alterations in the circuits that subserve the behaviour (Trudeau and Castellucci 1993; Byrne and Kandel 1996; T.E. Cohen *et al.* 1997; Cleary *et al.* 1998). A significant portion of the sensitization of the behavioural response is explained by presynaptic facilitation in a single type of *synapse. This is the synapse between the sensory neuron, which carries information from the skin, and the motor neuron, which commands the withdrawal response (Figure 5, p. 16, and Figure 59.). Synaptic facilitation is a form of use-dependent synaptic *plasticity that is expressed as an enhancement in the strength of the synaptic connection; as synaptic facilitation was found in *Aplysia* to correlate with major aspects of behavioural sensitization, it was accepted in this *system as a convenient cellular analogue of sensitization.

In the aforementioned sensory-to-motor synapse in *Aplysia*, a considerable part of the facilitation is induced by a modulatory neuron, which is activated by information about the sensitizing stimulus. This neuron releases modulatory substances, which activate a number of *receptors and their downstream *intracellular signal transduction cascades in the sensory neuron terminal. This culminates in multiple plastic changes, among them enhanced *neurotransmitter release by the sensory neuron on to the motor neuron that controls the withdrawal response. Both short-term sensitization, lasting up to a few hours, and long-term sensitization, lasting more than a day, could be *modelled by short- and long-term synaptic facilitation. Whereas short-term facilitation involves post-translational modifications, long-term facilitation requires modulation of gene expression, *protein synthesis, and morphological changes in the synapse, which are assumed to maintain the facilitation over time in spite of the ongoing molecular turnover (*consolidation). Studies of *classical conditioning in the same preparation have unveiled that facilitation is also a component of this elementary type of associative learning, only that in classical conditioning, the use-dependent enhancement in the synapse is specifically augmented by the *coincidence of the conditioned and the unconditioned stimuli (Abrams 1985). That classical conditioning in this system is an elaboration of sensitization is actually not at all surprising, considering that conditioning is of the α type, involving a pre-existing rather than a new response.

The analysis of sensitization in *Aplysia* is hence a *classical example of a reductive research programme in the field of memory research. It has focused on identified cellular processes in an identified locus in the

neuronal circuit that subserves the behaviour, and has succeeded in partially translating the behavioural phenomenon into cellular phenomena that are accessible to mechanistic analysis (*reduction). This programme has identified molecular devices that could perform functions of *acquisition of cellular information (e.g. serotonin receptors), storage (e.g. protein kinases), and readout, or *retrieval, of such information (e.g. potassium channels, components of the transmitter release machinery). A sizeable part of what is so far known about the molecular and cellular mechanisms of short- and long-term memory, is derived from the cellular analysis of short- and long-term facilitation in *Aplysia*. Hence, whoever wishes to understand the *zeitgeist in molecular neurobiology cannot afford to disregard sensitization in *Aplysia*.

Sensitization, although only a primitive form of learning, is of great importance in human behaviour. It can be demonstrated already in the neonate (Lipsitt 1990). Later throughout life, sensitization comes to contribute to a plethora of normal as well as pathological responses. Long-term sensitization was proposed as a model for phobia and generalized anxiety disorder (Marks 1987). Furthermore, 'stress sensitization', which is the augmentation by stress experience of the stress response upon re-exposure to a stressor (e.g. Nissenbaum *et al.* 1991), was invoked to explain why phobias and neurotic rituals relapse after trauma (Marks 1987; Marks and Tobena 1990).

Selected associations: Context, Generalization, Habituation, Surprise, Taxonomy

¹In α conditioning the conditioned response is intensification of pre-existing response to the conditioned stimulus; see *classical conditioning.

Simple system

A *system, such as an organism or a preparation containing neural tissue, that is less complex than other systems in the same category, and is used to model the category and to facilitate research that involves this category.

Interest in the intelligence of simple organisms, and their use to investigate problems of learning and memory, draws mainly from two conceptual frameworks: Darwinism (Boakes 1984), and *reductionism. The

Simple system

notion that evolution applies to the mind as well, undoubtedly combined with a keen interest in zoology and behaviour, has directed some investigators already a century ago to study the mental powers of organisms such as protozoa and insects (Peckham and Peckham 1887; Jennings 1906; Day and Bentley 1911). Starting at the 1950s and 60s, the use of simple organisms in neurobiology (Benzer 1967), as well as that of simplified preparations from such organisms (Kandel and Spencer 1968), has been further reinforced by the remarkable success of utilizing simple organisms to decode the genetic code and to unravel metabolic pathways.

The selection of a 'simple' organism for the investigation of learning and memory depends on the objective and on the context of the research programme. If the objective is to study the neurobiology of a particular species *per se*, the selection is self-explanatory. If the objective is primarily to advance understanding of a general problem in the neurobiology of learning and memory, the selection is based on properties that offer particular experimental advantages. These could be, for example, simple reflex circuits, large accessible neurons (Kandel and Spencer 1968; T.E. Cohen *et al.* 1997), or amenability to genetic analysis (Benzer 1967; Dudai *et al.* 1976; Tully 1996). Furthermore, whether an organism is regarded 'simple' depends on what is it compared with. In the context of the analysis of human *amnesia, studying a *rat is switching to a simple system, although the rat, of course, is far from being simple.

Intact simple organisms could be employed to analyse distinct phenomena of learning and memory, such as non-*associative learning, rudimentary associative learning, *cue revaluation, or elements of memory *consolidation. But the use of such organisms in the dissection of the physiological and molecular mechanisms that subserve the aforementioned phenomena requires a combination of *reductive and simplifying steps.¹ This results in preparations in which fragments of the nervous system, or even individual neurons only, are analysed (Rayport and Schacter 1986; Krasne and Teshiba 1995; T.E. Cohen *et al.* 1997; Frysztak and Crow 1997). In the simplified preparations, certain molecular and cellular phenomena could be used to *model a molar behaviour, for example, *synaptic depression and facilitation to model *habituation and *sensitization, respectively (T.E. Cohen *et al.* 1997), or activity dependent synaptic facilitation to model associative conditioning (Byrne and Kandel 1996).

The analysis of simple organisms and simplified neural preparations from such organisms has generated highly valuable insight into basic phenomena, processes, and mechanisms of learning and memory. Subsequent

analysis in more complex systems has established that some basic findings *generalize from the simple systems to the more complex ones (Bailey *et al.* 1996; e.g. *CREB, *consolidation, *immediate early genes, *intracellular signal transduction cascades, *protein synthesis). The caveats should not, however, be overlooked. First, 'primitive' organisms are often not so primitive (e.g. Srinivasan and Chang 1998), and miniature brains do not necessarily imply simplicity (*subject). The so-called 'simple organisms' surely did not evolve to supply neuroscientists with convenient tools to approach complex problems; these organisms were shaped in evolution to survive in a circumscribed ecological niche, and are therefore endowed with certain specialized (and intriguing) properties, but not with others. This means that whatever is the physiology and behaviour of these species, it has been adapted to fulfil needs that might be different from those of other species. But it also means that individuals belonging to primitive species clearly cannot perform some feats that are within the repertoire of more advanced species: likening contemplation in a worm to the retrieval of explicit knowledge in humans, is carrying the analogy a bit too far indeed. Second, within their phylogenetic limitations, some of the specialized tasks carried out by so-called simple organisms are themselves rather elaborate (e.g. Zeil *et al.* 1996). Third, even if the task is simple, the neuronal *algorithms that subserve it may prove complex when the surface is scratched (e.g. Wolpaw 1997).

In recent years, some of the enthusiasm for using simple organisms to analyse the neurobiological bases of behaviour has dwindled, because state-of-the-art molecular biology could now be used to approach problems in higher organisms that previously were approachable only in lower ones. Powerful *neurogenetics, for example, can already be practised in *mice, depriving *Drosophila* of its monopoly in the neurogenetic analysis of memory. It would be, however, a pity if simple organisms were to be abandoned. These species, in addition to being so interesting as such, do offer substantial advantages, for example, in deciphering the *representational code that are used in identified neural circuits that subserve discrete behaviours. In parallel with the aforementioned trend, the use of brain slices (e.g. Barkai and Hasselmo 1997) and of neuronal cell cultures (e.g. Tong *et al.* 1996) from complex nervous systems has gained much popularity, because such simplified preparations permit full exploitation of highly advanced cellular, molecular, and computational techniques (e.g. in the investigation of *long-term potentiation). It is likely that in the future,

simple systems may come to include also bionic hybrids of neural tissue and printed circuits (Kuwana *et al.* 1995; Maher *et al.* 1999).

Selected associations: *Aplysia*, *Drosophila*, *Honeybee*, *Model, Reduction*

¹For the definition of these two types of steps and the distinction between them, see *reduction.

Skill

1. Proficiency in the *performance on a perceptual, motor, or cognitive task, *acquired through cumulative experience.

2. The type of knowledge that subserves this proficiency.

The first systematic investigation of skill learning involved a skill that is now obsolete. This was the study of the acquisition of the American Morse code by employees of railway and telegraph companies (Bryan and Harter 1897, 1899). On the basis of these studies, Bryan and Harter proposed that the formation of skill is a multi*phase process, which involves the mastery of specific elementary *habits that become associated in a hierarchy. The expert is then able to perform the hierarchy of habits automatically, at a speed that in certain individuals approaches the physical limit of the task (Figure 60). The command of automaticity should therefore be given full respect in education: 'It is quite useless to raise the question whether or not children should acquire specific automatic habits. There is no escape from such habits... The wolf does not escape. Neither Shakespeare nor Caliban escape... Automaticism is not genius, but it is the hands and feet of genius' (Bryan and Harter 1899).

1. The spectrum of skills. Sending Morse messages involves a motor, or perceptual-motor skill. Decoding such messages involves primarily a perceptual skill. Other types of skill are cognitive, for example, problem solving. 'Skill' is also used, mainly in colloquial language, to refer to proficiency in other behavioural domains, such as emotional or social, without necessarily distinguishing between an innate (**a priori*) predisposition and an acquired ability. Emotional and social skill could be regarded as subtypes of cognitive skill. Cognitive skill is occasionally dubbed 'intellectual skill', but this applies only to humans and may connote

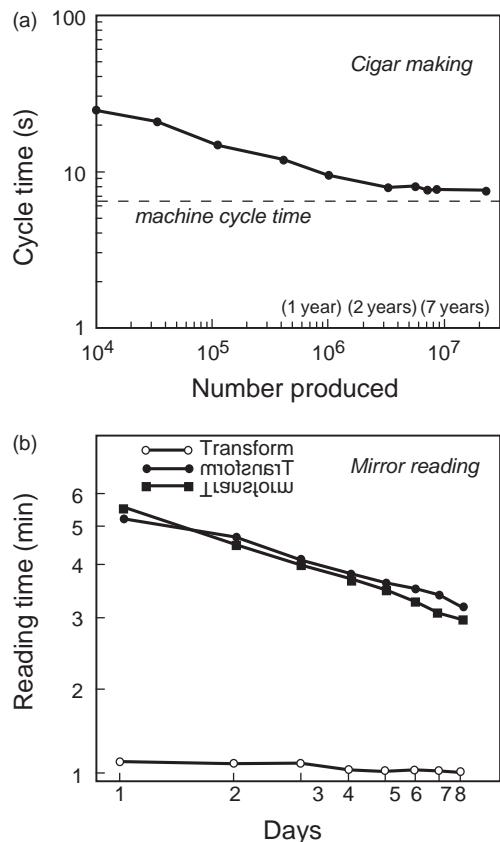


Fig. 60 The acquisition of skill. (a) The average speed of production of cigars by a group of girls operating cigar-making machines. The curve for the first 2 years fits a power function (see text). After producing about 3 million cigars, the performance of the workers approached the machine cycle time. (Adapted from Crossman 1959.) (b) The average reading time of a group of undergraduates for mirror-reading English text. Again, the curves fit a power function. (Adapted from Kokers 1968.)

pretentious capabilities. The term 'mental skill' should be avoided as all skills are mental. Skills could be performed in the absence of *conscious awareness, hence, are classified as non*declarative memory (Squire and Zola 1996). Their acquisition, however, may either involve conscious awareness, i.e. be declarative or explicit, or be independent of conscious awareness, i.e. nondeclarative or implicit.

2. The acquisition of skills. The analysis of all types of skill shows that their acquisition involves multiple phases.¹ The nature of these phases is the subject matter of theories of skill acquisition (e.g. Snoddy 1926; Crossman 1959; Fitts 1964; Anderson 1982; Logan

1988). These theories differ in the nature and number of phases, but basically share the view that the first phase involves selection of the proper *algorithm, and the later phase(s) involve(s) perfection and automatization of the suitable solution. Hence the first phase is called either 'adaptation' (Snoddy 1926), 'algorithmic' (Logan 1988), 'understanding' or formation of 'cognitive set' (Fitts 1964),² or 'declarative' (Anderson 1982); the later phase is 'facilitation' (Snoddy 1926), or 'automatization' (Logan 1988), or 'procedural' (Anderson 1982). The existence of phases in skill acquisition is supported by behavioural data, and more recently, by *functional neuroimaging data that show the recruitment of different brain circuits with practice (see below).

A common observation is that the improvement of performance with practice follows a power law: $\log C = \log B + n \log X$, where C =a measure of performance, X =number of trials or time on task, B , n =constants (Snoddy 1926; DeJong 1957; Crossman 1959; Newell and Rosenbloom 1981) (Figure 60). This is called the 'power law of performance', or 'of practice', or 'of learning'. Power functions are commonly associated in the literature with perceptual-motor skill, and sometimes are even taken as evidence that the type of learning is indeed such skill. In fact they are common to all learning that involves repetitive training (Newell and Rosenbloom 1981), including learning to *forget (Rubin and Wenzel 1996).

3. The *persistence of skills. Skills could be retained over years in the absence of further practice (Fleishman and Parker 1962), and sometimes even in the absence of recollection of having previously performed the task (Cohen 1984). What loss occurs is quickly regained by re-practicing (Fleishman and Parker 1962; see 'saving' in *experimental extinction).

4. The relationship between skill and other types of procedural memory. Automaticity is an attribute shared by other forms of procedural memory (Squire and Zola 1996; *taxonomy). The question arises what is the relationship between skill and these other forms of memory. Of special interest is the relevance of skill to repetition *priming. Whereas skill learning refers to a *generalized improvement on a task, priming refers to the improvement on a given item within the task.³ Is the latter a special case of the former? The views differ; priming and skill learning are considered manifestation of the same type of incremental learning process or mechanism by some authors (Logan 1990; Poldrack *et al.* 1999), but not by others (Schwartz and Hashtroodi 1991; Kirsner and Speelman 1996). A data-based argument brought up by the opponents of the single-process view is that priming is independent of

accumulative practice. A conceptual argument in favour of a unified-process approach is that even skill learning is limited to the specific task-related procedures, and therefore is not qualitatively so different from priming. It could be proposed, so goes this argument, that skill and repetition priming represent each a change along a continuum of generalization; the degree of generalization reflects the *level of the processing stream in which the modification occurs. Depending on the item variability in training and the amount of practice, the use-dependent alteration may result in learned information that does not *transfer to other items (repetition priming), or, alternatively, generalizes over a class of items (skill; Ofen-Noy *et al.* 2002). This view echoes the proposal that different types of learning, including declarative ones, involve a procedural component, yet differ, among others, in the resulting specificity of transfer (Kolers and Roediger 1984).

5. Which brain areas encode and retain skills? The approach to this question relies on two main types of *methodologies. One is the analysis of the performance of patients with 'global' *amnesia, Parkinson's disease, and Huntington's disease; the other, functional neuroimaging of brain activity during the learning and performance of skill in healthy human *subjects. The analysis of performance of amnesics, Parkinsonian and Huntingtonian patients provides information about brain areas that are *obligatory* for skill (*criterion). This type of studies is complemented by the investigation of the effect of circumscribed brain lesions on tasks that are considered to *model human skill in laboratory animals, e.g. the *monkey. The neuroimaging studies provide information about brain areas whose activity is *correlated* with skill learning and performance. This type of studies is complemented by cellular physiology methods in laboratory animals (e.g. Recanzone *et al.* 1993).

Despite their dense declarative amnesia, human patients with extensive damage to the mediotemporal lobe perform remarkably well on perceptual-motor, perceptual, and cognitive skill tasks (Milner *et al.* 1968; Brooks and Baddeley 1976; Cohen and Squire 1980; Cohen 1984). For example, with experience, they improve normally on motor tracking in a tactual maze (perceptual-motor skill), on mirror-reading (perceptual skill, Figure 60), and on solving the Tower of Hanoi puzzle (cognitive skill, Figure 61). All this, without recollection of having previously performed the task. These findings show that skill is not subserved by the same brain circuits that subserve declarative memory. In contrast to the success of amnesics on skill tasks, Huntington's and Parkinson's patients are impaired on

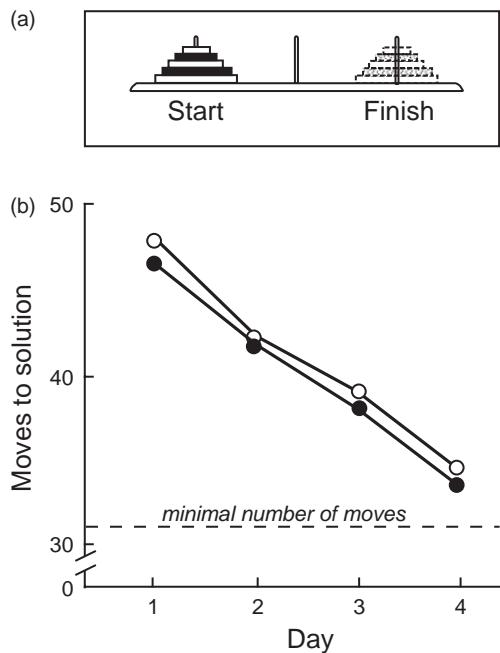


Fig. 61 The performance of amnesics on a cognitive skill. The Tower of Hanoi puzzle consists of five wooden blocks and three pegs (a). At the outset, all five blocks are arranged on the leftmost peg in size order, the smallest block on top. The subject is then asked to move the blocks from the leftmost peg to the rightmost peg, while moving only one block at a time, and without ever placing a larger block on top of a smaller one. The optimal solution, which involves shuttling the blocks back and forth on all three pegs, requires 31 moves. (Compare with the Tower of London, *planning.) In this experiment, training consisted of solving the puzzle four times per session on each of four consecutive days. The performance of amnesics patients on this task is indistinguishable from that of normal controls (b). A follow-up study showed that patient H.M. (*amnesia, *classic) retained the skill after 1 year. (Adapted from Cohen 1984.)

learning of perceptual-motor skill (Heindel *et al.* 1988), perceptual skill (Martone *et al.* 1984), and cognitive skill (Saint-Cyr *et al.* 1988). Huntington's disease and Parkinson's disease both involve striatal pathology, and therefore, the striatum has been proposed to subserve skill learning, similarly to its role in habit formation.

Functional neuroimaging can be used to identify areas that are activated during the acquisition and performance of skill in the normal brain (e.g. Seitz *et al.* 1990; Grafton *et al.* 1995; Karni *et al.* 1998; Petersen *et al.* 1998; Hund-Georgiadis and von Carmon 1999; Nadler *et al.* 2000; Poldrack and Gabrieli 2001).⁴ A few tentative generalizations could be extracted from these studies: (a) skill-related changes in brain activity are

distributed over multiple brain areas, some of which are task-specific and some task-independent; (b) the task-specific areas include modality specific cortical areas, whereas the corticostriatal system, and possibly the *cerebellum, are involved in skills that span sensory modalities and tasks; and (c) often it is found that the involvement of brain areas in skill learning and performance changes over time in the course of practice. The picture that emerges, although yet preliminary, is that the acquisition of skill involves changes in two types of *internal representations, those of the specific behavioural acts of the particular skill, and those of the 'syntactic' hierarchical routines by which the particular acts are perfected, bound, and executed. Further, above a certain degree of practice, the relevant internal representations may shift to brain circuits other than those employed in the early phases of training. This can be shown when comparing the activation of brain areas over training in an individual, or the activation in the brain of novices vs. experts (e.g. Hund-Georgiadis and von Carmon 1999). Exceptional skill benefits from particular behavioural routines (Ericsson and Lehmann 1996), and the talented brain may process the talent-related material in a unique way (Schlaug *et al.* 1995; Pesenti *et al.* 2001). An interesting question is whether this results merely from the perfection of normal brain resources, or from an innate predisposition in the structure of the brain, or, most likely, from both.

Selected associations: Birdsong, Habit, Instrumental conditioning, Priming, Transfer

¹'Phase' here means stages in the development of skill that are superimposed on the basic universal phases of memory, such as short-term memory, *consolidation, or *retrieval.

²On 'set' see *learning set. The terms 'understanding', 'cognitive set', and 'declarative' fit the discussion of human skill but not necessarily that of skill in other species.

³That is, whereas skill refers to types of stimuli, priming refers to tokens; on types and tokens see *system.

⁴It is noteworthy that a limited degree of gross localization of function can be obtained in certain skill paradigms by the use of behavioural methods in the absence of neuroimaging. Hence if a visual perceptual skill improves only in one eye without affecting the other, it could be inferred that the process occurs at low-level of the visual processing stream in the brain, before the site of binocular integration (Sagi and Tanne 1994).

Spaced training

Training with intercalated rest intervals.

In many situations, multiple training sessions with intercalated rest intervals (also termed 'distributed training') result in a more robust and long-lasting memory than the same amount of training with no rest intervals ('massed training'). This phenomenon was noted already in the early days of experimental psychology (Jost 1897). It has been observed in species far apart on the phylogenetic scale, from the most primitive to the most advanced (Melton 1970; Carew *et al.* 1972; Cornell 1980; Perruchet 1989; Payne and Wenger 1992; Yin *et al.* 1995; Kogan *et al.* 1996; Pereyra *et al.* 2000). In human *subjects it is unveiled in a variety of verbal, perceptual, and motor tasks, in both *declarative and nondeclarative memory *systems, in the laboratory and in *real-life situation, in adults as well as in infants.

The phylogenetic and ontogenetic conservation of the spaced training effect suggests that it relates to elementary processes and mechanisms of learning. Two main types of explanations have been proposed at the system *level. One is that as the spacing between repetition increases, the familiarity of the repeated items decreases, resulting in enhanced *attention and more thorough processing of the information. As a consequence, overall, the information is learned better under spaced conditions. Explanations of this type are termed 'deficient processing theories' (Greene 1989). The other type of explanations is that spacing allows richer variability and exploitation of the *context, which increases the number of possible *retrieval *cues for the repeated item. This, in turn, is expected to facilitate retrieval. Explanations of this type are termed 'contextual variability theories' (*ibid.*). Contextual variability theories can also be extended to imply that, whereas the experimenter deems the *stimulus equal when presented either in a spaced or in a massed training protocol, the subject may actually *perceive two different stimuli (e.g. Pereyra *et al.* 2000). It is noteworthy that spaced training can be demonstrated in even very simple conditioning *paradigms in which the context is kept highly constant; but one cannot exclude the possibility that brains of other species may discover with time magnificent changes and new worlds in what appears to us an extremely boring environment.

The recent introduction of molecular biology techniques to the analysis of learning and memory in *simple organisms has led to the emergence of a

molecular and cellular *model that attempts to explain the increased efficacy of spaced training. This model is embedded in the gene expression hypothesis of long-term memory. The hypothesis states that *consolidation of memory into a long-term form involves modulation of transcription factors and gene expression (*immediate early gene, *late response gene). Specifically, the model proposes that training induces both activator and repressor isoforms of *CREB, which is a type of molecular switch that controls the formation of long-term memory. The downstream processes subserving the formation of long-term memory are activated only when the amount of functional activator within the relevant nerve cells transcends a certain threshold. The key assumption is that immediately after training, enough CREB repressor exists to block the activator. With rest, however, the repressor inactivates faster than the activator. Therefore the activator accumulates with spaced but not with massed training (Yin *et al.* 1995). This highly simplified model thus provides an interesting attempt to link events at the molecular level to those at the system and behavioural level (*reduction; for a related model, see *flashbulb memory.)

Why had the superiority of spaced training evolved in evolution? One possibility is that it confers to species ranging from slugs to humans some extra advantage that we do not yet understand. It cannot be merely the opportunity to take a break and rest in the middle of a study session. Another possibility is that the superiority of spaced, as opposed to massed training, is a spin-off of the way synapses and neuronal circuits are built.¹ And, of course, it is also possible that both assumptions are correct, and that evolution had capitalized on the biological constraints.

The advantage of spaced training is not limited to its potential ability to illuminate elementary mechanisms of learning and memory. It can also be recruited to improve everyday memory (Landauer and Ross 1977; Payne and Wenger 1992). In fact it is one of the very few training and rehearsing procedures that has been repeatedly proven to be of some value in memory improvement (*mnemonics). Yet despite the simplicity of the procedure and the evidence for its effectiveness, for most people it is counterintuitive: when asked to provide a subjective rating, subjects tend to rate massed training as more likely to ensure proper recall than spaced training (Zechmeister and Shaughnessy 1980). The literature on spaced training is thus worth rehearsing, although preferably not in a massed fashion.

Selected associations: Consolidation, CREB, Mnemonics, Real-life memory

¹This claim that evolution is not necessarily the reflection of optimizing processes, but also the mere consequences of mechanistic constraints, is yet another example of the anti-*Panglossian paradigm, see *paradigm.

State-dependent learning

The phenomenon in which information learned in one state of the organism is *retrieved best if a similar state is reinstated at the time of testing.

The ‘state’ in state-dependent learning is taken to imply the internal, physiological, and mental milieu, but its reinstatement often requires elements of the original external milieu (*context). The phenomenon is also termed ‘dissociated learning’. The more general term ‘state-dependent learning’ is, however, to be preferred, as ‘dissociation’ connotes clinical meanings that are not intended.¹ The terms ‘state-dependent retrieval’, ‘state-dependent recall’, and ‘state-dependent memory’ are also used, sometimes with an underlying assumption that the key to the understanding of the state dependency lies in a particular memory *phase but not in another. In practice, state dependency is frequently induced by drugs or intoxication: this special case of state-dependent learning is known as ‘drug-dependent’ or ‘drug-dissociated’ learning.

Over the years, the fascination with state-dependent learning has been shared by scientists and non-scientists alike. The latter, though, became intrigued much before the former. It was noted long ago that somnambulists (sleepwalkers, such as Lady Macbeth, Shakespeare 1606), could in their trance do things that are forgotten in their waking state but pursued or recalled in a subsequent episode of sleepwalking (Ellenberger 1970). The same phenomenon was later demonstrated with ‘artificial somnambulism’, i.e. hypnosis (*animal magnetism, *ibid.*), to which spontaneous somnambulists were found to be especially susceptible. This phenomenon of hypnosis-dependent learning was exploited not only by shamans, performing magicians, and occasionally crooks, but also by authors and screenwriters. In *Dr Caligari*, one of the greatest *classics of the German Expressionist cinema (Wiene *et al.* 1919), the notorious Caligari hypnotizes the somnambulist Cesare to commit murders while in a somnambulistic trance. Perhaps the most popular state-dependencies were, however, attributed to alcohol and narcotics. In describing a *system of *phrenology,

Combe (1830, cited in Siegel 1982) recounts the story of an Irish porter who used to forget, when sober, what he had done while drunk, and yet could recapture the memory once he again became indulged in drinking. This story was later echoed in the writings of several eminent physicians, including Winslow (*On obscure diseases of the brain, 1860, cited in Eich and Birbaum 1982) and Ribot (1882, *amnesia). Additional cases of alcohol-dependent recall also found their way into fictional literature (Dickens, cited in Siegel 1982) and the cinema (Chaplin, cited in Bower 1981).

In Victorian England opium was occasionally used as freely as alcohol (Berridge 1977), and hence opiate-dependent recall became known as well. Opiate-dependent recall was the clue to a contemporary best-seller, *The moonstone* (Collins 1868). In this detective story, a young gentleman, Blake, worried about the safety of his fiancé who possesses a valuable diamond, hides the diamond while he is under the effect of an opium tincture (laudanum). He has no memory of the event, till a physician’s assistant advises him to recreate the drugged state. The author, Wilkie Collins, wrote from first-hand knowledge: he was himself an avid opium user, and the rumour went that he was unable to remember where in the novel he concluded the previous writing session unless he became drugged again (Siegel 1982).

Controlled scientific experimentation on state dependency has started with Girden and Culler (1937). They paralysed a dog with curare,² and then trained it in a *classical conditioning protocol to associate the sound of a bell with a shock-induced leg flexion. After training, the conditioned response was displayed in the presence of curare, vanished on return to the normal nonparalysed state and reappeared with re-administration of the poison. Conversely, conditioning in the absence of curare was undetected in the presence of the poison. Drug-dissociation learning was subsequently demonstrated by many groups of investigators using a variety of drugs and species (e.g. Overton 1964; Bruins Slot and Colpaert 1999; smoking can do the trick as well, Peters and McGee 1982). In many studies of drug-dissociated learning, rather large doses of drugs are needed, that also affect acquisition. Even the anecdotal alcohol-dependent memory in *Homo sapiens* was respectively verified in the laboratory using a group of joyous volunteers (Goodwin *et al.* 1969). Recall of single experiences displayed a greater sensitivity to drug dependency than *recognition. This latter observation was later found to *generalize to other situations of state-dependent learning.

Many drugs that can produce drug-dissociated learning affect the mood. It is therefore only natural to ask whether affective states *per se* could induce state-dependent learning. The answer is probably yes (Blaney 1986). It was reported that depressed patients, or normal subjects hypnotized to sadness for the sake of science, display a ‘mnemonic *bias’ toward the recall of unpleasant information (Lloyd and Lishman 1975; Bower 1981; Clark and Teasdale 1982). Similar results have been reported for other emotional disorders (e.g. panic disorder favours panic-related words; Becker *et al.* 1994). The question is whether this is state dependency *bona fide*, i.e. whether the altered mood induces mood dependency in the retrievability of items in memory irrespective of the affective valence of these items. An alternative possibility is that an altered mood at the time of training or testing promotes the learning or recall, respectively, of events or facts that agree with that particular mood. In such a case concordance between mood at learning and mood at retrieval is not obligatory, i.e. it is not true state-dependent learning. The phenomenon in which material is more likely to be attended, learnt, or recalled if it is consistent with the subject’s prevailing mood, is termed ‘mood congruency’ or ‘mood congruity’ (Bower 1981; Blaney 1986). Overall, the jury is yet out on whether the available data on mood-associated recall favour state dependency, mood congruency, or both (Blaney 1986; Pearce *et al.* 1990; Power and Dalgleish 1997). Regardless of the exact mechanisms, if depressed patients display a bias for depressing memories, they could be expected to become immersed in depressing thoughts and expectations, which in turn will augment and perpetuate the depression. This is a vicious cycle that could contribute to chronic depression (Clark and Teasdale 1982; Ingram 1984; for a critical review of similar ideas and ‘cognitive theories’ of depression in general, see Haaga *et al.* 1991).

Recently, neuronal, *reduced analogues of state-dependent *plasticity and learning have been reported (Wörgötter *et al.* 1998; Shulz *et al.* 2000). This, together with the analysis of *neurotransmitter and *receptor mechanisms in state dependency (Bruins Slot and Colpaert 1999), paves the way to further understanding of the molecular, cellular, and circuit mechanisms that implement state dependency at the behavioural *level. In the meantime, a practical caveat: the potential contribution of state-dependent learning to the outcome of behavioural experiments should not be ignored. A *control for state-dependent learning is highly advisable in every study in which drugs or conditional gene knockouts (*neurogenetics) are used to manipulate

only the acquisition or retrieval *phase but not both. Furthermore, state dependency must be kept in mind whenever *developmental, hormonal, circadian rhythm, or *nutritional states are not kept under control throughout the experiment. All this, because memory traces may trick us and disappear, only to resurface later, when the original state experienced by the subject in acquisition is reinstated.

Selected associations: Context, Percept, Retrieval, Transfer

¹In psychiatry, ‘dissociation implies disruption of integrated functions of personality (DSM-IV 1994).

²A blocker of the *acetylcholine *receptor that Native American warriors used to smear on their arrowheads.

Stimulus

1. An event or aspect of the environment that triggers a response in a *system.

2. A signal for action.

Originally, ‘to stimulate’ meant literally to prick or stub (*stimulus*, Latin for a goad or spur). Over the years, various concepts and usages of ‘stimulus’ have played a central part in the behavioural and neural sciences. Unless otherwise indicated, definition 1 is the one discussed here. Stimuli could be or could include *cues; further, definition 2 overlaps with definitions 3 and 4 of ‘cue’.

The *classic usage of ‘stimulus’ in memory research refers to an event that triggers a response in the behaving organism. The concept, however, spans *levels, from the behavioural to the molecular. At all levels, stimulus is a packet of information that triggers specific, or less specific, processes in the receiving system.

1. On stimuli and information. There are two basic approaches to information. One, ‘syntactic’, considers the quantity without considering the content. The other, ‘semantic’, considers the meaning and significance. The ‘syntactic’ approach is used in information theory, where ‘information’ is a mathematical abstraction that refers to the uncertainty in coding and transmitting data, irrespective of the semantics (*system). This efficacy of transfer is measured in ‘bits’. One bit is the choice between two equally likely possibilities; the number of bits required to select among n alternatives is $\log_2 n$. It is currently difficult, if not impossible, to translate the data in sensory stimuli into bits

(*capacity). Even when the number of bits will be known, still, itself it will tell us nothing about what these bits signify to the receiver. To understand this, we must either observe the behavioural or physiological effect of the stimulus under *controlled conditions, or decipher the neuronal codes used by the sender and the receiver (*internal representation). The semantics of the stimulus depends on at least some of the stimulus *dimensions.

2. On the dimensions of stimuli. Autonomous dimensions, which are independent of the *context and of the state of the receiver, involve modality (e.g. wavelength, chemical composition), intensity, duration, rate, frequency, and location in time and space. Contextual dimensions, e.g. saliency, refer to the relation of the stimulus to other stimuli. Subjective dimensions depend on the interaction of the stimulus with the receiver and include functional threshold (*sensitization), familiarity, hedonic valence, saliency, and efficacy.

3. On the source of stimuli. From the point of view of source–receiver interaction, stimuli differ in their purposiveness. Purposive stimuli¹ differ in the specificity of their target. Non-purposive stimuli are released inadvertently by animate or inanimate systems. Consider a rabbit hopping in an open field. The moving object is a stimulus that triggers attack by the fox. This stimulus is not released purposively by the source. When the rabbit discovers the attack, it may freeze (*fear conditioning), which is already a purposive stimulus to abort the attack; this purpose was selected by evolution and shaped the innate, *a priori behavioural repertoire of the species. As the meaning of purposive stimuli is context and receiver dependent, it is not necessarily what the sender meant to deliver. Nowhere is it better epitomized than in ‘pragmatics’, the discipline that studies the meaning of sentences in language (i.e. verbal stimuli, definitions 1 and 2) in the particular contexts in which they are uttered. The same is true for body language. Travel guides to certain countries carry special warnings about this problem.

4. On the effect of stimuli. Stimuli could do one of the following: (a) induce new pattern(s) of activity in the receiver, in which case the stimulus is said to be *instructive*; (b) augment or inhibit non-discriminatorily endogenous patterns of activity in the receiver, in which case the stimulus is *adjustive*. (c) augment or inhibit differentially endogenous patterns of activity in the receiver, in which case the stimulus is *selective*; or (d) leave the system as it is, in which case the stimulus is *ineffective*. In each of a–c above, the effect of the stimulus could be either immediate or latent, and may or may not *persist after the stimulus is gone (*memory, *plasticity).

A *reductive *taxonomy of stimuli encountered in learning and memory research:

- a. *The types of stimuli that affect the behaviour of organisms.* The behaviour of organisms is affected by sensory stimuli from the outside world, and by endogenous stimuli, which are either sensory stimuli from within the organism, or global mental states (e.g. hunger, anxiety), or specific mental operations (e.g. one thought as a stimulus for another, *associative memory). In most learning *paradigms, emphasis is placed on exogenous sensory stimuli. It is the experimenter who selects these stimuli, but the experimental *subject may not honour the selection (e.g. *classical conditioning, *context).
- b. *Sensory stimuli* are delivered from the external world to the front end of a specialized sensory channel in the organism, causing sensation, i.e. a functional change in a sensory *receptor. Sensory physiology textbooks distinguish four types of dimensions in sensory stimuli, which can be quantitatively correlated with sensation. These are sensory modality, intensity, duration, and location in sensory space (Martin 1991). ‘Proximal stimuli’ affect the sensory receptor directly, for example, chemicals that interact with taste receptors, or pressure applied to somatosensory receptors on the skin. ‘Distal stimuli’ interact with the receptor via proximal stimuli; hence a visual scene is a distal stimulus that interacts with the visual receptor via photons, which are proximal stimuli. This is a proper point to digress briefly into a conceptual issue. Dominant schools in philosophy trust that sensory stimuli are not autonomous entities but rather ‘sense data’, i.e. entities that exist as such only because they are sensed (Price 1950; *percept). This view is in accord with the stand taken in this book, that the world drives behaviour only via internal representations, which are inherently *biased *models of the world. In important chapters in the history of psychology, however, ‘stimuli’ did not connote mental processing. For example, Skinner (1938; *behaviourism) regarded ‘stimulus’ as part of the environment that affects behaviour, and ‘response’ as part of behaviour that is affected by the stimulus. The basic idea was that behaviour and environment can be broken into parts, which interact but retain their identity throughout an experiment. That brain processes are involved was not deemed relevant. This type of attitude was accompanied by highly sophisticated stimulus–response

Stimulus

('operant') *methodology and terminology (Guthrie 1935; Skinner 1938; Hull 1943; Bower and Hilgard 1981; *instrumental conditioning).² Another discipline in which the focus is on the phenotype of stimuli is ethology. A central notion is that of a 'sign stimulus', or 'releaser', which elicits a particular pattern of innately predisposed behaviour. A popular example is the spring fighting of the male stickleback, which is released by the sight of a conspecific male, or by elongated fish-like dummies with a red belly (Tinbergen 1969; for releasers consider also *birdsong, *imprinting).

- c. *Perceptual stimuli* are extracted by the brain from sensory stimuli, creating a *percept, which could become a memory. At this stage, the stimulus is already converted into an internal representation, encoded in the spatiotemporal activity of neuronal circuits, or populations. Further processing could be subserved by stimuli arriving from other neuronal populations (*cell assembly), i.e. 'interpopulation stimuli'.
- d. *Interpopulation stimuli* are delivered from one neuronal population to another. They are either the outcome of a percept, or of a global brain state (e.g. *attention), or of endogenous activity of the source circuit. The notion that there are 'stimulus-independent' states in the brain (e.g. McGuire *et al.* 1996) should therefore be regarded only as a pragmatic heuristic of a test protocol, not a *real-life state.
- e. **Synaptic stimuli* are either chemical ligands (*neurotransmitter) or ion currents. They engage receptors, *ion channels, and other membrane proteins, and subserve interpopulation stimuli (*d* above). Included here are also diffused ('volume') transmission and circulating hormones. So are glia-neuron messages (Araque *et al.* 1999).
- f. *Intracellular stimuli* are delivered from a molecular sender to a molecular receiver within a neuron. For example, a G-protein shuttling between a surface receptor and an enzyme, or a transcription factor shuttling between the *protein kinase and a regulatory site of a gene (e.g. *CREB, *immediate early gene, *intracellular signal transduction cascade). Intracellular stimuli hence operate downstream of intercellular stimuli (*e* above) and ultimately actualize the information in the latter. Ion currents could also serve as intracellular stimuli.

The breakdown of stimulus types by level reminds one of the idea that the world rests on turtles, that rest on turtles, that rest on turtles, 'all the way down' (Geertz

1973; *reduction). For if we proceed in it we could end up with elementary particles as stimuli. This is a dilemma of reductionism, which must be solved by reconciling the multilevel nature of memory with the need to focus on those levels of organization and function in which the most important attributes of memory emerge (Dudai 1992). In the future science of memory, 'correspondence rules' of reductive theories will permit investigators to translate events from the language of one level to that of another. In the meantime, suffice it to remember that *e* and *f* above relate to cellular plasticity and cellular storage, whereas points *c* and *d* relate to representational change, hence *bona fide* memory; and that from a phylogenetic point of view, the survival value of all the stimuli is judged at the behavioural level, *a*.

Finally, in considering memory, it is important to reiterate that not all effective stimuli are successful teachers, and that in many cases the system quickly relaxes into the pre-stimulus state (*homeostasis). Therefore, not every poststimulus change in the brain is a manifestation of learning and memory, even if the report ends up as a catchy title in a respected journal. It is also noteworthy that our interaction with stimuli is use dependent. Sensory systems change their sensitivity to change (e.g. Torre *et al.* 1995; *metaplasticity); the brain learns to extract stimulus attributes by perceptual learning (Goldstone 1998); and we construe stimuli in the context of *culture (e.g. Clark and Clark 1980). We also learn to anticipate some stimuli but not others. If there is a discrepancy between the expectation and the actual stimulus, we experience *surprise, which itself is an effective incentive to form a memory of that stimulus, or, more accurately, of its percept.

Selected associations: Attention, Cue, Dimension, Generalization, Percept

¹Purposiveness does not imply *declarativeness. The emission of the stimulus by the source may subserve a discrete purpose, e.g. warning, without the source being consciously aware of it. Purposiveness should also not be confounded with intentionality, which is the dimension of 'aboutness', considered to distinguish the mental from the physical (see *system).

²To do justice to schools of behaviourism: not all those who considered overt behaviour as the only legitimate type of datum in psychology, discarded the role of internal processes; all, however, regarded stimuli as critical circumscribed variables of the behavioural experimentation and theory (Tolman 1952).

Subject

1. The object of treatment or experiment.
2. An organism or thing under the authority, control, or influence of another organism or thing.
3. That which perceives, feels, thinks, or intends.

Discussion of the multiple meanings of ‘subject’ could occupy a lengthy monograph, covering subjects from philosophy and linguistics, via the exact and the natural sciences, to politics and law. The few selected definitions provided above are the most relevant to memory research. We could benefit substantially from paying attention to those implications of ‘subject’ that tend to be overlooked in the design and analysis of experiments. ‘Subject’ originates from Latin, where it had originally meant ‘to throw or place beneath’. Accordingly, experimenters frequently think that having thrown the subject into the experimental situation (definition 1) ensures control over that subject (definition 2). The truth is that to some degree or another, every subject, especially if unanaesthetized, is an entity that perceives, feels, thinks, etc. (definition 3). An experimenter must be tuned to these attributes, otherwise real embarrassments may ensue.

Although the subject is at the focus of the experiment, frequently the attention devoted to it by the experimenter is surprisingly minimal, even less than that allotted to the computer on which the paper reporting the experiment is later being written. It is not an outraging exaggeration to claim that in some subdisciplines in experimental neuroscience, except possibly those that deal with human subjects (**Homo sapiens*), many investigators are unaware of the spectrum of attributes of their subject. This is a mistake that may result in *artefacts. So here are some elementary truths about the subjects of memory experiments, which some investigators tend to ignore, yet you couldn’t afford doing so.

1. The subject has a history. It is never the featureless, utterly inexperienced mind that you might wished it were (definitely not a *tabula rasa*, Locke 1690). The appreciation that the subject’s life did not start with your experiment (though, unfortunately, it may end with it), is a must for the proper design, *performance, analysis and interpretation of behavioural and physiological experiments (e.g. *priming, *state-dependent learning, *transfer).
2. Individual subjects of the same species differ from each other. (That individuals from different species

are different should be obvious, although sometimes people tend to confuse species traits, expecting a *mouse to behave like a *rat, for example, in a problem box). This also applies to some degree to subjects that share the same genes (*neurogenetics), and moreover, even to subjects raised in the same environment—although, of course, the variability is smaller than in a genetically heterogeneous population in an heterogeneous environment (animals kept in different cages, humans raised in different cultures).

3. Miniature brains do not necessarily have miniature minds. A *honeybee can outperform the smartest of the elephants in some species-specific tasks. And miniature subjects are not homogeneous ‘atoms of behaviour’. Surely, complex species are expected to display more behavioural variability than *simple ones, and we should in no way jump to *anthropomorphism. A powerful tool for smoothening behavioural and physiological ‘noise’ is statistics (Fisher 1966; Martin and Bateson 1993; Kerlinger and Lee 2000). Yet smoothening the noise must be distinguished from neglecting important differences among individuals. Such differences are important, because they may provide clues to potential breakthroughs (Benzer 1967). Statistics is important, attentive observation is even more so. It is useful to keep in mind the following citation from Martin and Bateson’s (1993): ‘Our general advice is not to become obsessed by statistical techniques, nor too cavalier in their use. Statistical analysis is merely a tool to help answer questions, and should be the servant rather than the master of science.’
4. *Reduced, *simplified preparations (such as isolated *Aplysia ganglia, *hippocampal slices, cell cultures, identified *synapses), the subjects of *reductive research programmes and experiments, do have a history as well. This history modifies the state and the response of the preparation (e.g. Frey and Morris 1997; Dudai and Morris 2000).
5. The subject’s behaviour is always more complex than reflected in the data that you collect. This may be due to the fact that you have *a priori decided to choose only a selected parameter to study. Even Pavlov did it, and it was a key to his success: his dogs did a lot more than merely salivate in response to the metronome; Pavlov nevertheless decided to concentrate only on an easily quantifiable part of the conditioned reflex (Pavlov 1927). Another possibility is that you are not aware of the full spectrum of your subject’s behaviour, because of lack of familiarity with the *system.

Subject

6. The subject has its own idiosyncratic understanding and appreciation of the experimental situation. Furthermore, questions that appear simple and intriguing to you may be of no interest whatsoever to the subject (e.g. **Drosophila* pay attention to odours, students to music; most species will pay much attention to their own visceral sensations following the ingestion of food, surely more than following visual or auditory experience; *conditioned taste aversion). You must hence know which questions to ask and how to pose them, in order to satisfy the curiosity and boost the motivation of the subject to take part in the game (e.g. Pavlov 1927; Benzer 1967; Garcia *et al.* 1968).
7. The subject may trick you by doing what you wish it to do, by noticing your behaviour ('demand characteristics'; Orne 1962, see *bias; *Clever Hans). The subject may also be influenced by the behaviour of other subjects without you ever being aware of it (*observational learning).
8. Know thy subject. Pay special attention to it if you switch a species, a preparation or an *assay. Different species have different perceptions of the world and behave accordingly. An innate response pattern (*a priori) may be mistakenly taken by you as evidence for learning (e.g. Moore and Stuttard 1979; Wolfer *et al.* 1998; *artefact).
9. And last, but not least: beware of falling in love with your experimental subject, especially if it is only a fly (Dethier 1962). It will surely bias you, and may even become painful.

Selected associations: Anthropomorphism, Drosophila, Homo sapiens, Model

Surprise

1. A sudden and unexpected encounter.
2. Unanticipated contradiction between *percepts or thoughts and the predictions of organized knowledge.

The trouble with political jokes is that they often get elected. For most if not all the readers, encountering this statement here is a real surprise. This is precisely why it stands a good chance to be remembered. Surprise ('sur'-+'prendre', Old French, *prehendere*, 'to seize' in Latin) is a perceptual *dimension well known to affect the *acquisition of memory in *real-life; it may lead, for

example, to an enduring *'flashbulb memory'. Descartes regarded 'wonder', or 'sudden surprise', as one of only six primitive 'passions of the soul', and appreciated its role as a trigger of *attention and learning: 'It has two causes: first, an impression in the brain, which represents the object as something unusual and consequently worthy of special consideration; and secondly, a movement of the spirits, which the impression disposes both to flow with greater force to the place in the brain where it is located so as to strengthen and preserve it there...' (Descartes 1649). Note, by the way, how well this paragraph fits five centuries later into discussions of *functional neuroimaging: all you have to do is to replace 'spirits' with 'blood', but this deserves a separate discussion on the history of ideas. A more recent forefather of our scientific *zeitgeist, Darwin (1872), also appreciated the importance of surprise as a primitive, universal emotion, characterized by specific gestures and physiological response. He focused on unpleasant surprises, startles, and fears, whereas we all know that benevolent surprises do exist, albeit they do not show up too often. In contemporary neuroscience, 'surprise' and its roles in learning and memory can be discussed at multiple *levels, from the behavioural to the molecular and vice versa. Let's therefore look at some of its manifestations in the brain, neuronal circuits and individual neurons.

'Surprise' is basically a sudden, significant mismatch between the actual and the expected. In brains, this is between on-line inputs (be them sensory *percepts or endogenous *internal representations) and off-line internal representations, i.e. memories. Definition 2 above emphasizes two additional properties: (a) that the knowledge is organized, and not merely a collection of data, and (b) that such organized knowledge makes predictions about reality (*a priori, *planning). These properties are explicit in the terminology of cognitive psychology. In cognitive terminology, 'surprise' is a sudden discrepancy between input and a 'cognitive schema'. 'Schemata' are structured clusters of generic knowledge, that represent situations, events, actions, or complex objects, enable the comprehension of input, and predict future outcome of action (Eyesenck and Keane 1995; those schemata that contain organized sequences of stereotypical actions are 'scripts'). When external or internal data suddenly contradict the prediction of a schema, surprise follows. This may then motivate and enable the analysis of the discrepancy and the adjustment to it (Schutzwohl 1998). Thus, in a way, surprise is a sudden perturbation of cognitive *homeostasis.

Although the aforementioned framework connotes human or at least primate cognition, there is no reason why the basic elements should not be adapted to *reductive treatment of much simpler brains. Conditioning paradigms were particularly instrumental in casting light on the postulated role of surprise in learning in a variety of species. Consider, for example, the phenomenon called 'blocking', which is the inhibition of the conditioning to a stimulus, CS₁, in a compound CS₁ + CS₂ stimulus, by previous pairing of CS₂ with the UCS (*classical conditioning). A prevalent interpretation of the effect is that in order for an association between a CS and a UCS to be formed, the UCS must surprise the animal, but in blocking this is not the case, as CS₂ already predicts the UCS (Kamin 1969; for alternative interpretations see Mackintosh 1983). The analysis of conditioning has provided incentives as well as constraints for a number of formal *models of learning. Among them is the noted Rescorla-Wagner *algorithm (Rescorla and Wagner 1972), which, in a nutshell, concludes that the amount of learning is proportional to the amount of surprise. In other words, learning theories, not only layperson intuition, also mark surprise as a driving force in learning.

Recording the electrical activity of the human brain in action by electroencephalography (EEG, *functional neuroimaging), has identified brain waves that appear only under 'surprising' situations. The EEG of individuals that respond to a rare stimulus occurring randomly in a sequence of frequent stimuli, or to an omission of an expected stimulus, shows a characteristic wave about 300 ms after the surprising event ('P300 wave'; Sutton *et al.* 1965). Similarly, a characteristic evoked-response brain wave about 400 ms after the stimulus is detected in individuals that encounter an out-of-context word in a sentence reading task ('N400 wave'; Kutas and Hillyard 1980). These are striking physiological correlates that differentiate fast cognitive responses by time and type.

What are the brain circuits involved? In theory, one expects circuits that compare on-line with off-line representations, identify the mismatches, induce other circuits to generate the proper behavioural response, and trigger the proper long-lasting representational change. To be useful ecologically, these circuits must operate in the subsecond range, even if they process input modalities that are considered relatively slow, such as taste (Halpern and Tapper 1971). Plausible candidates are systems that involve *cortex (both frontal and modality specific), thalamocortical, or thalamocortical-brainstem circuits. Consider, for example, the following candidate scheme: on-line information is encoded in the brainstem or cortex or both, off-line

information in the cortex, and the thalamus does the comparisons (Ahissar *et al.* 1997). Furthermore, there are good reasons to assume that the match/mismatch output signal modulates diffused neuromodulatory systems, such as the cholinergic (*acetylcholine; e.g. Mishkin and Murray 1994; Naor and Dudai 1996), *dopaminergic (e.g. Schultz *et al.* 1997; Redgrave *et al.* 1999), or *noradrenergic (e.g. Kitchinga *et al.* 1997). These neuromodulators are then expected to regulate *intracellular signal transduction cascades in the target neurons, culminating in *synaptic remodelling and ultimately in long-term memory (Berman *et al.* 1998). Thus at the cellular level, the mechanisms that encode surprise merge with those that encode attention and subserve acquisition of memory. If we delve into the nuts and bolts of these signal transduction cascades, we could even end up with molecular models that account for the ability of surprising information to encode a robust *engram after only a single brief experience, by shifting instantly the balance of the signal transduction cascades and the transcription factors in favour of that configuration that activates the appropriate 'long-term *plasticity genes' (Bartsch *et al.* 1995; *CREB, *immediate early genes, *fear conditioning, *flashbulb memory).

It is noteworthy that some of the aforementioned studies, especially those involving cellular and molecular analysis, do not target 'surprise' specifically, but rather the reaction to unfamiliar events in general. This should not be taken to imply that unfamiliarity and surprise are utterly identical. Unfamiliarity can be detected by any sensory system with an access to memory; surprise as defined here requires in addition the ability to generate expectations on the basis of organized knowledge. In addition, novelty is a continuous dimension (many inputs are only slightly novel), whereas *bona fide* surprise is probably more of an abrupt event, conforming to a step function. Still, it is likely that brain mechanisms that subserve detection of surprise overlap with those that subserve the response to unfamiliarity in general. In all these cases, the brain compares the present to the past. In the case of surprise, an additional faculty is engaged, that of computing expectations and evaluating the significance of their sudden clash with reality, in real-time. We do not know whether even the simplest nervous systems that can detect novelty generate such rudimentary expectations and are engaged in comparison of pre-representations with on-line input (*a priori). In mammals, this ability is contributed, among others, by the frontal cortex (Fuster 1995a; Watanabe 1996; Daffner *et al.* 2000; *attention, *working memory).

Surprise

Surprises are effective incentives for behavioural modifications that contribute to survival. This is probably why the ability to detect them had been embedded effectively in our brain. Seen this way, the most important ones are the bad surprises, because they may kill; hence, Darwin was not off-track when he emphasized startling, nasty surprises (Darwin 1872; also ‘startle reflex’ under *attention, *sensitization). With the emergence of human *culture, our capacity to note mismatches with predictions of organized knowledge has gained additional functions, some of which are geared to create pleasure, not pain. Hence, it is said that surprise and ‘defamiliarization’ are at the basis of our appreciation of art (Shklovsky 1917). On the more practical side of life, surprises, although still mostly bad ones, contribute to our attitudes as consumers of goods (Maute and Dube 1999). And in the small world of universities, professors can exploit pedagogical surprises to enhance the success of their classes (Kintch and Bates 1977; Thorne 1999).

Selected associations: A Priori, Algorithm, Attention, Dimension, Sensitization

Synapse

A specialized junction between neurons, or between neurons and other types of excitable cells, capable of transmitting, processing, and retaining neural information.

The term ‘synapse’ (Greek for *syn-haptein*, ‘to make contact’) is commonly attributed to Sherrington (Foster and Sherrington 1897). It was actually proposed by Verrall, an expert on *classical drama, to replace *syndesm* (Greek for ‘chained together’), which was Sherrington’s first choice (Shepherd and Erulkar 1997). ‘Synapse’ was preferred because it was judged to yield a better adjectival form. It is left for the reader to judge whether ‘synaptic *plasticity’ indeed rhymes better than ‘syndesic plasticity’, but, in any case, it is too late for a change. In the background of the introduction of ‘synapse’ was one of the most important and heated debates in the history of the neurosciences (e.g. Brazier 1988; Finger 1994). Two ‘theories’ (*model) concerning the cellular organization of the nervous system coexisted toward the end of the nineteenth century. One, ‘the reticular theory of nervous organization’, promoted among others by Golgi, held that nerve cells are physically interconnected to form an uninterrupted web

(reticulum). This theory held the contacts between the extensions that branch of neuronal cell bodies are only specializations in a fused continuum of tissue. The opposing theory, dubbed ‘the neuron theory’ or ‘the neuron doctrine’, promoted among others by Cajal, held that nerve cells are discrete entities.¹ According to this doctrine, the junctions between neurons are specialized miniature devices that engage the juxtaposed individual units in the net. The neuron doctrine triumphed, although not without some skirmishes waged by the retreating ‘reticularists’ well into the twentieth century (Szentagothai 1975). Sherrington was a neurophysiologist who trusted that nerves terminate in free endings and that the transfer of information from these endings to their targets differs markedly from the propagation of information along neuronal branches. When requested to revise his contribution to an authoritative textbook of physiology (Foster and Sherrington 1897), he reasoned that as research on the functional junction between nerve cells had already matured to become an important topic in physiology, this type of junction deserved a special term. Hence the ‘synapse’ was born.

Synapses come in many flavours. They can be classified by their morphology, location, function (e.g. inhibitory vs. facilitatory), types of *neurotransmitters and their *receptors, etc. A major *taxony distinguishes ‘chemical’ from ‘electrical’ synapses. In chemical synapses, information is transmitted from one cell to another by chemical messages (neurotransmitters) over an intercellular gap. In electrical synapses, there is direct electrical communication between the juxtaposed cells by way of a specialized contact, called ‘gap junction’, which contains *channel complexes called ‘connexons’ (Goodenough *et al.* 1996). Two connexons, each contributed by one of the juxtaposed cells, interact, and align to form an intercellular channel, which subserves electrical coupling and exchange of small molecules. Cell–cell ‘on-line interneting’ via connexons occurs in many types of tissues. Electrical synapses are hence specializations in the nervous system of a ubiquitous type of cellular device that allows direct communication and synchronization of activity between adjacent cells. Communication via electrical synapses is fast but the direct coupling imposes some constraints, such as the inability to reverse the sign of the signal or amplify it on location. Electrical synapses do, however, display use-dependent plasticity, which may involve *intracellular signalling cascades triggered by chemical transmitters (Goodenough *et al.* 1996; Pereda and Faber 1996). Synaptic complexes that share elements of both electrical and chemical transmission are termed ‘mixed synapses’. An example for the use of electrical synapses

in the mammalian brain is provided by widespread networks of inhibitory neurons in the *cerebral cortex (Gibson *et al.* 1999). So far, electrical synapses have received less attention than chemical synapses, but recent years have witnessed a growing interest in their function in the brain.

As noted above, in chemical synapses, in contrast to electrical synapses, the two opposing neurons are separated by an intercellular gap, called the 'synaptic cleft'. The use of 'gap' or 'cleft' does not imply void; there is a rich microcosm in between the pre- and the postsynaptic membranes, and some of the molecules physically bridge the two sides. It is also noteworthy that, although we now take it for granted that chemical synapses exchange chemical messages, the nature of the information transmitted over the synaptic cleft in such synapses had been debated over many years. Two types of possibilities were considered. One, that the information is mediated by electric currents. The other, that it is transmitted by chemical substances. The existence of chemical transmission in the neuromuscular junction was proposed by Du Bois-Reymond in 1877 (cited in Dale 1938). A series of investigations conducted independently by Lewandowsky, Langley, Elliot and later Dale, Loewi, and others have provided convincing evidence

for chemical ('neurohumoral') transmission (Elliot 1904; Dale 1938, 1954; also *acetylcholine, *noradrenaline). The evidence had been provided first for synapses in the peripheral nervous system and only later for the central nervous system. Actually, for a while, some leading investigators considered chemical messages too sluggish to be useful for fast communication in the central nervous system. Notable among them was Eccles (1982). But even the lingering opposition finally succumbed to the data: 'Eccles and his team concluded that ... (transmission) could only be due to the release of a chemical agent from the endings of the afferent fibre... A remarkable conversion indeed! One is reminded, almost inevitably, of Saul on his way to Damascus, when the sudden light shone and the scales fell from his eyes' (Dale 1954).

Since their discovery, it has been realized that synapses are faced with an inherently tough job. Basically, they have to transmit information (*stimulus) with acceptable fidelity. But they had also been evolved into miniature transducers that filter, encode, process, modulate, associate and register chunks of that information for their own use and for the sake of the circuit. Accordingly, in the discipline of memory research, synaptic components have been assigned roles of elements in

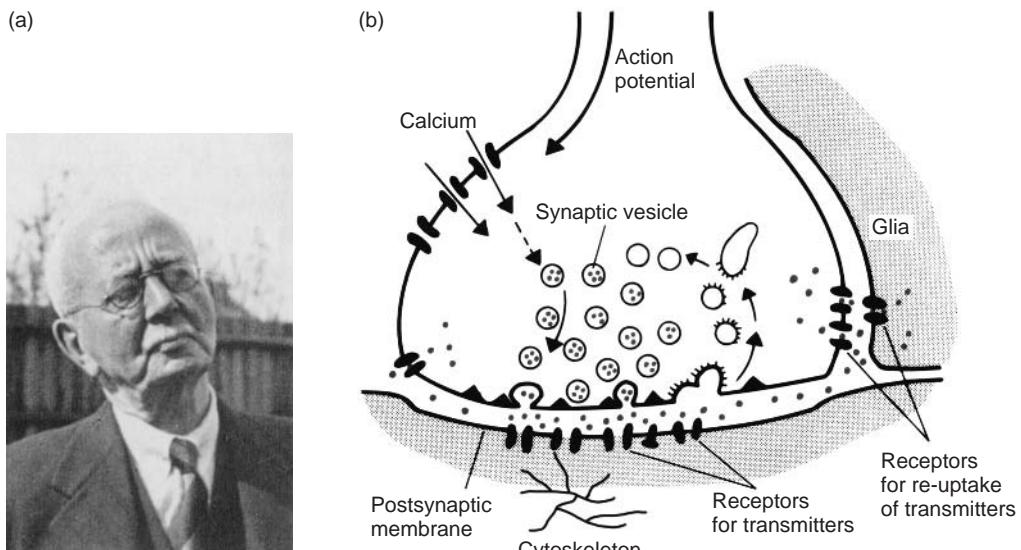


Fig. 62 (a) Sherrington, who is accredited with the introduction of the term 'synapse', and (b) a highly schematic representation of a chemical synapse. Only a few elements of the synapse are shown. The postsynaptic terminal and an adjacent glia cell are depicted in grey. Glia cells (from the Greek 'glue') are traditionally considered to provide neurons with physical and metabolic support; although it is now clear that they do much more (Araque *et al.* 1999; Ullian *et al.* 2001), their exact role in synaptic communication and in synaptic plasticity is still mostly an *enigma. For more on synaptic components and their function, see *calcium, *ion channel, *neurotransmitter, *receptor.

Synapse

miniature learning machines, such as *acquisition devices, *coincidence detectors and associators, storage devices, etc. (Dudai 1993; **Aplysia*, **Drosophila*, *long-term potentiation).² The synaptic job is carried out by webs of macromolecules in the presynaptic and the postsynaptic terminals. Parts of this web extend into the synaptic cleft as well. The macromolecular web includes *ion channels, *receptors, cytoskeleton, adhesion molecules, and more (Kuno 1995; Hagler and Goda 1998; Kim and Huganir 1999). The presynaptic terminal contains a highly specialized apparatus for transmitter release (Kuno 1995; Schiavo *et al.* 1995; Geppert and Sudhof 1998), regulated, *inter alia*, by presynaptic receptors for the same or other transmitters (Langer 1997; Miller 1998). The structure and function of the synaptic machinery is a dynamic function of the stage in *development, the individual experience of the synapse, and the ambient extracellular and intracellular input (e.g. *calcium; *glutamate; Okabe *et al.* 1999; Thomson 2000). Plastic changes could manifest themselves in anything from gradual alterations in synaptic efficacy, subserved by pre-, post-, or pre + postsynaptic mechanisms (Jessel and Kandel 1993; Markram *et al.* 1998; Thomson 2000), to a transformation from a silent synapse to one that starts talking (Atwood and Wojtowicz 1999). Some manifestations of synaptic *plasticity last for a fraction of a second to a few seconds only, but other forms of synaptic plasticity could last much longer (*long-term potentiation). To reshape itself in the long term, the synapse apparently takes advantage of local as well as cell-wide *protein synthesis facilities (Steward 1997; Casadio *et al.* 1999; Gardiol *et al.* 1999).

The notion that synaptic plasticity subserves developmental and behavioural plasticity is a tenet of neuroscience. In the neurobiology of memory as well as in *modelling, the twentieth century was in many respects the century of the synapse. It has become the major and sometimes the sole focus of attention at the molecular, cellular, and circuit *levels of analysis. The synapse was also identified as the prime target for multiple types of neuroactive drugs, including some that affect memory (*lotus, *nootropics). The popularity of the synapse stems from a smart choice of a domineering *reductive research programme, and from the availability of certain advanced research *methodologies. It is tempting to predict that in the twenty-first century, analysis of the synapse will become even further integrated into the analysis of *internal representations and their experience-dependent modification at the circuit and system level. The data so far do tell us that synapses are critical in making memories. But synapses may not be

sufficient and even more so exclusive agents in establishing a memory (*criteria). Because they are so interesting and captivating, and because we find them more or less amenable to analysis, becoming immersed in the fascinating world of the synapse could easily make one forget what the ultimate goal of memory research is. As far as memory is concerned, what counts for the behaving brain is not the individual synapse but rather the integrated contribution of many synapses to the coherent activity of the networks in which they operate.

Selected associations: Algorithm, Ion channel, Long-term potentiation, Plasticity, Reduction

¹When the term 'synapse' was introduced, the term 'neuron' had itself been a newcomer to the scientific jargon. It was coined by Waldeyer (1891), an ardent supporter of Cajal's neuron doctrine, only a few years earlier.

²Beware, however, of the '*homunculus fallacy', which equates the behaviour of the synapse with the behaviour of the brain or even the organism.

System

1. A set of units and their interrelationships.
2. A group of related elements organized for a purpose.
3. A portion of the universe selected for study.

'System' (from *sunistanai*, 'to combine' in Greek) is abundant in colloquial 'scientinglish'. 'Let me tell you about my system' or 'did you try it in your system' are only selected examples of ritualistic utterances of scientific *culture. An experimental system well-matched to the research goal is a key to successful research programmes. Prolific systems facilitate the road to academic tenure and fame, and trendy systems increase the probability of acceptance of manuscripts into respectable scientific journals. The popularity of 'system', therefore, deserves an attempt to put some order to the system.

What are systems? In the most general sense all systems are sets of interconnected units (definition 1). These units may be either concrete (e.g. parts of a machine) or abstract (e.g. concepts in a theory). In some cases the system is delineated on the basis of its assumed purpose (definition 2), but the teleological *raison d'être* may exist only in the eyes of the beholder. Even more anthropocentric is the view that a system is defined by its being selected for analysis (definition 3). None of

these definitions assumes anything about the composition, size, semantics, and goal of the system. Systems hence vary tremendously in their scale and complexity, dependence on other systems, interdependence of subsystems, function, and dynamics (e.g. Simon and Ando 1961; Mesarovic *et al.* 1970; Houk 1980*b*; Bhalla and Iyengar 1999).

The existence of systems. Systems may be either natural kinds or *artefacts. In many cases they are both. Consider memory research. ‘Non-*declarative memory’ is a heuristic term referring to an artefactual system; it is highly unlikely that all memory faculties included under the umbrella of this term indeed comprise a natural system. The hippocampal system (see *hippocampus) is a reasonable candidate for a natural system but its boundaries are not known for sure. The status of the *amygdala as a natural system is unclear. And is the cyclic adenosine monophosphate cascade (*intracellular signal transduction cascades) a natural kind or an artefact of erroneous *taxonomy?

The boundaries of systems. Systems impermeable to the rest of the universe are termed ‘closed’. Those with permeable boundaries are ‘open’. In open systems, the variables determined by causes extrinsic to the system are ‘input’, whereas those dependent upon the action of the system are ‘output’. In reality absolute impermeability is nonexistent, but the level of input and output may be extremely low. Open systems differ in their openness. Living systems are open but semipermeable, i.e. they allow some inputs but not others. For example, a neuron is encircled by a semipermeable membrane that allows only selective flux of materials (*ion channel, *receptor).

The relation of systems to other systems. From the aforementioned description it becomes evident that considering any system as truly independent of other systems is an illusion. Systems always harbour other systems and are themselves parts of still others. A paranoid conclusion is that systems are everywhere, and that everything is a system (for additional notes on the intractability of systems, see Gall 1986). The question arises, therefore, can we deal satisfactorily with variables in a system irrespective of variables in other related systems (*control)? Luckily, the prerogative of a scientist is to decide what ‘satisfactorily’ is in any given system, so that practically we may decide that interactions below a certain level are ignored. The assumption that variables outside the system are held for all practical means constant (and hence are irrelevant) is referred to as the *ceteris paribus* assumption (Latin for

‘other things being equal’). The usefulness of certain *simple systems derives from a focus on one or a few variables combined with adaptation of the *ceteris paribus* assumption.

The generality of systems. Systems chosen for analysis differ in their claim for generality. Some are ‘types’, others ‘tokens’. Type is a class, or a *taxonomic entity, possibly an abstraction only, characterized by sameness in certain *dimensions. Tokens are the particulars that instantiate the type. For example, in the previous sentence as well as in this present one, the word ‘the’ appears twice, but it is only one word. Hence, those were more than once, tokens of the type ‘the’.¹ The distinction between types and tokens depends on the *level of analysis and discourse. *Glutamatergic receptors are tokens of the type ‘*receptor’, but *N*-methyl-D-aspartate (NMDA) receptors (NMDAR) are tokens of the type ‘glutamatergic receptors’, and copies of the NMDAR are tokens of the type NMDAR. Usually the selection of a system for investigation (or of *models) is driven by a wish to understand the type by studying the token. For example, selection of *Aplysia* as a model system for the analysis of learning and memory, was not guided by an irresistible urge to comprehend the mental life of a slug, but rather by the realization that it provides convenient advantages that might allow understanding of types of simple learning. In general, defining the understanding of a type as the immediate objective of the research programme is mostly impractical, for the research itself always boils down to the analysis of tokens. But if we were to conclude that no tokens could illuminate anything about the (hypothetical) corresponding types, many investigators would have lost interest in their systems.

Information and systems. Systems encode information, although in our current understanding of brain systems we rarely understand for sure what the specific information is. It is pertinent to note that ‘information’ has different meanings in different treatments. In everyday language, ‘information’ refers to knowledge, i.e. the meaning and significance (*semantics) of input and output. In contrast, in information theory, ‘information’ is a mathematical abstraction that refers to the uncertainty in coding and transmitting data, irrespective of the semantics (Shannon and Weaver 1949; Wiener 1961; Pierce 1961; *stimulus). This efficacy of transfer is measured in ‘bits’. One bit (*binary digit*) is the choice between two equal likely possibilities. Selection of one of four alternatives requires two bits, and so on; the more alternatives, the more bits are needed to select among them. The number of bits required to select

System

among n alternatives is $\log_2 n$. Even if the number of bits is known, it tells us nothing about what these bits signify to neither the sender nor the receiver. A major goal of the neurosciences is to decipher not only the ‘information’ processed by a nervous system, but also to unveil its meaning (*capacity, *internal representation).

Mental and physical systems. Memory, at least in its more complex manifestations, connotes mental activity. In discussing memory systems it is therefore pertinent to ask what distinguishes mental from physical systems. By posing this question one does not, of course, claim that mental systems are not physical; the issue is merely what turns ‘mental’ mental. A traditional criterion is that mental systems display ‘intentionality’, whereas physical systems do not (Brentano 1874). In philosophy, ‘intentionality’ is ‘aboutness’; mental systems exist in states (‘intentional states’) which are about something, for example, belief, hope, etc. In fact, in most of the systems studied in the biology of memory, the distinction between the mental and the physical is not an acute issue, especially if the system in question is simple and the experimental approach highly *reductive. However, when one approaches issues such as complex *declarative representations, *planning, and possibly even highly developed capabilities of *observational learning, the issue becomes relevant, although not necessarily solvable.

Selection of a system. So how should one select a system for the investigation of memory? Idiosyncratic *bias and training background notwithstanding, several considerations are still noteworthy. First, it is useful to choose a system that provides optimal access to the *methods and level of analysis that one wishes to pursue. In other words, as in many other facets of life, the trick is to match aspiration, capability, and availability all together. Second, although one may wish to illuminate a type, in practice a useful token must be selected, which allows fragmenting the problem into approachable segments. Further, the *ceteris paribus* prerogative should be exploited liberally, yet without being too serious about its validity. And third, never lure yourself to think that you know everything about your system. At the end of the day, sometimes even in its beginning, it will tear off its disguise and present itself as a metasystem or a subsystem of yet another unfamiliar system.

Selected associations: *Anthropomorphism, Bias, Generalization, Model, Subject*

¹The distinction between ‘type’ and ‘token’ goes back to the physicist and philosopher Peirce in the nineteenth century, but itself is a token

manifestation of a much older type distinction between ‘universals’ and ‘particulars’: see Armstrong 1989; also on ‘realists’ vs. ‘nominalists’ in *Ockham’s razor.

Taxonomy

The systematic grouping of entities into categories according to some *method of arrangement or distribution; classification.

The tendency to categorize the world into ‘similar’ and ‘different’ is fundamental to human cognition. It underlies folk knowledge systems in orally-reliant societies as well as sophisticated taxonomies in science (Durkheim 1912; Levi-Strauss 1962; Smith and Medin 1981; Sokal 1985; Berlin 1992). It is shared to some degree even by species far remote from us on the phylogenetic scale (Giurfa *et al.* 1996). The term ‘taxonomy’ itself is, however, a newcomer to language: *taxinomie*, or *taxonomie*, was introduced in 1813 into French to denote classification of entities, and the discipline that deals with such classifications (from *taxis*+*nomie*, meaning *arrangement*+*method* in Greek; Le Maxidico 1996). It then found its way into English. In biology, ‘taxonomy’ came to be associated predominantly with the discipline that classifies biological species (Mayr 1981). But the term is also widely used in other domains of knowledge to denote classifications of a variety of natural kinds, concepts, and artefacts.

A major issue concerning taxonomies of natural entities is whether they represent ‘natural’ types or only creations of the human mind. Some claim that ‘natural’ reflects the state of affairs in nature; others that it only reflects the capacities of the human mind; and still others that both the above coincide, as the human mind is expected to have evolved to equate ‘natural’ in nature with ‘natural’ in mind (Sokal 1985). A potential clash of ‘natural in mind’ and ‘natural in nature’ is illustrated in the taxonomy of biological species: early schools of taxonomy relied on the phenotypic similarity of organisms and therefore shared much with primitive taxonomies; later taxonomies already rely on the more refined scientific understanding of phylogenesis (Mayr 1981; Sokal 1985). Certain classifications do appear intuitively ‘unnatural’. Consider, for example, the fictitious taxonomy attributed by Borges (1952) to a Chinese encyclopaedia, *Celestial emporium of benevolent knowledge*. According to this, animals are divided into: ‘(a) those that belong to the Emperor,

(b) embalmed ones, (c) those that are trained, (d) sucking pigs, (e) mermaids, (f) fabulous ones, (g) stray dogs, (h) those that are included in this classification, (i) those that tremble as if they were mad, (j) innumerable ones, (k) those drawn with a very fine camel's hair brush, (l) others, (m) those that have just broken a flower vase, (n) those that resemble flies from a distance? The beauty of this taxonomy is in its poetic oddity (*surprise). However, as classifications are intended to facilitate handling and analysis of information, even the aforementioned emporium could have made some sense from the point of view of a ruling Emperor. Further, we should not forget that to the modern mind, 'primitive' classifications of natural phenomena may appear rather confused, even though they were considered perfectly logical to the contemporary mind (Hallpike 1979). For example, the Greek world was depicted as composed of four basic elements, water, air, fire and earth (Plato, *Timaeus* 32b–c); hence taxonomies are *culture dependent and what is regarded as 'natural' in 2001 may not be so in 2100.

Taxonomies prevail at every branch of knowledge and *level of analysis. Examples in the neurosciences are types of neurons, glia, *ion channels, *receptors, *neurotransmitters, *intracellular signal transduction cascades, neuronal firing patterns, brain regions and pathways, etc. These 'types' contain multiple 'tokens', i.e. specimens or instances of the type (Dudai 1993; *system). The taxonomy most characteristic of memory research is no doubt that of memory itself. 'Memory system' could be described as an organized structure of interconnected neural substrates, encoding experience-dependent *representations that subserve some characteristic type(s) of behavioural and cognitive function(s) (Tulving 1985; but see below). Each system could hence be specified by phenotypic, functional, structural, and possibly phylogenetic *criteria (e.g. Tolman 1949; Sherry and Schacter 1987; Shettleworth 1993; Schacter and Tulving 1994).

The mere notion that memory is not monolithic pre-dates science. Over the years, multiple axes or *dimensions have been used to classify memory. For example, sensory *modality*: 'In memory, all things are kept distinct and according to kind. Each is brought in through its own proper entrance: the light and all the colors ... all these enter in, each by its own gateway, and are laid away within it ...' (Augustine 400). Or *duration*, i.e. whether short or long lived (James 1890; Hebb 1949; *phase). Or *actualization*, i.e. whether active or inactive at a given point in time (Lewis 1979; *retrieval). Or the *processes* that drive the system, either top-down, concept-driven, or bottom-up, data-driven

(Roediger 1990).¹ Additional candidate dimensions are illustrated in *collective memory, *dimension, *learning, *prospective memory. Most taxonomies of memory are not mutually exclusive; one could consider a short-term, visual memory, or an inactive, long-term memory.

A cardinal *criterion in the prevailing taxonomy of long-term memory is that of *conscious awareness, i.e. whether the information is accessible to conscious recollection or not. This type of dichotomy was imported into modern neuroscience from philosophy. Kant (1781) distinguished representations with or without consciousness; de Biran (1804) spoke of 'mechanical memory', in which recall is a 'simple repetition of movements', and 'representative memory' in which recall involves 'the clear appearance of ... (an) idea'; Bergson (1908) differentiated between habit, the 'memory that repeats', and 'memory per excellence', or 'the memory that imagines'; and Ryle (1949) distinguished 'knowing how' from 'knowing that'. 'Knowing how' is also known as 'practical knowledge', and 'knowing that' as 'propositional' or 'factual knowledge' (Bernecker and Dretske 2000).

The 'that' vs. 'how' dichotomy is supported by analysis of memory deficits in human *amnesics and to a certain degree by animal *models of amnesia (Mishkin *et al.* 1984; Squire and Zola 1996; Eichenbaum 1997a). Accordingly, the current *zeitgeist taxonomy of memory systems in the brain sciences depicts two metasystems of long-term memory, *declarative (the 'that' system, alias 'explicit') and nondeclarative (the 'how' system, alias 'implicit') (Schacter 1987; Squire and Zola 1996; Figure 63). Declarative memory is further divided into memory for facts ('semantic') and for events ('episodic', 'autobiographical', Tulving 1983). Some authors draw a distinction between 'episodic' and 'declarative' (Tulving and Markowitsch 1998). Similarly, in epistemology, 'knowledge by acquaintance', i.e. of people, places, and things, is distinguished from propositional or factual knowledge (Bernecker and Dretske 2000).

Declarative memory is subserved by diencephalic and mediotemporal structures (*cerebral cortex, *hippocampus, *limbic system). Some authors propose that brain systems that subserve *episodic and semantic memory are partially dissociable, with only episodic memory being fully dependent on the hippocampus (Vargha-Khadem *et al.* 1997; see Tulving and Markowitsch 1998 for support of this view, and Squire and Zola 1998 for a different position). Nondeclarative memory is commonly further subdivided into the following systems (Figure 63): (a) non*associative

Taxonomy

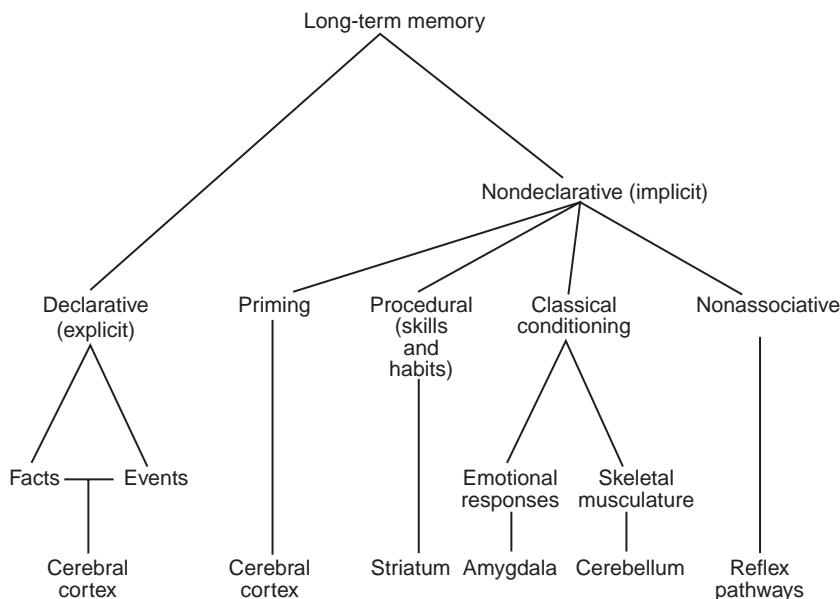


Fig. 63 A taxonomy of long-term memory, adapted from Milner *et al.* (1998). Selected brain areas that subserve each type of memory system are indicated at the bottom of the diagram.

memory, i.e. *habituation, and *sensitization, subserved by specific reflex pathways; (b) *classical conditioning, which is further classified into conditioning of musculoskeletal reflexes, subserved among others by the *cerebellum, and conditioning of emotional responses, subserved among others by the *amygdala (*fear conditioning); (c) procedural memory, i.e. memory for *habits and *skills, subserved by a corticostriatal system; and (d) *priming, which, in its multiple variants, is believed to be subserved by cortex. It can be readily seen that, whereas the classification of declarative memory is based on a unified concept and seems 'natural', non-declarative memory is defined by exclusion, and its subtaxa are rather heterogeneous.

The zeitgeist taxonomy of long-term memory systems evokes several types of interrelated problems:

1. *Criteria*. The notorious 'problem of the criterion' pops up again. In order to classify correctly we must know a lot about the system, but in order to know a lot about the system we must be able to classify it correctly. What shall we use as the decisive criterion for the delineation of a memory system? Common behavioural (phenomenological) properties? The faculties affected by circumscribed brain lesions? The evolutionary history of parts of the brain? As mentioned above, Tulving (1985a) proposes to

consider both functional neuroanatomy and behaviour, but the same brain structure could contribute to different tasks, and a seemingly similar behavioural output could reflect different computational goals and *algorithms. For example, perceptual and conceptual priming both involve nonconscious modulation of the processing, retrieval, or production of a mental item by prior exposure to specific information on that item or on items associated with it. But one could come up with very different systems that share this property. So is there a natural 'priming system' in the brain?

2. Which leads to the issues of **system vs. process* and **system vs. attribute*. Is priming a memory system, or is it a cross-the-board process, or a manifestation of automaticity of different processes, shared by *skill systems (e.g. Logan 1990)?
3. Which leads to the issue of *superfluity*. This taps into the tension between the mind's tendency to classify and the continuity of nature (Aristotle, *Parts of Animals* 642b5–644a12; for selected examples see *amygdala and *limbic system). For it is rather easy and even appealing to come up with new types of memory systems, and the minute they are proposed, to come up with neurobiological and behavioural justification, turning the tentative proposal into a premature *fait accompli*.

4. Which leads to the other facet of the coin, **generalization*. We could err in grouping into a unified memory system the capabilities of species far remote on the phylogenetic scale. For example, to regard some memory performances in rodents as declarative as opposed to nondeclarative may overgeneralize and disregard the accomplishments of the evolution of the primates. ‘Implicit’ vs. ‘explicit’ may better fit the tests used, but again, the issue of whether even these terms apply to lower invertebrates, which are on a different branch of evolution, is questionable. Disregarding this difficulty could culminate in the pursuit of **red herrings*. Hence taxonomy should be better used a heuristic aid to research rather than a guiding criterion.

Selected associations: Criterion, Dimension, Model, Memory, System

¹On additional aspects of top-down vs. bottom-up processing, see *attention, *binding, and *insight.

²This question makes sense only if we consider definitions 1 and 2 of *system. Definition 3 of *system leaves us with the convenient freedom to declare anything a ‘system’.

sums. Both groups were later subjected again to a history test. Although both groups got the same score on the first history test, group A fared much better on the final history test. The conclusion was that improvement gained by practise in memorizing one subject of instruction (poetry) was transferred to memory work in other subjects (history): ‘...the results do appear... to strengthen the case of those who wish children to learn much poetry; it is not an obstacle, but an aid, to the acquisition of other knowledge’ (Winch 1908).

Transfer is said to be ‘positive’ if the experience on the first task results in improvement on the subsequent task, and ‘negative’ if that experience on the first task impairs the performance on the subsequent task (e.g. Woltz *et al.* 2000). Of course, experience on task *i* could result in positive transfer on task *j* but negative transfer on task *k*. As transfer is such a comprehensive term, qualifiers are used to specify the type of transfer under consideration. Only the two major uses of the term will be outlined here:

1. *Transfer of training* refers to the contribution of training on one *skill to the performance on a different skill. Some authors use the terms ‘transfer of training’ and ‘transfer’ interchangeably. However, in the behavioural literature ‘transfer of training’ conventionally implies intentional training on a particular overt behaviour, whereas ‘transfer’ extends also to higher cognitive processes such as the formation of concepts and hypotheses (see below). This distinction notwithstanding, the demonstration of transfer of training in even ‘simple’ *classical or *instrumental conditioning may also involve the formation of hypotheses and concepts (e.g. Schusterman 1962; *learning set). The study of Winch (1908), mentioned above, epitomizes a simple transfer of training experiment. Multiple protocols of transfer of training have been developed, and with them measures of the efficacy of transfer (Gagne *et al.* 1948; Murdock 1957; Hammerton 1967; Kolers and Roediger 1984). These measures commonly reflect better performance on the initial encounter with the new task, or ‘saving’ of training time or trials (on ‘saving’, see also *experimental extinction). Clearly, efficient transfer of training procedures is of great practical importance, as it could save time and money on training for specific jobs, either in the real situation or in simulators (Hammerton 1967; Hammerton and Tickner 1967).

In our discussion so far we have considered transfer of training as an intertask phenomenon. A somewhat different point of view propounds that even in what is formally considered by the experimenter as a single task, *recall is actually a ‘retrieval task’ that replays the

Transfer

The contribution of experience on one task to *performance on a subsequently different task.

Teachers have appreciated transfer much before neurobiologists did. The teachings of the *classics, when practised, were not necessarily for school children to become experts in Homer or Virgil. The idea was that such studies have a general disciplinary value that will be transferred to the intellect at large. This is why educational psychologists were driven to investigate transfer. They had to prove that some educational *methods do have merit. In doing so they have also developed basic research methodologies of tremendous value. Consider, for example, the use of *control groups: it was introduced in research on transfer in schooling (Thorndike and Woodworth 1901a,b; Coover and Angell 1907). A brief example should suffice to illustrate this type of early studies: a group of schoolgirls in London were instructed to memorize a history text and subsequently tested for their *recall. The girls were then divided into two groups. Group A practised poetry over 2 weeks, whereas group B was engaged in working

Transfer

*acquisition task'. As a consequence, performance on retrieval could benefit from transfer of experience on acquisition. This is further discussed as 'transfer appropriate processing' (Morris *et al.* 1977) under *retrieval.

2. *Analogical transfer* refers to the use of a familiar problem to solve a novel problem of a similar type (Gick and Holyoak 1983; Reeves and Weisberg 1994). The familiar problem is dubbed the 'source problem', 'base analogue', or 'base domain', and the new problem the 'target problem' or 'target domain'. For example, the popular depiction of the Rutherford model of the atom uses an analogy to the solar system (the base domain) to understand atomic structure (the target domain); the nucleus is depicted as the sun and the electrons as the stars (Gentner 1983). Much of our thinking is subserved by noticing similarities and analogies and generating *metaphors (Tversky 1977; Gibbs 1994). It is doubtful whether we could construe the world otherwise, although probably only a minority of scientists would agree with Nietzsche that 'truth is a moving army of metaphors' (Nietzsche 1873). By the way, 'metaphor' in Greek means 'transfer', in the colloquial meaning of 'transfer'.

Over the years, a number of 'theories', or *models, of analogical transfer have been advanced (Reeves and Weisberg 1994). They propose multiple stages in analogical transfer. First, there is the *acquisition of information about the base and target domains. This could occur long before the attempt is being made to solve the problem. Next there is the noticing of the base domain and its relevance. This critical stage echoes *insight. Next comes the application of the analogy to the target domain. If hints are provided, the situation is termed 'informed transfer'; otherwise, it is 'spontaneous transfer'. What type of information is used by the brain in doing all this? It helps to realize that problems can be defined at multiple *levels of information. The visible details of the particular problem are elements of the 'surface structure' of the problem, whereas the underlying abstract rules and principles comprise the 'deep structure'. Problems with different surface structures could share a deep structure. One aspect in which models of analogical transfer differ is their view of the relative contribution of 'surface' and 'deep' structures, or of data and *stimuli vs. rules, to the successful analogy (Reeves and Weisberg 1994; for a window to related debates in the cognitive sciences, see Gentner and Medina 1998).

A widely cited example will serve to illustrate the surface and deep structure. In this example, a problem entitled 'the radiation problem' is the target problem, and another, 'the general problem', the base

problem (Gick and Holyoak 1983). The radiation problem is about a physician, who is faced with a patient with a malignant, life-threatening stomach tumour. It is impossible to operate on the patient. Radiation can destroy the tumour, but at the desired intensity the ray will destroy the healthy tissue on the way to the tumour. Lower density radiation is harmless to the healthy tissue but will not affect the tumour either. What shall the physician do? Now, here is the general problem: a country is ruled from a strong fortress by a dictator. A rebel army general leads his army to capture the fortress. Many roads lead to the fortress from different directions. All of them are mined. The mines are set to be detonated by the passage of large army units but not by small units. An attack by the entire army at once, which otherwise would capture the fortress, will detonate the mines. The solution: dispatch the soldiers in small units via many roads so that the entire army arrives together at the fortress at the same time. Subjects given the general problem were more likely to solve the radiation problem. Its solution: reduce the intensity of the rays but irradiate from several directions simultaneously (this is actually the correct clinical procedure). The two problems differ in their surface elements (physician, patient, hospital, vs. general, fortress, army, etc.), but share a deep structure (disjoining followed by *coincident convergence).

Transfer protocols are incorporated into a variety of studies on *engrams (e.g. Karni and Bertini 1997; Buckley and Gaffan 1998). They are used among others to measure the *generalization and extent of learning as a function of the activity (or damage) in a particular brain area. The identity of the brain areas involved depends on the paradigm used; for example, somato-sensory *cortex in motor skill. It is not yet established which brain areas are specifically critical for analogical transfer, although the frontal cortex is a safe bet.

A timely issue concerning transfer relates to the interplay between the extent of generalization of knowledge that is required to support transfer on the one hand, and the extensive specialization demanded from modern technological society on the other. To be effective, transfer must involve some degree of similarity, in data, procedures, rules, or cognitive *maps, between the source and the target tasks. Modern technology encourages more and more differentiation and specialization in order to master skills at an expert level. This may reduce substantially the overlap between old and new skills. How will it affect our ability to transfer knowledge from previous to future jobs? The problem surely calls for rethinking and identification of those cognitive skills that could promote efficient

transfer of knowledge from what we know today to what we will have to know tomorrow. The impact on our educational and training systems might be profound.

Selected associations: Acquisition, Generalization, Learning set, Priming

Working memory

- 1. A memory *system that holds information in temporary storage during the *planning and execution of a task.**
- 2. The process in which newly *perceived information is combined with *retrieved information during the planning and execution of a task, to form and maintain short-lived *internal representations that guide the behavioural response.**

'Working memory' is one of the most important and exciting concepts in modern neuroscience, and rightly so. It refers to a cognitive faculty that is essential for mentation and complex behaviour. This faculty subserves much of our ability to interact with the world in a flexible and intelligent manner, and is essential for thought, planning, and language. For example, reading these lines and combining them into a meaningful message, requires working memory. It is doubtful whether without working memory there would have been a Homer, a Shakespeare, a Mozart, or a Newton, and an audience to appreciate them. A mind without working memory is thus expected to be a rather dull place.

The idea that there should be a cognitive faculty that 'holds things in mind' temporarily, probably occurred long ago to thoughtful individuals while practising their own working memory. The term 'working memory' itself was introduced by Miller *et al.* (1960) in referring to a postulated quick-access brain space where plans can be retained temporarily while they are being formed, manipulated, and executed. Working memory is hence some type of 'short-term memory' (Baddeley 1986; *phase). However, despite the overlap, 'short-term' and 'working' memory are not the same. Generally speaking, 'short-term memory' is a more comprehensive term, which refers to all internal representations that last for only a short while. It is a universal faculty of nervous systems that can learn. In contrast, 'working memory' combines *attention,

short- and long-term memory, retrieval, computations over representations, and planning and decision making, to yield goal-directed short-lived internal representations. It is engaged in on-line processing of data from sensory channels (*percepts) as well as from long-term stores, and maintains the selected representations in a limited *capacity store only until the task is completed. The faculty of working memory is considered to have reached its pinnacle in primates and especially in humans, where it takes years to mature (Luciana and Nelson 1998). Species other than primates display rudimentary capabilities of working memory, e.g. rats while navigating in a *maze or solving olfactory riddles (Olton 1979; Staubli *et al.* 1995; Mumby 1995).

An influential cognitive *model of working memory considers three types of components: a 'central executive', 'phonological loop', and 'visuospatial sketchpad' (Baddeley and Hitch 1974; Baddeley 1986). The 'central executive' is an attentional control system, the 'phonological loop' deals with speech-based information, and the 'visuospatial sketchpad' with visual and spatial information.¹ In recent years, many efforts have been devoted in an attempt to map in the brain the postulated central executive and its subordinate functions. In the process, much has been learned about candidate brain substrates of working memory in primates. In the *monkey, the data are based on circumscribed brain lesions, cellular recordings, and their correlation with performance on *delay tasks that are considered to tax working memory (e.g. Goldman-Rakic 1992). In humans, the data are based on the study of the behaviour of selected brain-damaged patients, as well as on the *functional neuroimaging of patients or healthy volunteers, using tests that tax visuospatial or verbal working memory (e.g. Paulesu *et al.* 1993; Bechara *et al.* 1998; E.E. Smith *et al.* 1998; Ungerleider *et al.* 1998; Prabhakaran *et al.* 2000).

In a nutshell, the findings indicate that working memory is subserved by multiple distributed systems, which vary in their identity from one type of working memory task to another. In all cases, however, the frontal lobe plays a central part (Miller *et al.* 1960; Fuster 2000b). Within the frontal lobe, there is division of labour, which appears more intricate as one increases the resolution of the experimental techniques and the sophistication of their use. The dorsolateral and ventrolateral prefrontal cortex differ in their contribution to various types of working memory tasks, but the functional determinants of the specialization and subspecialization are not yet clear. These determinants may relate to the type of information processed (e.g. visual vs. verbal); to the role in maintaining internal

Working memory

representation over the task as opposed to selecting information from other brain areas; and to other attributes of the computations performed over multiple types of information (Petrides 1995; Goldman-Rakic 1996; Ó Scalaidhe *et al.* 1997; Owen 1997; Rushworth *et al.* 1997; Rowe *et al.* 2000). Some of the neurobiological findings so far can be construed within the framework of the aforementioned Baddeley–Hitch model (Baddeley 1998). In addition to the dorsoventral prefrontal dissociations, at least in humans, laterality also counts: the left hemisphere plays a more prominent part in the proposed ‘phonological loop’, whereas the proposed ‘visuospatial sketchpad’ is subserved primarily by the right hemisphere (Baddeley 1998; E.E. Smith *et al.* 1998). The location of the hypothetical ‘central executive’ (Goldman-Rakic 1996; Roberts *et al.* 1996; Baddeley 1998; Carpenter *et al.* 2000) is also not yet established. It is probably embodied in the operation of parallel, distributed polymodal circuits (*homunculus).

To the student of memory, the cellular basis of working memory offers a conceptual challenge (Goldman-Rakic 1995, 1996; *dopamine). Working memory is designed specifically to hold information only transiently. In other memory systems, often the trick is to retain information over an extended period of time, whereas here, it is to prevent the information from lingering too long and interfering with subsequent thought and action. Are the cellular mechanisms

of working memory different from those in other memory circuits? For example, do incoming signals in working memory circuits activate *immediate early and *late response genes, culminating in cellular remodeling? If so, what is the role of these changes, provided that working memory is not stored in the long term? Or is some type of memory stored even here in the long term? Are fast molecular ‘memory erasures’ involved (e.g. see protein phosphatases in *protein kinase)? Or is the gimmick in the unique mode of operation of the circuit? Studies of working memory may eventually affect current conceptual *paradigms concerning the role of cellular change in the retention of internal representations.

Finally, a note on terminology. In discussions of human memory, the concept of working memory is occasionally extended to include those situations in which information is being held temporarily for periods much longer than just the few seconds it takes to execute an ongoing cognitive task. For example, suppose I travel to a scientific meeting out of town; I remember the number of my hotel room as long as I am there, say a day or two, and then get rid of this information as it becomes useless. Is this ‘working memory’? By some accounts it is, because it is a piece of temporary information that is usable only for the purpose of a transient task, in this case, getting back to my room. But on a second thought, it is not. Essential to the original concept of working memory is the active use of the memory (*taxonomy) under *attentional control* throughout the execution of the task.² Clearly, my central executive, wherever it is, is not busy with my hotel room number throughout the meeting. Therefore, remembering the number of a hotel room number, or the position of a car in a parking lot, is a type of temporary memory, which deserves special attention from dedicated investigators, but is definitely of a different kind than the *bona fide* working memory.

Selected associations: Attention, Internal representation, Performance, Prospective memory, Retrieval

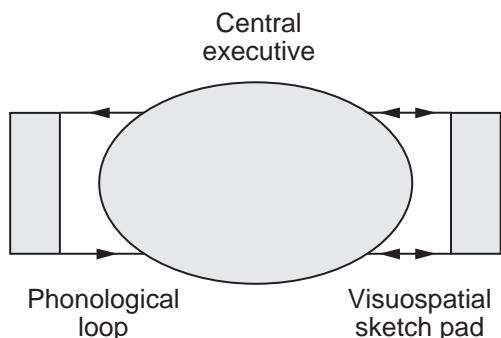


Fig. 64 The influential *model of Hitch and Baddeley depicts working memory in the human brain as two ‘slave’ systems controlled by a limited *capacity central executive. One system, the phonological loop, is specialized for processing language material, whereas the other, the visuospatial sketch pad, is concerned with visuospatial memory. A new version of the model adds a capacity to *bind temporary episodic representations in an ‘episodic buffer’ (Baddeley 2000; not shown). Attempts to map working memory into the brain, which are facilitated in recent years by the introduction of *functional neuroimaging, implicate the prefrontal cortex and its interconnections with other cortices in multiple working memory functions. (After Baddeley 1986.)

¹A revised version of the model proposes a fourth distinct component, or alternatively a subdivision of the central executive, termed the ‘episodic buffer’, which *binds on-line and off-line information into transient episodes, i.e. events integrated across space and time (Baddeley 2000).

²Which should remind us that in animal studies as well, ‘working memory’ should be reserved to those situations in which the subject can be convincingly assumed to *attend the task information over the trial, or over a closely packed series of brief trials. This is unlikely to apply to protocols that last several hours.

Zeitgeist

1. The spirit of the time.

2. A collection of *paradigms, beliefs, and opinions that dominates a *culture or discipline at a given period, and moulds the intellectual climate against which new findings, interpretations, ideas, and *models are judged.

'Zeitgeist' (German for 'spirit of the time') was introduced into intellectual dialectics by the Romanticism, the anti*classical cultural movement originating in late eighteenth century Europe that displayed heightened interest in nature, emotional expression, and imagination. In the beginning, the meaning of 'zeitgeist' ranged from a semi-mystical force that shapes human history (Hegel 1820) to an opinionated cultural world view (Goethe 1827). Its current meaning is conveyed by definition 2 above. Occasionally the use of the term in the exact and natural sciences is considered purple prose. But what should concern us here is not whether the term itself is trendy or not, but rather what the concept tells us about the way science is practised.

It is not difficult to identify distinct zeitgeists in the history of memory research. A few examples should suffice. Introspection was the zeitgeist in the early days of psychology in Europe (Boring 1950a). *Behaviourism, the doctrine that only publicly observed behaviour is psychological datum, was the zeitgeist in North America for a substantial part of the twentieth century. The sweeping attitude that analysis of the *rat can illuminate universal properties of brain and mind was another long-lasting zeitgeist (e.g. Munn 1950). And the focus on memory in laboratory settings, remote from *real-life situations, is yet another example.

The zeitgeist in the neurosciences and behavioural sciences is not a coherent systematic theory or unified conceptual framework, but rather a collection of paradigms, assumptions, beliefs, and attitudes. Some are more central to the world view of the practitioners of the discipline, some less, all dominate the field, and all, or almost all, have opponents that actively oppose the mainstream or just sit there quietly harbouring the hope that the stream will divert its course. The following list is a limited selection of elements of the contemporary zeitgeist in the science of memory (for a representative manifesto see Milner *et al.* 1998). Note that not always are the elements as stated here a faithful formulation of the views of those individuals who promote the zeitgeist; rarely do they speak exactly the same language. Some of the statements are a bit exaggerated, but still, they do reflect the spirit:

1. Learning and memory are implemented in *synaptic change. Even when the proposed change involves the neuronal cell body and nucleus (Dudai and Morris 2000), the ultimate focus is still on the synapse.
2. *Long-term potentiation (LTP)=memory (e.g. Stevens 1998). There are, though, recurrent cracks in this zeitgeist (e.g. see discussion in Shors and Matzel 1997).
3. Long-term memory=synaptic remodelling and growth (*development).
4. *Classical conditioning is the tip of the iceberg of intricate information processing in even simple brains.
5. The major natural *taxonomy of mammalian memory distinguishes explicit (*declarative) from implicit (non-declarative) memory. A bold version of this zeitgeist claims that the classification is honoured even in primitive species without a real brain.
6. *Functional neuroimaging of the brain is bound to present us with the *engram.

There were elements of the zeitgeist that persisted till recently but not any more. For example, that it is not productive to approach the mechanistic bases of emotional memory (for the antithesis see LeDoux 1996); or that the study of consciousness 'does not fit' serious active neuroscientists (it does, though admittedly, the growing number of publications on the subject sometimes raises the question whether this zeitgeist was not abandoned prematurely).

What establishes a zeitgeist? The question merits detailed analysis of specific zeitgeist test cases, a worthy task for historians and sociologists of science (ample raw data are available, e.g. Worden *et al.* 1975). It is tempting, though, to suggest some possibilities. Frequently, one identifies one or a few single discoveries whose outcome can be generalized to a large number of problems and systems. Take LTP as an example. It suggests a cellular *model of *plasticity and learning; it can be searched for in many types of pathways and synapses in a variety of preparations and conditions; drugs that block it may be tested on multiple types of learning; many types of pharmacological congeners may be tested on LTP once the role of a certain *receptor (*glutamate) has been identified; many mutations (*neurogenetics) can be analysed for their effect on LTP, etc. etc. This creates lots of work for lots of people. The use of LTP can hence spread rather efficiently over the entire field of research on neuronal plasticity, infect multiple types of professionals, and recruit them all into the field of learning research. It is plausible to

Zeitgeist

assume that some of these investigators would have not been attracted to memory research had it not been for the availability of the new cellular *assay. Success is clearly contagious, but is not enough: the recipe for a zeitgeist requires additional ingredients. It does not hurt to have dominant investigators that keep blowing the horn. And even this may not suffice. Some earlier zeitgeist may lay the ground for the development of later ones. Consider the zeitgeist notion that gene knockouts are a key to the molecular analysis of memory machinery. This idea was successfully developed in the fruit fly, *Drosophila*, but the number of research groups working on memory mutants in *Drosophila* was never larger than five at a time. The *geist* reached the right *zeit* only when the *mouse entered the scene, because the mouse is a mammal, lots of information is available on its brain and behaviour, but, even more importantly, its brain is more relevant to ours. So here is a manifestation of another timeless zeitgeist, which clearly transcends neuroscience, namely, that we think that we are at the centre of the universe.

Whereas it might be difficult to pin-point in each case why a certain zeitgeist has prevailed, the fact that it did is easily noticed. It is reflected in the preferential acceptance of papers to trendy journals, in the selection of speakers in international conferences, and ultimately in chapters in textbooks that set the tone for the next generation. In rare cases, the zeitgeist may even prevent solid science from being published for years; the inability to publish on the properties of *conditioned taste aversion because it contradicted the zeitgeist concerning how *associative learning should behave, is an example (Garcia 1981). Furthermore, nowadays, one should watch for commercial interests in promoting the zeitgeist. Having said all that, it might seem that stating that a zeitgeist could sometimes slow down the pace of discovery may look like beating a dead horse, and that the discussion of zeitgeist is superfluous. But it is definitely not. The reason is twofold. First, dead horses often prove to be phoenixes; it wouldn't do harm to repeat the warning against conservative paradigms, dominant opinions, and overenthusiastic *esprit de corps*. But, second, zeitgeists carry marked benefits as well, and should not be demoted merely because they are zeitgeists. Most importantly, we shouldn't forget, they might be simply true! In addition, they attract funds. They bring in new investigators, sometimes with types of training new to the discipline (e.g. modellists into LTP, experimental psychologists into neurogenetics). They add to the cohesion of scientific communities and foster collaborations. They also promote reproduction of experiments and ultimately multiple discoveries (Ogburn and Thomas 1922; Merton 1961), all of which are critical for

good science. And, almost paradoxically, they target paradigms for future revolt, which may in due time modify the zeitgeist (e.g. Boring 1950b; Chomsky 1959; Hebb 1960; Breland and Breland 1961; Neisser 1978).

The Janus face of zeitgeists hence complicates life. The personal sentiment is, as in many other cases, a function of training and personality. Some prefer the security of the zeitgeist, some the thrill of the rebellion. May be the attitude should be influenced by noting what the outcome of either conformism or revolt might be. The first risks stagnation, the latter provokes doubts and stimulates new intellectual expeditions, even if some of these end up only in *red herrings. Therefore, at least from the point of view of the scientific culture, it would be nice to keep in mind the following rule, although practise it in moderation, especially before reaching academic tenure: whatever discipline, whatever problem you are engaged in, *a priori, question thy zeitgeist.

Selected associations: Culture, Paradigm, Scoopophobia

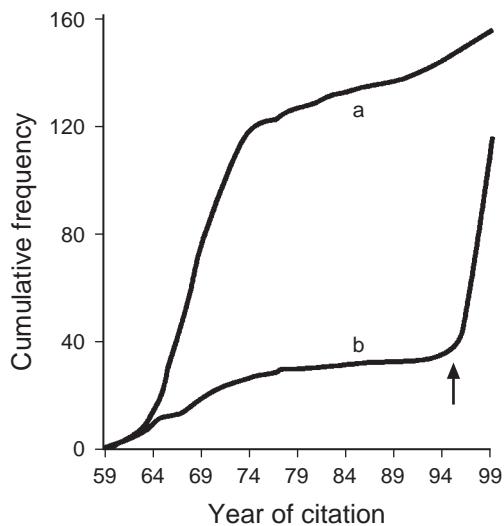


Fig. 65 Zeitgeists in transition. In 1959, the American psychologist James Deese published two papers on human memory in two respectable professional journals. One (a; Deese 1959a) dealt with veridical memory, the other (b; Deese 1959b) with *false memory. The graph depicts the frequency of citations of these papers from their publication to the end of 1999. Until the 1990s, veridical memory was congruent with the zeitgeist of memory research; but then the zeitgeist changed, questioning the fidelity of memories became fashionable, and Deese's paper on false memory gained popularity (arrow). The data till 1997 are adapted from Bruce and Winograd (1998), and those for 1998–99 are compiled from the Science Citation Index Expanded, Web of Science V. 4.1, ©ISI, Institute for Scientific Information. For another example of a bibliometric measure of zeitgeist, see *LTP.

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