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Drugs and Human Memory (Part 1)

Clinical, Theoretical, and Methodologic Issues

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EVERYTHING in life is memory, except for the thin evanescent slice of the present. Memory is a crucial and sustaining mental function that shapes our existence. All other cognitive functions would be meaningless or impossible without the ability to record and recall previous experience. Memory, in addition to bringing learned facts and ideas back to mind, affects our behavior in an unconscious way. We lose the connection to ourselves and with others, and life becomes void of its essence as tragically displayed in patients with severe dementias when memory is lost. Memory research is one of the most fascinating and flourishing areas of science today. A revolution has occurred in our knowledge and understanding of the capabilities and failures of this fascinating mental function, and what happens to the brain when we learn, remember, and forget. There have also been some recent advances in the search for memory-enhancing drugs. Development and testing of drugs for prevention and treatment of patients with impaired memory are vital in a world with a progressively increasing age population.

Memory as a component of behavior was once the exclusive province of psychology. Currently, its study has been extended to include also the domains of molecular biology, pharmacology, and several clinical disciplines: neurology, psychiatry, and anesthesia. Psychopharmacology research, the study of the psychological effects of drugs, is at its best when it is conducted by multidisciplinary teams with expertise in psychology, pharmacology, and medicine. Given the massive and rich literature on memory and the exponential proliferation of publications examining the effects of drugs on memory, one would expect the facts, theories, and methodologic issues of the investigations to be brought together in one review, but this has not been completed. There are at least two reasons for this oversight.

First, the dilemma of jargon and memory nomenclature intimidates the novice.[1] Psychologists use many ways to describe the same phenomena based on their theoretical predisposition, resulting in a seeming myriad of terminologies, which can be confusing. For example, are there differences between short-term memory, primary memory, immediate memory, and working memory?

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Table 1. Historic Mileposts for Drugs and Memory Research

1799	**Sir Humphrey Davy** described the effect of nitrous oxide.
1848	**John Snow** reported the amnesia associated with inhalation of diethyl ether.
1885	*Ebbinghaus* started the objective studies of memory.
1890	*William James* distinguished between short-term and long-term memory.
1925	**Davidson** reported the first controlled experiment of a drug and memory using nitrous oxide.
1927	*Ivan Pavlov* discovered classic conditioning.
1930s	**McKinney** and **Marshall** advocated the use of nitrous oxide to study the psychology of memory.
1950s	**Steinberg et al.** reported a series of studies on the effects of nitrous oxide and memory.
1960s	*Atkinson and Shiffrin* described the two memory systems; short- and long-term memory.
	Dundee et al. and **Hardy and Wakeley** identified the amnesia produced by benzodiazepines and scopolamine.
1970s	**Ghoneim et al.** tested systematically the effects of a wide group of drugs on memory.
	Tulving distinguished between episodic and semantic memory.
	Baddely proposed an alternative to the short-term store, using the term *working memory.*
1985	*Graf and Schacter* distinguished between implicit and explicit memory.
2000	*Eric Kandel* was awarded the Nobel Prize for discovering the central role synapses play in memory.

Investigators' names associated with research on drugs and memory are shown in bold, and those associated with pure memory research are italicized. Investigators associated with awareness during anesthesia are not included.

Psychologists also use different models of memory to account for experimental data both qualitatively and quantitatively and different tasks according to their subareas, *e.g.*, experimental psychology or clinical psychology. Contrasting terms are used to describe various memory processes without drawing correlations among the various concepts. For example, what is the relation between implicit *versus* explicit learning and episodic *versus* semantic memory (concepts developed by experimental psychologists), and how do they relate to the Wechsler memory scale, the Bushke task, or the Rey auditory verbal learning test (used by clinical psychologists)? The second reason for the lack of a comprehensive review is that clinicians and pharmacologists are seldom familiar with assessments of memory and the choice and implications of the appropriate tests. They often get the erroneous impression that a complex mental function such as memory, with its individual variability and its well-known frequent failings, such as absentmindedness, distortions, and blocking, would not be susceptible to good research or yield reliable data. Studies by anesthesiologists, who were interested in finding premedicants, which suppress memory of their patients, were generally viewed as uncontrolled anecdotes unlikely to help in analysis of this mental function. Studies conducted in animals using chemicals were overlooked by most psychologists because of their unfamiliarity with the pharmacologic sciences. Thus, it came to pass that although the history of effects of drugs on memory is as old as the history of research on memory itself, it is only recently that psychologists have begun to notice the intellectual possibilities in this type of research.[2–4]

This article tackles some fundamental and basic issues about learning and memory and their interactions with drugs. It examines such topics as aims of research on the subject, assessment of memory, and specific methods in the design of studies. It emphasizes the how and why rather than reviewing and cataloging the effects of each drug or groups of drugs on memory. This article is meant to appeal to a broad readership without expertise in the psychology or psychopharmacology of memory. The first goal is to provide such readers with general information about memory and its psychopharmacology. The second goal is to make such readers more informed "consumers" of research on drugs and human memory so that they will be able to evaluate research claims in terms of soundness of the methods used to generate the data. The third goal is to assist the novice investigator in planning and conducting experiments and to give other readers the opportunity to consider research in this area as a worthwhile part of their careers.

Memory through History

Brief History of Memory Research

The German psychologist Ebbinghaus in the 1880s started the objective and quantitative study of memory[5] (table 1). He invented the notion of nonsense syllables (such as BIK, QEH) as standardized, homogeneous test items. He learned lists of these items by reading them aloud and then tried to recite them from memory at various time intervals afterward. Through experimenting on himself, Ebbinghaus introduced many important ideas and methods about memory. One of his key contributions is the provision of the prototype for memory research. The current memory experiment consists of three phases: (1) a study or encoding phase in which material is presented to the subject; (2) a retention interval; and, finally, (3) a test or retrieval phase in which the subject attempts to respond to a question, the answer to which involves the use of the initially studied information. Research strategies have consisted largely of variations in the conditions for each phase.[6]

The Russian physiologist Ivan Pavlov[7] discovered classic conditioning (1927), an associative learning procedure in which two different kinds of events are temporally paired with one another. For example, a dog may come to associate the sound of a bell and the presenta-

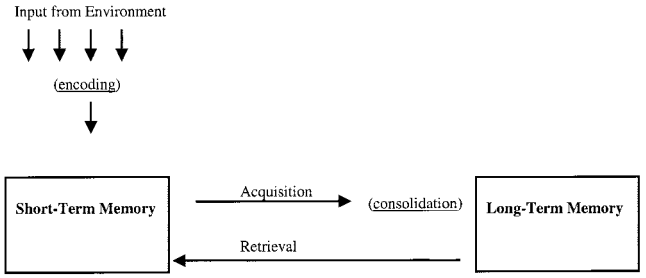

Fig. 1. A modified two-store model of memory.

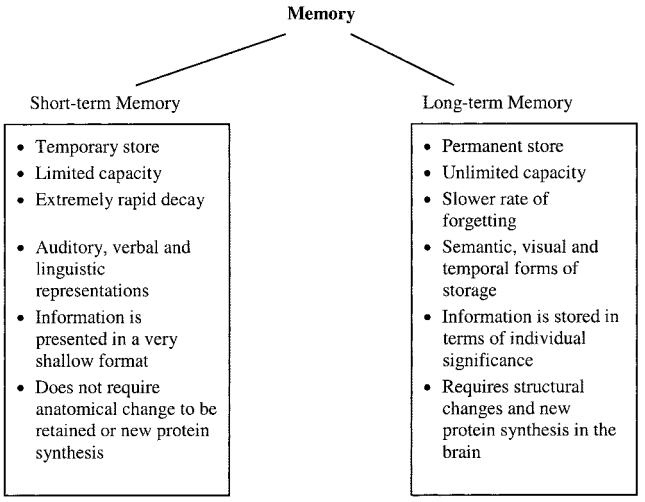

Fig. 2. Characteristics of short-term *versus* long-term memory.

tion of food so that it salivates when the bell sounds, even in the absence of food. The dog has learned that the bell predicts the food's presentation.

The American psychologist William James[8] made a sharp distinction between short-term (STM) and long-term memory (LTM). STM lasts seconds (which can be extended to minutes with active rehearsal), as when one looks up a telephone number and then holds it in mind for a few moments until he dials it. By contrast, LTM can last weeks, months, or even a lifetime and involves reaching back into the past.[9] In the late 1960s, Atkinson and Shiffrin[10] published a widely quoted article that described the two memory systems in more detail (fig. 1). The STM system receives information from sensory registers (*e.g.*, visual, auditory, olfactory, gustatory). Continued rehearsal determines whether the contents of the STM would be transferred to the LTM or would be lost by entry of new information. LTM is viewed as a permanent store in which information may be maintained indefinitely or may be subject to autonomous decay. This contrasts with STM, the temporary store of very limited capacity that stores information in a shallow or nonmeaningful format, such as the sound or articulation of the item (fig. 2). In addition to the description of these two systems or stores, several processes were also described. *Encoding* represents the first stage of mnemonic processing when information is encountered. Sensory stimuli are converted into a form that can be placed into memory and the material is acquired or learned. *Consolidation* is an intermediary stage; a durable permanent memory trace is formed through gradual reorganization where it can be stored or retained. *Retrieval*, the process of bringing information out of storage to be recalled or remembered, is the final stage of memory.

Tulving[11] made a distinction between two types of LTMs: *episodic memory*, which is memory for particular times and places, and *semantic memory*, which is memory for facts that a person has built up over the course of his or her life. So, for example, a question such as "What did you eat for dinner last night?" relies on retrieval from episodic memory, whereas a question such as "What kind of meat do you prefer?" relies on retrieval from semantic memory. Episodic retrieval may be accompanied by a type of awareness called *autonoetic* (self-knowing) *awareness*. The recollection of a particular time and place of the first accident when driving a car, for example, is infused with emotions, thoughts, and feelings of reexperience of a moment from the past. Semantic memory, by contrast, is characterized by *noetic* (knowing) *awareness* only. There is no feeling of reliving any previous episode when the fact that 100 cm is equivalent to 1 m is recollected.[12,13] Tulving[14] later introduced a third system, *procedural memory*, or memory for perceptual, motor, and cognitive skills. Schacter, a student of Tulving, developed another dichotomy in LTM[15] between explicit and implicit memory (fig. 3). *Explicit* (or *conscious* or *declarative*) *memory* refers to the intentional or conscious recollection of previous experiences, such as the details of an appointment to visit with a friend, as assessed by tests of recall or recognition (also called *explicit* or *direct tests* because reference is made to the study phase during testing). *Implicit* (or *unconscious* or *nondeclarative*) *memory*, by contrast, refers to changes in performance or behavior that are produced by previous experiences on tests that do not require any intentional or conscious recollection of those experiences (the tests are called *implicit* or *indirect tests* because no reference is made to the study phase).[16] The motor skill of riding a bicycle might have been learned years ago, and some things about the first experience might be remembered. However, the ability to ride even after years of nonuse is independent of any conscious recollection of that experience or ability to describe the skill. (It should be noted that although many authors use the term *procedural memory* to imply the memory subsystem concerned with learning and retention of motor skills, others use the term as synonymous with implicit memory.)

Also in 1974, Baddeley and Hitch[17] proposed an alternative to the STM store, using the term *working memory*. It consists of three components capable of both

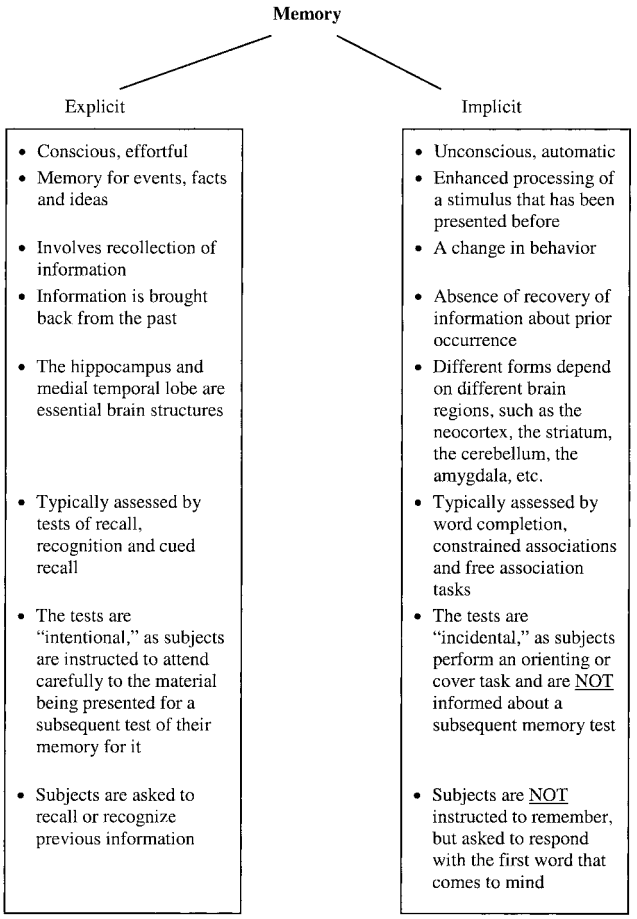

Fig. 3. Characteristics of explicit *versus* implicit memory.

storing and manipulating information: a *phonologic loop* for the maintenance of verbal information (such as spoken words and meaningful sounds), a *visuospatial sketch pad* for the maintenance of visuospatial information (such as faces and spatial layouts), and a *central executive* for attentional control. The central executive component has been postulated to integrate the two slave systems, link them with information from LTM, and manipulate the resulting representation. Over the years, however, there were data that did not fit readily into this framework.[18] For example, the memory span for sentences tends to approximate 16 words, in contrast to a span of approximately 6 for unrelated words. Therefore, Baddeley[19] recently suggested a fourth component, namely the *episodic buffer*. It is assumed to act as a temporary storage system capable of holding information from the slave systems of working memory to be integrated with and linked to LTM. It is controlled by the central executive, using conscious awareness as a major retrieval strategy (fig. 4).

We will use the terms *STM* and *working memory* as synonymous for simplicity in this review, despite the distinctions between the underlying models that have been cited previously. The reader should also note that STM may refer in the animal learning literature to later

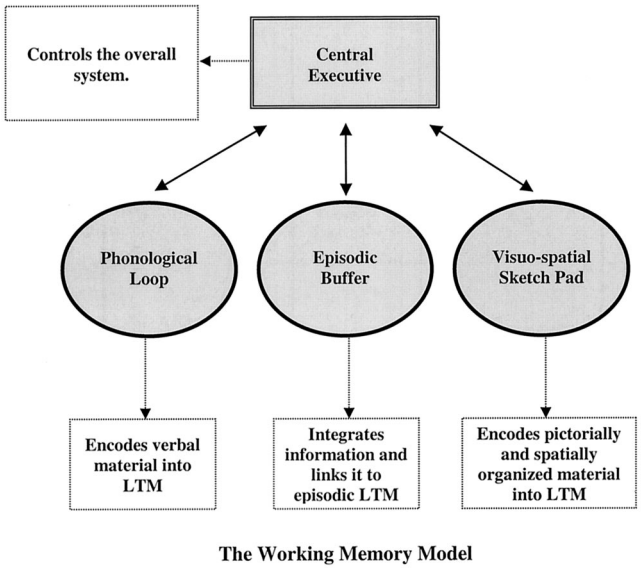

Fig. 4. Model of working memory. LTM = long-term memory.

components of memory, up to the time of the establishment of stable LTM.

Eric Kandel, the American neurobiologist,[20] started working on the molecular mechanisms of memory in the 1970s that culminated in his award the Nobel prize in the year 2000 for discovering the central role synapses play in learning and memory. He used a simple experimental model, the sea slug Aplysia, combined later with work on mice. He showed that weak stimuli give rise to certain chemical changes in synapses, and these changes are the basis for STM. In contrast, stronger stimuli cause structural changes in both presynaptic and postsynaptic cells, associated with the growth of new synaptic connections or retraction of preexisting ones, which are the basis for LTM.

Short History of Drugs and Memory

The notion that drugs affect memory is as old as the history of the systematic study of human memory and is concerned in its early stage almost exclusively with nitrous oxide (table 1). Sir Humphrey Davy described the effect of the gas on memory in 1799 (cited in Cherkin and Harroun, 1971).[21] John Snow[22] reported the amnesia associated with the inhalation of diethyl ether in 1848. Davidson reported in 1925 the first controlled experimental investigation of a drug on memory and cognition using nitrous oxide[23] and acetylene.[24] Both chemicals impaired memory, and the impairment was related both to the difficulty of the memory task and to the concentration of the drug administered. McKinney[25] (1932) and Marshall[26] (1937) advocated the use of nitrous oxide to study the psychology of memory. Steinberg *et al.*[27–29] extended these early findings in a series of studies in the 1950s. Nitrous oxide produced temporary amnesia by impairing the ability to store new information and therefore reduced interference with infor-

mation learned before drug administration. The method of administration of the drug and its dose were identified as important factors. Clinical reports by anesthesiologists, specifically Dundee *et al.*[30] and Hardy and Wakely[31] in the 1960s on the amnesic properties of different premedicants, identified the benzodiazepines and scopolamine, which later became the most widely investigated drugs in relation to memory.

In the 1970s, there was a resurgence of psychologically oriented or theoretically motivated studies of drug effects over a wider and more sophisticated scale. In a large series of studies, Ghoneim *et al.*[32–42] tested the effects of benzodiazepines, scopolamine, opioids, propranolol, subanesthetic concentrations of nitrous oxide, ketamine, surgical anesthesia, marijuana, polydrug abuse, caffeine, and other drugs. These and other studies provided a detailed analysis of drug effects on memory and supplied converging evidence for its theoretical constructs. The history of learning and memory for events during anesthesia is as old as the history of anesthesia itself. Early observations by Cheek[43] (1959), Wolfe and Millett[44] (1960), and Levinson[45] (1965) in anesthetized patients preceded the reports of what we now know as implicit memory by Warrington and Weiskrantz[46] (1968) and Milner *et al.*[47] (1968) in amnesic patients and the distinction between implicit and explicit memory[48] (1985). (For reviews, see Ghoneim.[37,38]) Studies in this area have important clinical significance as well as theoretical relevance for investigating the role of consciousness in memory. (For more reviews of the history of drugs and memory, see Polster[3] and Curran[49]). Table 1 shows the overlap between the history of memory research and the action of drugs on memory.

Aims of Research on Drugs and Human Memory

Evaluating Drugs Used Clinically

The measurement of both therapeutic and adverse effects of drugs on memory and their mode of action is important as part of the evaluation of existing and newly developed drugs and finding new brain-targeted therapeutics.[50] Some drugs, *e.g.*, anesthetics, anxiolytics, sedative-hypnotics, antidepressants, and neuroleptics may impair memory, whereas others hold some hope of improving it. If amnesia is produced, it may be therapeutically desirable or essential, as in the practice of anesthesia, or it may be an undesirable side effect of treatment, as in therapy of anxieties, insomnia, depression, epilepsy, and schizophrenia. Memory and cognitive impairments in patients taking these drugs may endanger them and the public and may cause serious occupational difficulties by affecting job performance and quality of life.[51–55] Such impairments may also cause legal difficulties arising from not recalling one's actions.[56] Elderly patients taking several psychoactive drugs can experience confusion and memory loss, *pseudodementia*, which may be misdiagnosed as organic dementia. Researchers usually study the types of memory and cognition affected, the magnitude and duration of the effects, and drug–drug and drug–disease interactions.

Modeling Memory Deficits in Pathologic Disorders

Some drugs may mimic alterations in memory produced by diseases. For example, the pattern of memory impairment produced by scopolamine has been suggested to be similar to that seen in Alzheimer disease, and benzodiazepine-induced effects have been likened to that seen in Korsakoff disease, postencephalitic amnesia, and amnesias due to temporal lobe damage.[57–61] Treatment with *N*-methyl-D-aspartate receptor antagonists, *e.g.*, ketamine, produce cognitive and behavioral dysfunction similar to those of psychosis and dissociative disorders.[62,63] These drugs may therefore provide pharmacologic models of these disorders, which can be used to evaluate new drugs designed to counteract or prevent cognitive impairment associated with these disorders before their use in long and costly trials in diseased populations. These models may also help in understanding the neurochemical mechanisms of diseases because the molecular mechanisms of many of these drugs are known (table 2). However, drug models have two main weaknesses: (1) contamination of the memory effects of drugs with their sedative effects, which is important because patients with organic amnesias usually do not have sedation or drowsiness; and (2) limitations of the profile of memory impairment produced by the drugs compared with the broader spectrum of dysfunction caused by disease, *e.g.*, impairment of remote memory in dementias, although it is spared by drugs.

Understanding the Psychoneurobiology of Memory

Understanding the psychoneurobiology of memory is the most sophisticated and challenging aim. It is essential to combine the strategies of cognitive psychology with those of neuroscience to understand the organization of a very complex mental function such as learning and memory. The integration of knowledge at the molecular, cellular, and systemic networkings and organismal levels with detailed studies of learning and memory as a behavior seems to be the most logical approach. Memory is one of the few mental processes that has undergone such comprehensive research. The chain of studies that are leading slowly to a complete account of memory is shown in figure 5. The idea of using drugs as tools to study behavior and its biologic substrates is not new.[64] Also, the study of dysfunction has always been a rich source of inference about function in physiology and medicine. Most drugs that modulate memory act through specific receptors and neurotransmitters, and some act through hormonal and neuropeptide systems. Activation of cell receptors produces changes in cell

Table 2. Advantages of Using Drug-induced Amnesia in Healthy Volunteers to Model Organic Amnesias and to Elucidate Normal Memory Mechanisms

Variable	Healthy Volunteers	Patients with Organic Amnesias
Participant recruitment	Subjects are readily available	No. is limited, particularly patients with pure amnesias
Baseline measurements	Available	Rarely available
Manipulation of degree of amnesia	Possible, by varying the drug dose	Difficult; may be possible to define levels of amnesia (*e.g.*, mild, severe)
Reversible and repeatable changes in memory	Available	Impossible
Control group	Easily provided	Difficult
Identification of stages of processing information	Identified by timing the drug administration	Difficult
Brain changes	Pharmacologically defined in all subjects	Brain injuries tend to be different and/or diffuse
Conducing studies as tightly controlled experiments	Possible	Studies of correlational nature are often the only strategy available

function, which result in a change in memory performance. Therefore, one should be able to predict the neurobiologic events that contribute to a certain change in a specific type of memory.

Another advantage of drug research is the fact that many of the studies conducted by psychologists in healthy subjects often rely on contrived conditions to simulate types of memories that are impaired in pathologic amnesias. For example, subjects are presented with stimuli under suboptimal conditions to simulate the dissociation between explicit and implicit memories. The lack of success of such an approach is exemplified by the contentious nature of the so-called implicit learning, mainly because of the difficulty of ensuring that all subjects are unaware of all the information to be learned.[65,66] Use of anesthetics or sedative hypnotics provides a much better alternative for studying the relation between memory and consciousness, provided that the level of awareness can be monitored to ascertain its absence. The effects of varying the level of conscious-

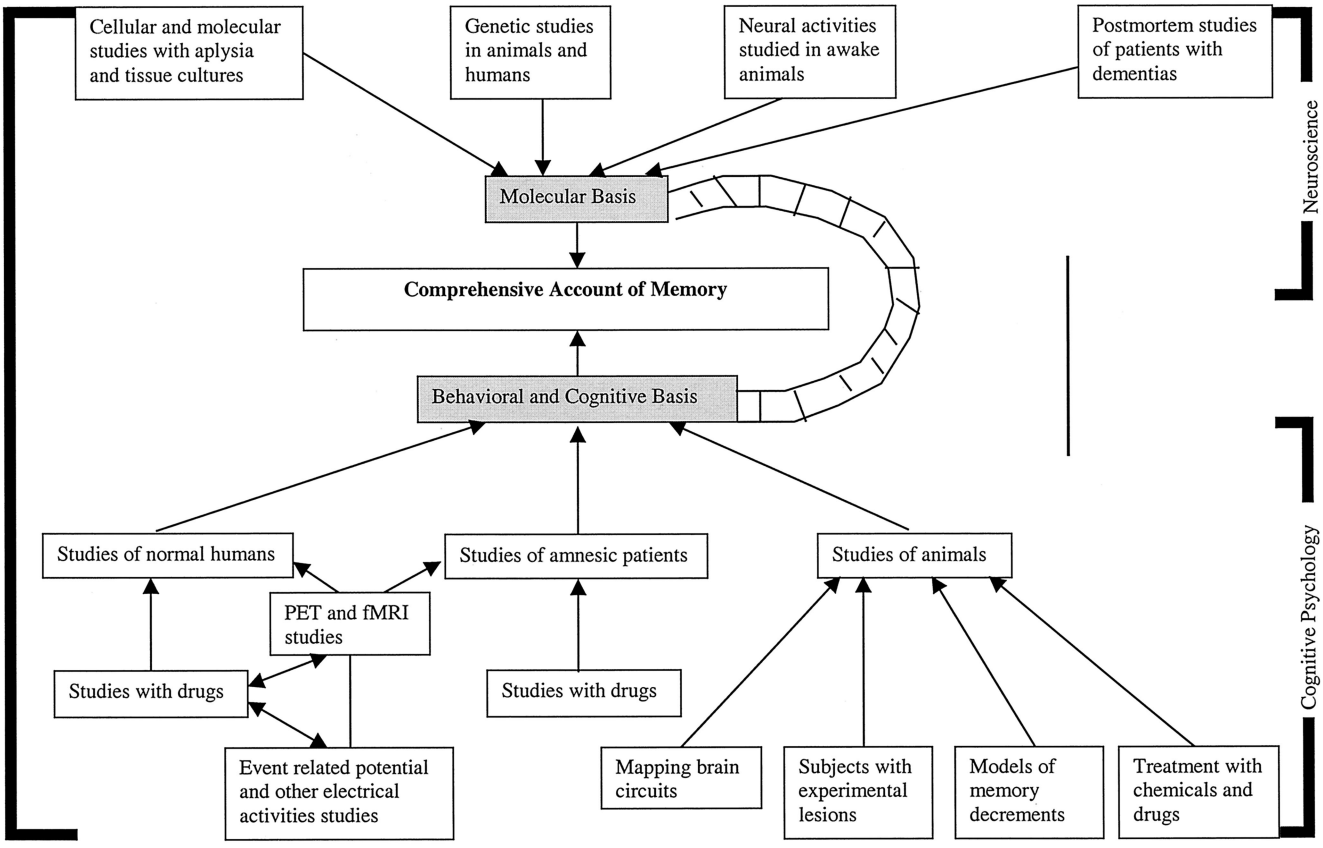

Fig. 5. Chain of studies of cognitive psychology and neuroscience that bridge the gap between the two disciplines with the promise of a comprehensive account of memory. fMRI = functional magnetic resonance imaging; PET = positron emission tomography.

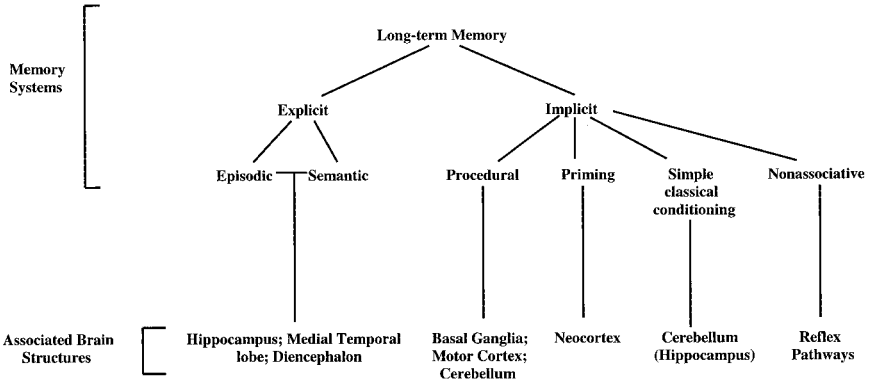

Fig. 6. A taxonomy of long-term memory and its associated brain structures.

ness by varying the dose of drug is another of many advantages (table 2).

Unfortunately, drugs have not fulfilled their lofty promises of substantially advancing knowledge about learning and memory. They have only provided converging evidence of already existing hypotheses.[2,67,68] Perhaps the main reason is that currently available drugs are rarely completely specific; they tend to affect targets other than those against which they are intended, and there are interactions among the different neurotransmitters. However, the postgenome era offers exciting therapeutic targets of exquisite selectivity. The genetic dissection of the pharmacologic functions of receptor subtypes, approaches such as monoclonal antibodies and recombinant proteins that target the cell surface or extracellular sites, and the use of macromolecules that address intracellular targets[69–71] are promising strategies for new types of drugs. We predict that drug studies will be an important complement to other studies that investigate memory and will help to generate and shape future theories.

Classification of Human Memory

Memory Systems

Figure 6 shows a taxonomy of memory that organizes memory into various types, each associated with some main brain structures and specified behavioral functions. It should be noted, however, that memory function is a distributed process, and a number of the same brain regions are involved in multiple systems, as will be explained in the section on neuroimaging. The division includes various parameters, *e.g.*, temporal parameters (short-term *vs.* long-term), level of consciousness (explicit *vs.* implicit), and contents (events *vs.* facts). The systems shown in the figures have been defined above with the exception of priming, a subsystem of implicit memory. *Priming* is a change in the ability to identify or produce an item as a result of a specific previous encounter with the item. For example, subjects are presented with a list of words containing the word *pension*. After a retention interval, the response *pension* would be facilitated by the request to complete the word beginning *PEN____*. Such priming is termed *repetition* or *perceptual priming* to distinguish it from another two forms of priming, *associative priming* (where previous presentation of *bread* facilitates the response *butter*) and *conceptual priming* (where previous presentation of exemplars of the category *metal* facilitates the response *chromium*).

It should be noted that there are single-system alternatives to the multiple memory systems hypothesis,[72] which has been adopted in this review. The single-system hypothesis follows a processing approach that focuses on specific operations or component processes during encoding and retrieval, which are demanded by specific tasks.[73] For example, the more deeply or meaningfully information is processed, the more well retained it will be.[74] This contrasts with the focus on the availability and functional capacity of brain regions required for specific tasks that are postulated by multiple memory system theorists. It is probable that both the systems and processing approaches are complementary rather than incompatible.[75]

Memory Processes

As we mentioned before, *encoding* is the process of converting sensory stimuli into a form that can be placed into memory, *i.e.*, a memory trace and new information are learned or acquired. *Consolidation* is the process of forming a durable record of what has been acquired. STM is converted to LTM, shifts in storage occur from the medial temporal lobe of the brain (hippocampus) to the neocortex, where the new information is held, and there is formation of new protein. Finally, *retrieval* is the process of bringing information out of storage to be recalled (fig. 1).

One definitional issue is distinguishing between learning and memory. It is convenient to think of learning and memory as two separate processes, acquisition and retention. Acquisition and retention are not quite synonymous with learning and memory, but both are always required to demonstrate that learning or memory has occurred. Generally, when we speak of learning, we

place major emphasis on the investigation of the problems of acquisition. When we study memory, we are concentrating primarily on the problems of retention. However, for learning to be demonstrated, some new information must be acquired and retained until tested. Similarly, for memory to be examined, some information must first be acquired.[76]

A distinction of memory that is closely related to the memory processes is the dissociation between anterograde and retrograde memories or amnesias. *Anterograde amnesia* refers to inability to learn new information, which is demonstrated by impaired memory of material presented after drug intake or occurrence of brain pathology. *Retrograde amnesia* refers to an absence of memory for information and events before drug intake or onset of brain injury. Damage to the hippocampus produces anterograde amnesia and retrograde amnesia for memories that were acquired before the damage but had not yet migrated to the neocortex. Drugs cause anterograde amnesia, whereas head injuries, epileptic convulsions, electroconvulsive therapy, and treatment of animals with inhibitors of protein synthesis cause a period of retrograde amnesia by interfering with the consolidation phase[77] (fig. 1).

Another characteristic of memory processes is *state-dependent retrieval*. The notion is that retrieval depends on the external stimulus conditions (context), the internal state of the person (state), or the emotional feeling (mood) when information was learned. Ideally, these conditions should be matched at encoding and retrieval to ensure maximal recall, while their mismatching may decrease the accessibility of information. Thus, subjects have been found to recall a larger number of words when they were tested in the same room in which they had studied than when they were tested in a different room.[78] What subjects learned when inebriated with alcohol[79] or marijuana[80] was remembered better in the same state as compared with a sober state. However, the demonstration of state dependency in humans has been rather inconsistent, although it is a well-documented finding in the animal literature.[81,82]

Assessment of Memory

The Three Phases of a Memory Experiment

Memory can be measured in many ways, but most experimental studies have used a three-stage procedure:

1. a *study* (or *encoding* or *learning*) *phase*, in which subjects are exposed to a set of target materials, such as a list of words
2. a *retention interval*, which can vary in duration and may involve the performance of an unrelated task
3. a *test phase*, in which memory for the target materials is measured

Designing a Battery of Tests

Materials. Researchers may use verbal or nonverbal materials. Verbal materials are most often used and include digits, words, sentences, paragraphs, and longer prose passages. There are extensive normative data on attributes of words[83,84] with measures such as language frequency of usage,[85,86] image-evoking ability,[87] concreteness, meaningfulness, familiarity, and emotionalism, which allow control of the stimuli. Nonverbal materials that have been used include photographs of unfamiliar faces, drawings of simple objects, drawings of geometric forms, and learning motor skills. Visual memory is superior mnemonically to verbal memory. Paivio[88] has suggested that pictures are more likely to be encoded and stored in two independent codes, verbal and imaginal. Pictures also generally yielded stronger effects in affective priming studies.[89] There seem to be different brain mechanisms underlying face and object recognition.[90] There is normally better recognition performance with objects than faces.[91] However, interestingly, facial recognition seems to be less susceptible to drug-induced impairments.[61]

The presentation of verbal materials may be auditory or visual. Auditory presentation tends to give a slight advantage, particularly over the last few items of the list—the so-called modality effect.[92] It may also be advantageous in drug studies because hearing remains preserved until loss of consciousness and visual effects of some drugs, *e.g.*, anticholinergics, may interfere with visual perception. It is the only paradigm that can be used in studies of memory during anesthesia.

Memory Tests. Memory tools are (or should be) theoretically driven and grounded, based on theories or inferences about the structure of memory and the unobservable elements of memory systems, subsystems, and processes. In addition to their assessment functions, these tests should provide the empirical foundation on which contemporary and future theory have been built.[6] The utility of any theoretical account of memory is based on the effectiveness and adequacy with which that aspect of memory can be demonstrated in the laboratory. Without valid tests to be used, both theorizing and application of theory are obviously limited. A battery of memory tests whose components probe memory systems, subsystems, or processes is included in table 3. Our focus is based on the psychopharmacology literature rather than on pathologic memory disorders. For the latter, the components of the battery would be varied to meet the demands of the characteristic impairments.

Short-term or Working Memory. The tests for this type of memory assess perception and attention in addition to measuring the capacity of STM. This capacity tends to be very small, on the order of seven plus or minus two items.[93] Subjects are presented with the items and then asked to recall them immediately. The

Table 3. A Battery of Memory Tests

Task	Memory Type	Condensed Description	Stimulus	Response	Score
Digit span	STM (phonologic loop)	Subjects are presented with a sequence of digits and immediately asked to recall the sequence. A new sequence of increased length is presented after each successful trial.	Sequence of digits	Recall the digits in the same order	Maximum sequence length that can be correctly recalled
Spatial location span	STM (visuospatial sketch pad)	Subjects are presented with a matrix of cells, some of which are blackened. Subjects are immediately asked to reproduce the blackened cells in their correct locations. The number of blackened cells is increased after each successful trial.	Blackened cells	No. of blackened cells correctly reproduced	Maximum number of cells correctly reproduced
Multiple-trial free recall	Verbal learning	Subjects are presented with a list of words (*e.g.*, 30 words at the rate of 2 s/word). The list is repeated six times in different random orders. After each presentation, subjects are permitted 2 min to recall as many of the words as possible from the list in any order.	Words	Correct words	No. of correct words recalled per trial
Free recall	Episodic memory (retrieval)	Subjects are presented with a list of words (*e.g.*, 16–24 words at the rate of 1 word/s). Immediately after the last word is presented, subjects are given 2 min to write as many of the words as they can remember. One variation to clear out the contents of STM is to give the subjects a distractor task in which they count backward by 3 from a random three-digit number before they are asked for recall of the list. Another variation is to ask for delayed recall 20 min or more after presentation of the list, during which subjects are engaged in other tasks.	Words	Correct words	No. of correct words recalled
Recognition	Episodic memory (retrieval)	Subjects are presented with a list of words similar to ones described above. After a delay period, subjects are presented with the words that have already been presented, mixed with new words. The subject's task is to recognize which words are old and which are new.	Words	Recognize old words	No. of old words; problems of guessing or chance success must be addressed
Category generation	Semantic memory	Subjects are asked to list as many animals as they can in 1 min or as many words beginning with the letter T as they can in 1 min.	Category or cue	Items that belong to a category or a cue	Nos. of correct items
Word completion	Implicit memory (repetition priming)	Subjects are presented with a list of words and are instructed to judge the words on some attribute. After a retention interval, subjects are presented with a list of three-letter word stems and are asked to supply the first words beginning with those letters that come to their minds.	Words	Completion of word fragments	Degree to which previous exposure to a word helps with its identification
Constrained associations	Implicit memory (conceptual priming)	Subjects are presented with a list of category exemplars and are instructed to judge the words on some attribute. After a retention interval, subjects are presented with the categories and are asked to give the first eight instances of each category that come to their minds.	Specific categories	Exemplars of each category	Degree to which previous presentation of category exemplars facilitate their citations

STM = short-term memory.

immediate recall and the small number of items presented make it an STM test. We use two tests: (1) *memory span for digits*, which measures the capacity of the phonologic loop; and (2) *memory span for spatial location*, which measures the capacity of the visuospatial sketch pad.[94] The attentional control of the central executive may be assessed by a dual task that combines a concurrent recall of sequences of digits with performance of a visuospatial task. There is no convenient measure yet of the capacity of the episodic buffer.

Episodic Long-term Memory. For reasons of simplicity, efficiency, ease of control, and wide use, we recommend a free recall task. In our laboratory,[95] this simply requires the presentation, visually or orally, of a list of noncategorized 16–24 or more words, one at a time, at a fixed pace (*e.g.*, one word every 2 s). After the last word is presented, subjects are asked to recall as many of the words as possible in any order during some limited time period (immediate free recall), or recall may be postponed for a predetermined period of time, with the interval filled with other activities, before recall begins (delayed free recall). Differences in the number of words recalled in immediate and delayed free recall provide a rough estimate of STM capacity, and delayed free recall performance can be taken as a measure of episodic LTM.

Repeated trials of the list of words allows a detailed analysis of the specific effects of a drug on learning. Consequently, the free recall technique can be used efficiently to estimate learning, STM capacity, and episodic LTM. Use of normative data for the word lists allows control of level of difficulty of the stimuli and ensures approximate comparability across repeated tests.[96] Curran[97] and ourselves[98] are among investigators who suggest the use of a free recall test as a standard in every psychopharmacologic study to increase the comparability of different studies from different laboratories. We have used the test with a wide variety of drugs and populations and have been impressed with its sensitivity and versatility.

We recommend a *recognition task* as another test for retrieval from episodic LTM. In contrast to free recall, subjects are provided with cues as they attempt retrieval. Words that have been presented before are mixed with new words, and the subject's task is to recognize which words are old and which are new. There are two types of recognition tasks. In a free-choice (yes–no) recognition test, items are presented singly as a random-order sequence of old and new items, and subjects are required to judge each item as either old ("yes") or new ("no"). In a forced-choice recognition test, each old item is presented and grouped with new items, and the subject is asked to choose which of these items is old. For example, suppose *dog* was among the words on the list that was learned, and *house* was not. On a free-choice test, subjects might decide whether *dog*, *house*, and each of a number of other words was old or new. On a forced-choice test, subjects might be presented with pairs of words such as *dog–house* and, for each pair, would decide which word was old. Performance on either task depends on the relation between the new and the old words with respect to semantic similarities and perceptual features. For example, old words that are paired with synonyms constitute a more difficult task than if they are paired with semantically unrelated words. This must be controlled to ensure comparability across repeated tests and between different laboratories.

Guessing or chance success may be a factor in performance in recognition tests. In most drug research, primary interest focuses on comparing performance in two or more conditions, rather than on determining whether performance exceeds chance levels. However, there are circumstances in which the question of whether performance exceeds the chance level is important, *e.g.*, when the null hypothesis is that a drug treatment, such as general anesthesia, completely obliterates learning. The chance level is more clearly defined and deviations from chance are more readily testable in a forced-choice than a free-choice recognition test. For instance, in the example of a forced-choice recognition test given above, when subjects are presented with a pair such as *dog–house* and required to decide which word is old, they have a 50% chance of guessing correctly in the absence of any memory trace. In contrast, in a free-choice recognition test with 50% of the items being old, one cannot as confidently state that there is a 50% chance of guessing correctly because subjects might vary in their propensities to categorize items as old, *e.g.*, one subject might classify 75% of all items as old, whereas another might classify only 25% as old.[97] By setting a lenient criterion for classifying items as old, a subject may achieve a high rate of "hits" (correctly classifying old items as old), but may also experience a high rate of "false alarms" (incorrectly classifying new items as old). Another subject may set a stricter criterion for classifying items as old, resulting in comparatively lower rates of both hits and false alarms. Both types of responses should be considered. One simple approach is to analyze a measure such as hits minus false alarms as a single overall gauge of performance.[99] Signal detection theory offers more sophisticated methods for dealing with this issue, provided that the assumptions underlying these methods are satisfied. In the signal detection approach, a measure designated as d' is calculated to represent the discriminability between the old and new items.[100,101]

Semantic Long-term Memory. This type of memory is encyclopedic knowledge about the world that a person has built up over the course of his or her life. Because drugs do not produce retrograde memory impairment, this type of memory is not expected to be affected by psychopharmacologic agents unless drugs are administered to subjects over a long period of time.

Table 4. Example of the Calculations of a Priming Score

List 1		List 2	
PENSION		CLOCK	
EXPAND		SEASON	
AFFORD		TEACHER	
Test			
	Target Responses by Subjects, %		
Word Beginnings	Subjects for Whom List 1 Was Played	Subjects for Whom List 2 Was Played	Priming
AFF _____	15	7	8
SEA _____	8	16	8
CLO _____	12	12	0
PEN _____	20	10	10
EXP _____	18	15	3
TEA _____	9	16	7
Mean priming			6

For subjects for whom list 1 was played the word beginnings corresponding to list 2 words serve as distractors on the test, and *vice versa* (usually, each list consists of more than three items). The priming score for each word beginning is the percentage of subjects who were presented with the list containing the corresponding target word who give that word on the test, minus the percentage of the other subjects who give the word on the test, *i.e.*, the baseline rate of spontaneously giving that word. The bottom row shows the mean priming score for all word beginnings.

Many of the tests used to probe semantic knowledge are used in intelligence testing, and the test we use in our battery is no exception. The tests assess retrieval from semantic memory. Even if we devise a new semantic learning task (*e.g.*, learning new words and facts) and compare it to episodic learning, the results will be ambiguous because subjects can take advantage of their episodic memory to recall the new semantic material.

Implicit Long-term Memory. We use two tasks that measure two types of priming: perceptual or repetition priming and conceptual priming. *Tasks of priming memory* use a study phase and a retention interval similar to the recall and recognition tasks of explicit memory. In the test phase, however, no reference is made to the previous study phase, and subjects are not told that they are performing a memory test.[102,103] Instead, they are simply instructed to perform a new task (in our laboratory, after the subjects perform the recall and recognition tasks, we tell them "Now, we would like you to do something different. . ." to enforce in their minds the idea of an incidental "nonmemory" test). Subjects are asked to complete the word stems where there is more than one correct completion with the first words that come to mind and to give examples of supplied categories with the first exemplars that come to mind. Typically, half of the items in the test phase are repetitions of target items. The other items are unrelated to the study phase targets and provide a baseline measure of performance. For example, as seen in (table 4), the investigator prepares two lists of words: one of them is presented, and the other serves as distractors. Priming is measured as the difference in performance, as gains in accuracy with target items relative to distractor or baseline items,

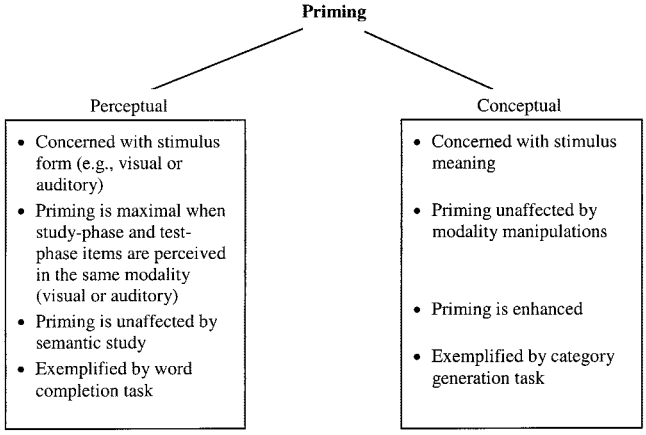

Fig. 7. Characteristics of perceptual *versus* conceptual priming.

a difference that is due to study-phase exposure to the target items. In the constrained association task, subjects are presented with category exemplars (*e.g.*, pear, tangerine) and then during the test phase are asked to give examples of fruits. Priming occurs when subjects are biased to produce previously presented category exemplars.

Although many priming tasks are well characterized as predominantly perceptual or conceptual in nature, it is likely that most tasks have some elements of each.[104] Figure 7 summarizes the differences between the two types of priming. One important distinction is that perceptual priming reflects previous processing of stimulus form, while conceptual priming reflects previous processing of stimulus meaning. Perceptual priming is maximal when study phase and test stimuli are perceptually identical and is reduced when there is a study-test change in modality;[105] *e.g.*, the list of words is presented auditorily but is tested by presenting subjects with written stems of words and asking them to write completed words. Even when the same modality is maintained between the presentation phase and the test phase, priming effects are greater when the same voice is used in the two phases, and priming suffers when the fundamental frequency of a single speaker's voice is changed between the two phases.[106] Priming may also decrease for visual material when details such as type font or type case are changed between study and test phases.[107] Another distinction is that perceptual priming does not depend on semantic or elaborative encoding of an item at the time of the study. By contrast, conceptual priming is maximal when study-phase processing enhances semantic analysis of stimulus meaning and is often unaffected by changes in modalities of the study-test phases.

Possible Contamination of an Implicit Memory Task by Explicit Memory. The type of instructions given to the subjects and the nature of the tasks differ between direct and indirect tests. For direct tests, subjects are instructed to study carefully the material being

Table 5. Process Dissociation Procedure

Type of Procedure	Instructions to Subjects	Memory Systems Used	Result of the Test
Usual priming procedure	Use the first word that comes to your mind to complete these stems.	Possibly both explicit and implicit	Completion of the stem with the word previously presented
Exclusion test of process dissociation procedure	Complete the stems with a word that was *not* previously presented.	Implicit only	
Inclusion test of process dissociation procedure	Complete the stems with words that were previously presented, or if you cannot recall them, use the first word that comes to your mind.	Both explicit and implicit	

presented during the encoding phase and are required to make a conscious effort to remember it during the test episode. In contrast, for indirect tests, subjects are required to perform some orienting or cover task during the study phase to ensure their attention to the material being presented without processing the information in a meaningful way (*e.g.*, they are asked to rate the meaning of each word on a scale ranging from *dislike very much* to *like very much*). Subjects are not informed about a subsequent memory test, to ensure only incidental (unintentional) learning. They are also not informed that the experiment has anything to do with remembering during the test episode. Despite these precautions, performance on an indirect task may involve both conscious and unconscious memory processes. For example, the word-completion task can be performed using implicit memory by "saying the first words that come to mind," or it can be done by explicitly recalling the words that have been presented (*pension*, *expand*, and *afford* in the example that was mentioned above). Also, the word-completion task may help to cue memory through presentation of the word stems (*e.g.*, PEN), an advantage that is absent in assessment of explicit memory by a free recall task.

Anesthetics may ensure that subjects are unaware of the information to be learned, provided that one can monitor the level of hypnosis to ascertain the absence of "islands" of consciousness.[38,66,108] Another method to dissociate explicit and implicit influences on memory performance is to use the *process dissociation procedure* introduced by Jacoby.[109] To understand this procedure (table 5), assume that subjects respond to the word-completion procedure by completion of the stems with the previously presented words, *e.g.*, in the previously presented *PEN____* with *pension*. In the usual priming procedure, both conscious recollection and implicit memory may help in achieving this result, as was mentioned before. Therefore, in the *exclusion part*, subjects are instructed to complete the stems with a word that was not previously presented. Now, explicit memory would suppress the use of *pension*, whereas unconscious responding leads to its use. In the *inclusion part*, subjects are instructed to complete the stems with words that were previously presented or, if they cannot recall them, to use the first word that comes to mind. Thus, both explicit and implicit systems would be involved. The procedure compares performance on both tests. Implicit memory would result in a higher proportion of completion with the word *pension* in both tests because the subjects cannot recollect the words. On the other hand, explicit memory would enhance performance only in the inclusion test. Further discussion of the method can be found elsewhere.[110,111]

Implicit memory can also be investigated using *tasks other than those that assess priming effects* (fig. 6), although their use is uncommon in the psychopharmacology literature. Thus, the learning of a new motor skill (procedural implicit memory) can be tested using a task such as mirror drawing (fig. 8), in which the subject is tested on the success of using a pencil to trace between the two outlines of a star, trying to avoid going outside them while viewing her/his hand in a mirror. Simple classic conditioning can be tested using the eye-blink response to air puff, galvanic skin response condition-

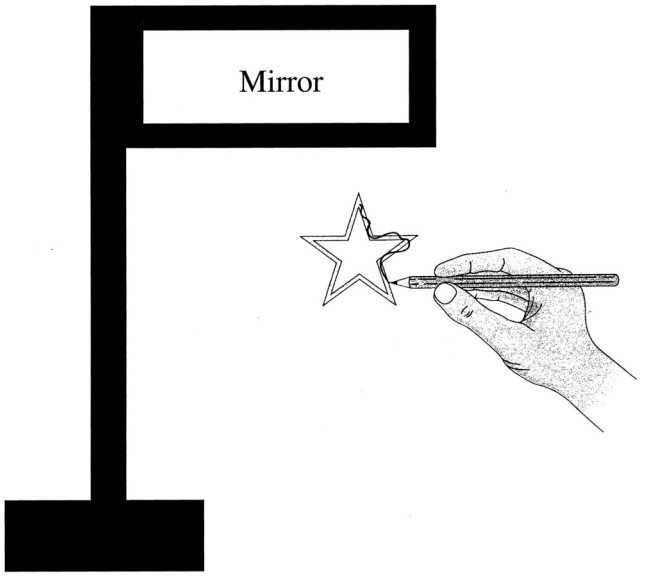

Fig. 8. Mirror drawing.

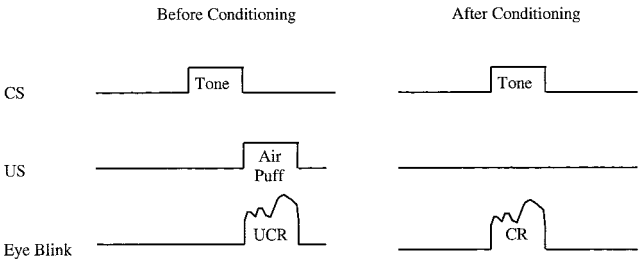

Fig. 9. The events of a Pavlovian classic conditioning trial both before and after a conditioned response is established. *Upward deflection* of the trace indicates stimulus or response onset. CR = conditioned response; CS = conditioned stimulus; UCR = unconditioned response; US = unconditioned stimulus.

ing,[112] and salivary conditioning. The latter method has not been used recently. The essential features of classic conditioning (fig. 9) involves an *unconditioned stimulus*, *e.g.*, a blink response to an air puff in the eye, reliably evoking a measurable *unconditioned response*, movement of the eyelid, along with a *conditioned stimulus*, an auditory tone, that has been shown by test not to elicit the unconditioned response. The conditioned and unconditioned stimuli are then presented repeatedly to the subject in a specified order and temporal pacing, and a response similar to the unconditioned response develops to the conditioned stimulus that is called the *conditioned response*.

The investigator, through analysis of the goals of the research and prediction of the type and magnitude of memory changes, may elect to shorten the battery or substitute one memory task for another, *e.g.*, presentation of an organized list of several categories instead of a list of unrelated words, or serial recall in which subjects are instructed to recall items in the order in which they are presented instead of recall in any order the subject chooses.

Use of Neuropsychologic Tests

Clinical neuropsychologists frequently use a battery of fixed tests as opposed to the tests described above, which are taken from the experimental psychology literature. The best known and best developed is the Wechsler Memory Scale, Third Edition.[113] These test batteries were designed to assess memory in patients with brain pathologies and have the advantages of the availability of normative data and test materials. Generally, however, they are not suitable for psychopharmacologic research for the following reasons:

1. The tasks in these batteries have been designed to detect deficits produced by organic injuries to the brain, not modest changes produced by drugs. The lack of sensitivity becomes apparent when used in the latter condition.
2. The tasks may not be adequately related to current models of memory and do not provide complete measures of its functions.
3. The batteries have not been constructed to answer questions of particular importance for a given type of drug and a specific investigation. There are no provisions for extending assessment in some areas or shortening assessment in others. They also have procedural constraints, *e.g.*, instructions, pacing, and other procedural factors that cannot be varied.
4. Instruments that use a derived memory index or quotient[114] must be scrutinized carefully to be certain that different memory functions are not being combined into a single measure. For example, an instrument that combines measures of STM and LTM may erroneously conclude that a memory impairment is present when, in fact, there may be only a major defect in attention or may inflate the overall assessment in case of LTM impairment.

Therefore, despite the inconveniences for the researcher preparing testing materials and the absence of normative data, the more sophisticated tasks derived from the experimental psychology literature are the ones recommended for psychopharmacologic investigations.

Tasks Examining "Everyday Memory" Demands

The ecological (or face) validity of a task is the extent to which the test mirrors real life settings. One may argue that a subject's responses on a test of recall of a word list may not reflect the subject's responses in real life situations. One usually does not test his or her own recall of lists of words except in a few situations, *e.g.*, grocery shopping. In daily life, one is concerned with questions such as "Did I take my medicine?" "Where did I place the car keys?" and so forth. The ecological study of memory— especially memory for life events—is a relatively recent addition to the methods of memory research.[115] Few studies of drug-memory research have used tasks involving "everyday memory" and almost always have used other standard tests, *e.g.*, subjects are shown a movie and are asked later about their memory of its details, or use of metamemory questionnaires. The problem with such tasks is gathering data to establish their ecological, construct, and criterion validities.

Differences of Memory Tests from Clinical Laboratory and Related Tests

Physicians are familiar with clinical laboratory tests, which they routinely use for diagnosing diseases and monitoring treatments. A simple example is measurement of the concentration of albumin in plasma. There is a range for normal values, an accepted standard or a standard reference test assesses the accuracy of the method used in a particular laboratory, what the test measures is obvious, the test is universally applicable, it can be repeated indefinitely (so long as reproducibility of the measurements have been evaluated), and other tests can be performed on the same sample.

Most physicians are not as knowledgeable about memory tests, and some are naively puzzled by the absence of a universal battery of tests that would diagnose and quantify memory impairments, similar to the battery of tests that are used for diseases such as diabetes mellitus, hyperparathyroidism, and a myriad of others. Some wonder why tests of memory do not use electrophysiologic measures or brain imaging. Understanding the differences between the two types of tests is probably the first step in answering these questions. Memory is not a single faculty but a compendium of different types of systems and processes. Under the influence of certain drugs and diseases, some memories are impaired, whereas others are spared. Therefore, no one or two tasks can accurately measure all of its aspects. Clinical laboratory tests are based on chemical, physical, histologic, microbiologic, immunologic, or other pathologic changes in the body that are related to a specific disease, whereas memory tests are based on performance measures. Memory is evaluated by monitoring day-to-day activities (*e.g.*, remembering to turn off the stove and lock the front door before you leave the house) or behavior on memory tests rather than physiopathologic measures such as recording the electroencephalogram or using brain-imaging techniques. Electrical activity of the brain and activation patterns in different brain regions are important adjuncts in the study of memory, but they can not by themselves define a successful or faulty memory.[94] They depend crucially on their companion memory tests performed during scanning.

Clinical laboratory tests are both clinically driven and clinically based and are used to support data obtained in the medical history and physical examination. In contrast, memory tests are (or should be) theoretically driven, based on theories or inferences about the structure of memory or the unobservable elements of memory systems and processes.[6]

Memory tests necessitate interaction with the patient, which may not be the case with clinical laboratory tests. Memory tests are done with the patient and not to the patient, as in the case of clinical laboratory tests. Therefore, subjects who are confused, disoriented, marginally alert, or uncooperative may not be capable of valid testing. Like any performance measure, memory tests depend on the ability and willingness of the subject to respond. The ability and willingness of a subject to respond are determined by a number of sensory and nonsensory factors, *e.g.*, the level of motivation. Therefore, the test battery may include tests of perception, attention, and psychomotor testing such as simple reaction time. In addition, analyses such as those involving the theory of signal detection[100,101] can enable separation of nonmnemonic factors from those involved in memory. Clinical laboratory tests are universally applicable, and a standard test or battery of tests is acceptable for particular pathology, whereas the selection of appropriate tests for a particular study of memory ultimately rests with the researcher. For example, if one was to investigate recall of events during anesthesia, tests that distinguish between explicit and implicit memories would be the most relevant, whereas tests that assess performance in terms of working memory *versus* LTM or episodic *versus* semantic processes would not be appropriate. Memory tests may not be suitable for all ages, diseases, and drugs. Education, race, general intelligence, occupation, and skills can influence the level of performance.[116] Performance on the digit span test is not impaired by most drugs but is impaired by dementia and subanesthetic concentrations of inhalation anesthetics.[35]

An accepted standard or a standard reference test is usually available for clinical laboratory tests, but not usually for memory tests. A range of normal values usually must be established for a particular study of memory as part of the research protocol. A range of normal values for clinical laboratory tests already exists. Interpretation of the results is more obvious in clinical laboratory tests than memory tests, where one test may be more sensitive than another. For example, the provision of cues or the correct context during the test phase allows easier retrieval of the original information. Clinical laboratory tests can be repeated indefinitely, and other tests can be performed on the same sample, but this is not the case with memory tests. Limitations such as possible interference of the tests with each other confounding the results or fatigue of subjects make assessment of memory difficult. Finally, the issue of relevance of statistical significance *versus* behavioral significance is more of a concern for memory tests. Will a decrease of 4 words in a delayed recall test of a 24-word list compared to controls be crucial? In some situations, the answer is probably no. However, there are situations in which memory and cognitive function must be high and situations in which performance is already compromised, *e.g.*, an elderly patient.

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Drugs and Human Memory (Part 2)

Clinical, Theoretical, and Methodologic Issues

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Design of Experiments

Fundamentals of a Memory Experiment and Two Manipulations

THE skeleton of the memory experiment should have three phases: a study or acquisition phase, a retention interval, and a test or retrieval phase. Testing *acquisition versus retrieval* is a common experimental manipulation. For example, subjects might be required to learn one or more lists of words before drug administration and then asked to recall the material during the period of drug action (table 6). For most drugs, recall would not be impaired, even if the subjects seem to be very drowsy and sedated. In contrast, recall of word lists learned after drug administration would be greatly reduced.

Another manipulation is to test for *state-dependent memory* or to control its effects. The most common design has been the 2 × 2 (table 7), in which subjects learn material in either a drug or a placebo state and later try to recall the information in either the same or the opposite state.[82] There would thus be four groups of subjects assigned to the following treatment conditions during acquisition and recall: drug–drug, drug–placebo, placebo–drug, and placebo–placebo. Symmetrical state-dependent memory would be demonstrated if the drug–drug and placebo–placebo groups recalled better than the drug–placebo and placebo–drug groups. Asymmetrical state-dependent memory would be demonstrated if the drug–placebo group recalled less than the drug–drug group. The subject is further complicated by the sensitivity of state-dependent effects to the type of memory tasks used.[117,118]

The Definitive Standard

For drug studies, the definitive standard design is the randomized, prospective, concurrent assignment of subjects to the drug and placebo groups, under double-blind conditions, in which neither the subjects nor the researchers can determine which treatment is being used. Unfortunately, there are circumstances in which this strategy may not be feasible. It may not be possible to "blind" patients to some treatments that have recognizable effects, *e.g.*, treatment with general anesthetics. It may not be ethical to use a placebo group, *e.g.*, in surgical and invasive procedures that require a sham procedure, or if there is a risk of exacerbation of illness.

Comparison Groups

Investigation of drug effects has one significant design advantage over many studies of cognitive impairments: the possible use of *pretreatment and posttreatment comparisons*. Premorbid assessment is usually not available when impairment is caused by trauma or disease. In studying the effects of drugs, however, it is possible to compare the behavior of the subject, both before and after administration of the drug, allowing unambiguous attribution of behavioral changes to the influence of the drug. A second fundamental design component is the use of a *nondrug (placebo) control* sample in which subjects receive identical treatment except for administration of the drug. Both design elements are essential. Pretreatment–posttreatment comparisons alone are inadequate because practice on experimental tasks, environmental influences, fatigue, and a host of other factors can change behavior over time and affect the comparison of performance before and after drug administration. Comparison of treatment and control groups alone is also inadequate unless it can be established that the groups are equivalent before treatment. Otherwise, an observed difference could have existed regardless of treatment or a true difference could have been masked by different baseline measurements between groups.

Inclusion of a placebo control group is particularly important in assessing the influence of a drug on learning and performance. In several of our studies, we have noted little or no difference in performance between pretreatment and posttreatment with an active drug.[95] These failures to find significant differences might be incorrectly attributed to a lack of a treatment effect except that the control group performance showed marked improvement in the same task from pretreatment to posttreatment. For example, figure 10 shows performance in learning sequences of 15 digits. Placebo subjects demonstrated an immediate improvement from their first test to their second, with no further improvement. For diazepam-treated subjects, the improvement was delayed, with greater delays for higher doses. In other words, the drug suppressed the usual performance improvement that occurs with repeated practice, thereby showing a reduction in new learning caused by the drug. Thus, a placebo-controlled design is essential to assess practice effects. Otherwise, drug effects may be confounded with practice effects.

An "*active" control* group, *e.g.*, a group treated with a

Table 6. Experimental Design to Test for Acquisition *versus* Retrieval Deficit

Presentation of the first set of lists
Drug or placebo administration
Delayed recall of the first set of lists
Presentation of the second set of lists
Retention interval
Delayed recall of the second set of lists

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Table 7. Experimental Design for State-dependent Memory

	Drug State during Recall	
Drug State during Learning	Drug	Placebo
Drug	D-D group	D-P group
Placebo	P-D group	P-P group

D = drug; P = placebo.

benzodiazepine when investigating a new potential amnesic agent, may also be included in the design. This would be advantageous when the sensitivity of the tests used has not been established, as a safeguard against false-negative results, and as a standard for comparison with the new drug–induced effects.

Issues Related to Studies of the Long-term Effects of Drug Abuse

Methodologic flaws are common in studies of the effects of drug abuse on cognition. The majority of the studies have not included measures of premorbid cognitive function, raising the possibility that differences between drug users and controls existed before the onset of drug use, rather than being caused by drug use. Some studies have not included a control group of nonusers. To convincingly demonstrate cognitive deficits in drug users, comparison with an appropriately matched control group is essential. Many studies have involved sample sizes too small to provide valid conclusions. These methodologic flaws can be avoided by measuring premorbid cognitive function, including a control group, and using a large sample size. To control for the possibility that drug abusers were poorer mentally and intellectually before starting their abuse, Block *et al.*[40] pioneered matching drug users and nonusers on their previous scores during the fourth grade on the Iowa Test of Basic Skills achievement tests.[119] Another methodologic constraint in studies of recreational drug users is the fact that most subjects use more than one drug. It is therefore important when investigating one specific drug to take a careful drug history and set strict maximal limits on the frequency and quantity of use of other drugs when recruiting subjects.

Pharmacologic Factors

Dose–Response Effects

One of the most elementary considerations in pharmacology is the relation between the size of the dose administered and the size of the measured behavioral response. However, the simple assumption that larger doses result in greater effects than smaller doses may not be true. For example, midrange doses of physostigmine exert positive effects on memory performance, whereas higher and lower doses impair it.[120,121] Other "memory-enhancing" drugs, such as epinephrine and other endogenous stress hormones, may also show similar "inverted-U" dose–effect curves.[122–125] This shape of the curve has been variously explained as being due to the high doses inducing hyperstimulation effects, producing state dependency, or facilitating learning of other interfering material.[126] Other drugs may show a biphasic action on behavior, with small doses improving and larger doses impairing behavior.[127]

Effects of Repeated Administration

Tolerance. *Tolerance* has been defined as a shortened duration and decreased intensity of drug effects after repeated administration. Short-term tolerance to psychoactive drugs may develop within the time course of a single dose. Behavioral impairment may recover toward baseline levels while the plasma concentrations of the drug remain relatively high. This has been demonstrated for many drugs, including barbiturates, benzodiazepines, caffeine, and cocaine.[128–130] The rapid distribution of a drug in and out of the brain may produce the same effects as short-term tolerance. Experiments with steady state blood concentrations may be needed to distinguish between distribution effects and short-term tolerance.

With repeated administration, long-term tolerance to the behavioral effects of psychoactive drugs can develop.[131,132] The opposite effect to tolerance has occasionally been reported. Repeated administration of cocaine may produce *sensitization* or heightened responses.[133,134]

Pharmacokinetic–Pharmacodynamic Relations

The relative ease of measuring a psychotropic drug concentration in blood (or other body fluids) compared with objective dynamic measurements of memory or other central nervous system (CNS) effects has led many

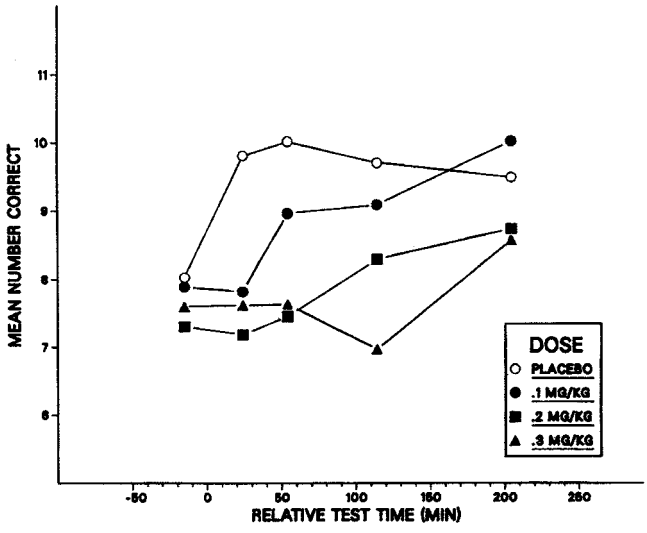

Fig. 10. Mean number of digits recalled at intervals before and after diazepam and placebo treatments. Zero was the time of drug administration. A different random 15-digit number was presented each time. The score represents the mean of three trials. From Ghoneim *et al.*[95]; used with permission.

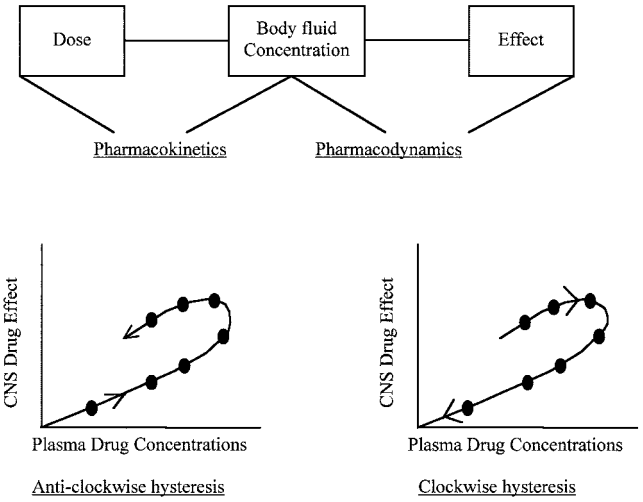

Fig. 11. Definitions of pharmacokinetics and pharmacodynamics and types of hysteresis.

to assume that blood concentrations are synonymous or linearly related to drug effects, which may not be true. If a continuous or repeatable discrete measure of a drug effect can be obtained with concurrent measurement of drug blood concentrations, it is possible to develop pharmacokinetic–pharmacodynamic (PK-PD) modeling concepts to characterize relevant parameters that quantify drug effects.[135] There are several advantages for studying PK-PD relations[136,137]: (1) It allows more complete understanding of the determinants of drug action, including phenomena such as distributional delay of effect, formation of active metabolites, and short-term tolerance. (2) It quantitates the effects of the drug on the brain by calculating values for parameters such as $Cp50_{AMN}$ and $Cp50_{SED}$, which represent the plasma drug concentrations required to produce one half of maximal amnesia and sedation.[138] As valid measures of intrinsic drug potency and brain sensitivity within an individual, those parameters allow exploration of the psychotropic differences between drugs and explanations of effects of factors such as aging and drug–drug and drug–disease interactions on the drugs' actions. (3) The information would make it possible to design optimal infusion schemes for drugs during conscious sedation and anesthesia or during investigations of their behavioral effects. (4) It provides a rationale for monitoring drug plasma concentrations as indicators of clinical efficacy or toxicity and use for medicolegal purposes.

Several steps are involved in studying the PK-PD relation and evaluating drug action: (1) *Pharmacokinetics* describe and predict the time course of concentrations in body fluids, usually blood (fig. 11). Arterial blood sampling allows for the calculation of accurate data during drug distribution and the rate of blood–brain equilibration.[139] It is the preferred site because most of the studies in the literature evaluate the effects of single bolus doses or relatively short infusions and are performed during the distribution/redistribution phase. The issue of plasma protein binding is also of importance[140,141] because the unbound (free) drug in plasma is presumed to represent the drug fraction that is available for transport across the blood–brain barrier. (2) *Pharmacodynamics* describes the time course and intensity of drug effects (fig. 11). This is the difficult step and is the reason for the deficiency of adequate studies of the pharmacokinetic–amnesic relation for drugs. The behavioral tests must be short, amenable to frequent repetitions, and sensitive to low drug doses and concentrations. The brevity of the tests reduces subjects' fatigue, and the test sensitivity allows determination of memory function over a wide range of drug concentrations. We developed in our laboratory the use of a 15-digit number serial learning task, repeated over three trials for such studies.[95] The task is sensitive, short (approximately 3.5 min), and can be administered as frequently as desired to correspond to changing drug concentrations. The task may also be administered several times before the actual study to reduce improvement in performance over time. There is virtually no limit to the numbers that can be generated by a computer, unlike words or pictorial lists. To compensate for any residual practice effects, one may use a placebo correction. Changes over baseline scores after administration of active medication are corrected by subtraction of scores at corresponding times after placebo administration. (3) *PK-PD modeling* describes the relation between the dose (concentration) and its effects. Data should be obtained from repeated and simultaneous sampling over a wide range of drug concentrations. A mathematical model is developed that fits the data and allows inference of the effect site concentrations based on plasma concentrations. Various PK-PD models may be used.[135–137,142] The most appealing is the sigmoid E_{max} model, because of its similarity to the receptor binding model. Interpretation of the concentration–effect relation can be complicated by the lack of a temporal relation between the two variables, so-called hysteresis. Two types of cognition–blood drug concentration curves may be found (fig. 11). The drug effect may decrease with time for the same drug concentration, described as clockwise hysteresis as shown by the arrows in figure 11. This may be caused by tolerance (short- or long-term), progressive learning of the task, and the presence of active antagonistic metabolites.[143,144] It is not possible to separate tolerance from learning without a placebo control. The formation of active antagonistic metabolites is rare, but there are a few examples of metabolites that alter the dynamics of the parent drug by modifying its kinetics, *e.g.*, 5-hydroxy-pentobarbital.[144] The presence of clockwise hysteresis has some important practical applications. Medicolegally, blood concentrations may not adequately predict impairments from these drugs.

Table 8. Methods for Dissociating the Effects on Memory and Sedation

Method	Typical Findings	Examples
Equate effects on sedation and determine whether two or more drugs have differential effects on memory	Different drugs produce same sedative effects but different effects on memory.	Green *et al.*[147] (1996), Curran *et al.*[148] (1998)
Assess the development of tolerance to sedative and memory effects	Tolerance to sedation develops before tolerance to memory effects.	Ghoneim *et al.*[149] (1981), Lucki *et al.*[151] (1986), Curran *et al.*[150] (1994), Tata *et al.*[152] (1994)
Assess the degree of reversal of agonist effects on sedation and memory by antagonist	Differential reversal depends on ratio of dosage of agonist to antagonist and their times of administration.	Curran and Birch[153] (1991), Hommer *et al.*[154] (1993)
Assess the degree of differential dose–response curves for sedation and memory	Sedation and memory show different dose–response curves.	Roache and Griffiths[155] (1985), Rich and Brown[156] (1992), Weingartner *et al.*[157] (1995)
Measure differential effects on early and late components of the auditory event-related potential	Early components are affected similarly by sedatives, whereas later components are affected more by amnesics.	Curran *et al.*[148] (1998), Veselis *et al.*[158] (2001)*
Statistical—covariance and more sophisticated statistical analysis	Covariance of sedation measures leave significant drug–placebo differences on memory. Amnesic drugs produce memory impairment before they cause significant sedation.	Ghoneim and Mewaldt[159] (1990), Curran[160] (1991), Veselis *et al.*[138] (1997)

From Curran[49]; modified with permission.

* Also, more recently, Veselis RA, Reinsel RA, Feshchenko AV, Johnson R: Thiopental and propofol effects on memory are dissociable by event related potentials. Poster presented at the 50th Annual Meeting of the Association of University Anesthesiologists, Milwaukee, Wisconsin, May 1–3, 2003

Another type of drug concentration–effect curve can demonstrate anticlockwise hysteresis. The effect of the drug increases with time for a given drug concentration, which, when taken sequentially, produces a direction that is counterclockwise. A common cause is the delay for a drug to be transported from the systemic circulation (sampling site) to its site of action and then to elicit a measurable response. This type of hysteresis may be missed because of infrequent early sampling and assay of the drug in venous rather than arterial blood.[139,142] Another cause is the production of active metabolites from the parent drug. These would have maximum concentrations and a combined peak activity at some later time compared with the parent drug concentration.[145] Other uncommon causes are delayed drug action, drugs working through a cascade reaction, and short-term sensitization or up-regulation of receptors.

The applicability of mathematical models to describe the pharmacodynamic response becomes questionable when hysteresis occurs. The hysteresis must be collapsed or removed. One frequently used approach assumes an effect compartment[146] to correlate memory changes with changes in the blood concentrations of drug. It can be thought of as the kinetically defined biophase of the CNS actions of the drug. The drug effect is directly related to its concentration at the receptor site. A link model[142] describes the transfer between the plasma and effect compartments. The equilibration delay between the compartments is characterized by the rate constant k_{e0} with units of reciprocal time, which governs the transfer of drug.

Specificity of Memory Effects

All of the drugs currently available for human use that are capable of producing amnesia also cause sedation. There is no drug that only affects memory. For theoretical and clinical reasons, it is important to separate the effects on memory systems from impairments in attention, arousal, or mood. It is also important when investigating potential memory-enhancing drugs to separate effects on alertness, attention, and fatigue from genuine effects on learning and memory. The general consensus is that drug-induced amnesia is independent of sedation. Table 8 summarizes the approaches that have been used to dissociate the effects on memory and sedation. One method is to study two or more drugs that produce the same effects on sedation but different effects on memory. For example, Green *et al.*[147] compared chlorpromazine with lorazepam in doses that produced equal degrees of sedation but found that memory was impaired only by lorazepam. Curran *et al.*[148] compared the effects of diphenhydramine with those of scopolamine and lorazepam. In the doses used, the three drugs produced similar levels of sedation, but the antihistamine did not impair memory. It should be noted, however, that because tests of sedation and memory may vary in difficulty, dissociations of this kind do not provide compelling evidence for independence between the two behaviors.

Another method of demonstrating the specificity of the memory effects of drugs is to study the rates of development of tolerance to the actions of the drug. Overall, the evidence is that tolerance develops to sedative effects much faster than it develops to memory

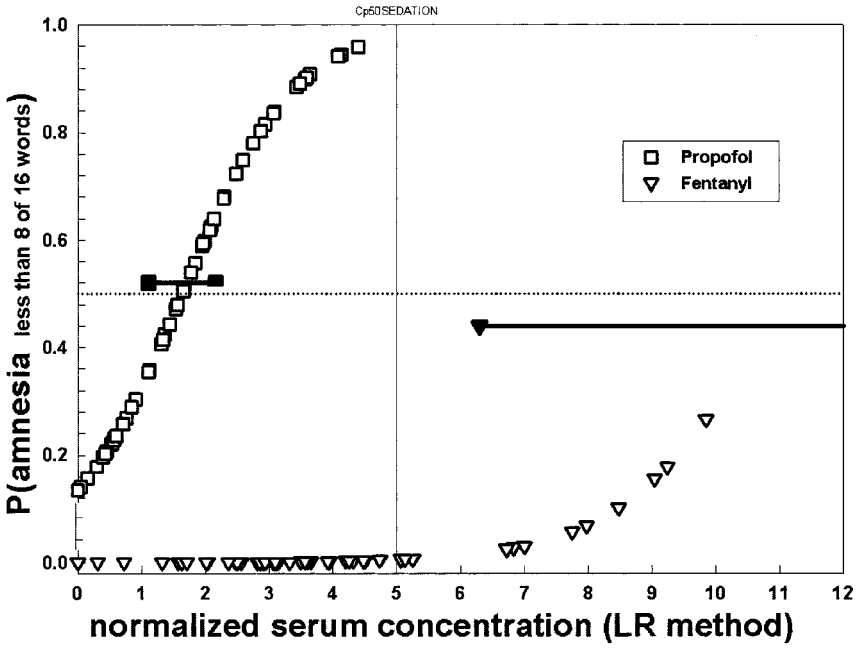

Fig. 12. Probability of amnesia being present as a function of normalized serum concentration using a logistic regression (LR) model. *Amnesia* is defined as recognition of fewer than half of the words presented. Confidence intervals for $Cp50_{AMN}$ are given as *horizontal bold lines* for each drug. The *vertical line* at x = 5 represents the $Cp50_{SED}$. From Veselis *et al.*[138]; modified with permission.

effects. For example, tolerance develops to the sedative effects of diazepam after its 3-week administration to healthy volunteers but not to its amnesic effects.[149] Tolerance develops to the memory effects of alprazolam after 8 weeks of treatment in patients[150] and at least 6 months after treatment with other benzodiazepines.[151,152] An alternative way of dissociating the two effects would be to show differential reversal of amnesic and sedative effects by an antagonist. Use of small doses of flumazenil[153] or pretreatment with flumazenil before administration of a benzodiazepine[154] results in reduction of sedative effects without relief of memory impairment. A fourth method of dissociation is through demonstration of different dose–response curves for sedation and amnesia.[155–157] Using the auditory event-related potential with different groups of drugs that produced equivalent sedative but differing amnesic effects, Curran *et al.*[148] and Veselis *et al.*[158] (also more recently, Veselis RA, Reinsel RA, Feshchenko AV, Johnson R: Thiopental and propofol effects on memory are dissociable by event related potentials. Poster presented at the 50th Annual Meeting of the Association of University Anesthesiologists, Milwaukee, Wisconsin, May 1–3, 2003) reported that early components of the event-related potential were affected similarly by sedatives, whereas later components were affected more by amnesics. Statistical methods are also important for showing this dissociation. Analysis of covariance can be used to separate effects attributable to sedation. However, covariance assumes a linear relation between variate and covariate, and the relation between memory and sedation maybe more complex than that.[159,160] More recently, Veselis *et al.*[138] used several statistical scaling procedures, normalization of drug concentration levels, and arbitrary standards of memory and sedation to compare memory performance after equisedative doses of four drugs (midazolam, propofol, thiopental, and fentanyl). These drugs exhibited very different sedation and amnesia relations for the same criteria of felt sedation and objective memory impairment. For example, propofol at low serum concentrations showed a high likelihood of exceeding the criterion of memory impairment well before it met the criterion of sedation. In contrast, fentanyl exceeded the sedation criteria and showed low probability of amnesia for the same concentration range (fig. 12). Finally, Eger's group has demonstrated chemical compounds that suppress learning without causing sedation in animals[161–163] and shown that the two functions need not be inseparable.

Brain Imaging

Introduction

Functional neuroimaging opens a window to view the brain at work. It provides a unique *in vivo* opportunity to study the neurobiology of human memory and its functional and neural architecture. It is also a rapidly developing, highly interdisciplinary and complex technical field, requiring multidisciplinary teams of scientists (in physics, radiologic science, mathematics, statistics, computer programming, engineering, cognitive neuroscience, and medicine).[164] Brain imaging has been used relatively recently to investigate several areas of memory, including the nature and function of components of the memory systems and regional cerebral blood flow changes associated with performance of memory tasks under the influence of drugs.[165–169] Many new insights have been gained, and these in turn promise a deeper understanding of the foundations of memory.

Principles

The two major techniques are positron emission tomography (PET) and functional magnetic resonance imaging (fMRI). Both measure neuronal activity by assessing changes in local cerebral blood flow. For the PET method, a radioactive tracer is injected immediately before the start of a cognitive task. The radiotracer accumulates in the brain in direct proportion to the local blood flow. For the most widely used fMRI method, called BOLD (blood oxygen level dependent), images are generated through changes in blood oxygenation that accompany neuronal activity without the need for a radioactive tracer. When neural activity increases, local blood flow and oxygen consumption increase, but the former increases more than the latter, resulting in a local increase in the amount of oxygenated blood and a net decrease in deoxyhemoglobin. Deoxyhemoglobin is paramagnetic, resulting in local magnetic field changes that provide the imaging contrast.[170]

Research Design

At least two issues need to be considered when planning neuroimaging studies, as discussed here.

Control of Other Mental Activities during the Scanning Period. If the researcher wants to construct, for example, an episodic memory retrieval task in which the subject recalls orally during scanning the words of a list learned earlier, changes in blood flow should be the result of memory retrieval and not due to other mental activities. A common strategy is to use a paired image subtraction design. In addition to the scan during the word list recall, another scan is taken during a control condition that shares the same mental operations except for those of explicit retrieval. For example, we asked the subjects in our laboratory[171] to repeatedly count "1, 2, 3, . . ." aloud at a rate of approximately 1 number/s, which is expected to match the rate of verbal output during the memory test. This repetitious rehearsal in short-term memory of a vastly over-learned and automatized sequence should minimize episodic memory retrieval. Subtracting the blood flow maps during the control state, which accounts for speech activity, from those during the activation state would identify the regions that are involved in the desired memory task. This subtraction method has been criticized. There is no guarantee that the performance in the experimental task will differ from the control state in only one way. Also, the addition of the extra processing component *per se* in the experimental task may affect processes common to the experimental and control tasks. If so, it would not be possible to subtract them out.[172] Nonetheless, the majority of results from studies of memory have been generated by this method, and robust and reliable patterns of activation have been demonstrated.[173]

Some researchers also use a resting state as a baseline. Subjects lie quietly without specific instructions regarding mental activities. Critics argue that the variability in the mental state during such a condition is such that it may not serve a useful purpose.[164] In our laboratory, we ask the subjects immediately after the period to describe what they had been thinking to discern differences in mental states between subjects in the experimental and control groups.[174]

Control of Stimulus Presentations Relative to the Scanning Sequence. The characteristics of the stimulus, its mode of delivery, its timing, and its timing and duration in relation to the scanning periods must be precisely controlled.[175]

Image Acquisition

A widely used PET radiotracer is oxygen-15–labeled water ($H_2{}^{15}O$), which has a half-life of approximately 2 min, allowing a series of injections to be performed every 12–15 min. For each injection, the cognitive task and scanning are performed during the time that the labeled blood perfuses the brain. It provides a 40-s window on brain activity, with a spatial resolution of approximately 6–10 mm. The advantages of PET include relatively silent scanning, accessibility of the patient for monitoring, and the ability to provide quantitative as well as relative measures of blood flow. The latter is important in studies with drugs that may affect global cerebral blood flow, either directly or indirectly, *e.g.*, *via* changes in arterial carbon dioxide tension ($Paco_2$). The advantages of fMRI compared with PET include the avoidance of exposure of subjects to ionizing radiation and improved spatial and temporal resolution. Its limitations are confining the subject inside the scanner, with its risks of limited monitoring and claustrophobia in some individuals, acoustic noise, and signal artifact at the base of the brain.[164]

Methods with High Temporal Resolution

Both PET and fMRI have high spatial but poor temporal resolution. Conversely, electroencephalography, event-related potentials, and magnetoencephalography rapidly measure the current flows induced by synaptic activity. *Electroencephalography* and *event-related potentials* quantify electric potentials with electrodes at the scalp. *Magnetoencephalography* is a newer technique in which the magnetic fields associated with current flow within neurons induce a current in a detection coil on the scalp. To pick up these small signals, the detection coils are coupled to a superconductive device within a magnetically shielded room.[164] However, the accurate localization of neuronal current flows based on data generated by these methods alone is problematic. Recently, techniques have been developed that use both hemodynamic and electromagnetic measures to arrive at estimates of brain activation with high spatial and temporal resolutions. These methods range from simple juxtaposition to simultaneous integrated techniques.[176]

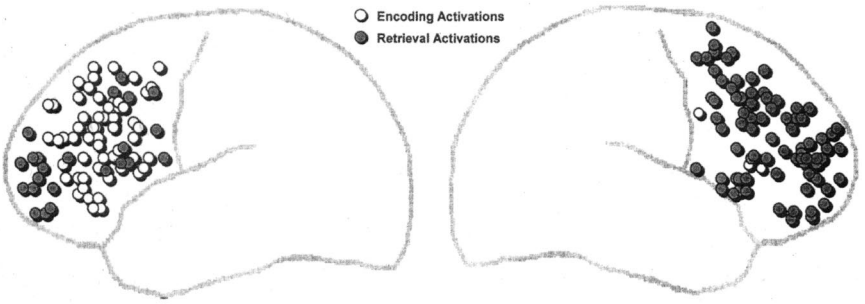

Fig. 13. Hemispheric asymmetrical involvement of left and right prefrontal cortex during episodic encoding and episodic retrieval. From Nyberg and Cabeza[173]; used with permission.

Image Processing and Analysis

Images are reconstructed before statistical analysis. They are corrected for sources of noise in the signal due to scanner drift or artifacts, are realigned to correct for slight head movement, and may undergo spatial smoothing.[164] Usually the subject's functional results are displayed on his/her own structural magnetic resonance imaging scan; otherwise, images are transformed to a stereotactic coordinate space, based on a common template.[177] This is done to counteract individual differences in brain size and gyral anatomy and facilitates group analyses, as well as the communication of results across laboratories. Typically, the comparison of blood flow maps associated with the cognitive task and its control is performed using a *t* test, regression, or multivariate statistical approaches.[178,179]

Brief Summary of the Neural Basis of Memory

Tulving *et al.*[180] proposed the hemispheric encoding/retrieval asymmetry model. According to this model, the prefrontal regions in the left hemisphere tend to be differentially activated during episodic encoding and semantic retrieval, whereas the right prefrontal regions tend to be differentially involved during episodic memory retrieval (fig. 13). Considerable evidence supports this model,[181] although some critics have argued that this hemispheric asymmetry seems to depend to some extent on the type of stimuli used.[182,183] The latest version of the model acknowledges that the right prefrontal lateralization of episodic retrieval seems less complete than originally proposed.[184] A second general observation of the neuroimaging literature is that prefrontal regions seem to interact with posterior brain regions during memory encoding and retrieval.[173] *Episodic encoding* usually involves activation of the left prefrontal, left temporal, and anterior cingulate regions. The left hippocampus is usually involved with verbal material, and the right hippocampus is involved with nonverbal materials.[185–187] There are two functional neuroimaging studies that demonstrate that activation of the amygdala at encoding is correlated with later recall of emotional material.[188,189] *Episodic retrieval* usually activates the right prefrontal region, the anterior cingulate region, the cerebellum, and the hippocampus.[190,191] *Semantic retrieval* is usually associated with activation of the left prefrontal, left temporal, and anterior cingulate regions.[190,192] For *working memory*, the central executive is typically associated with activation of prefrontal regions, the phonologic loop is associated with the parietal regions (for storage) and the Broca area (for rehearsal), and the visuospatial sketch pad is associated with the occipitotemporal, occipitoparietal, inferior prefrontal, and superior prefrontal regions. Object maintenance tends to be left lateralized, and spatial maintenance tends to be to be right lateralized.[193,194] *Priming* is accompanied by reductions in the amount of neural activation relative to naive or baseline task performance (fig. 14). Decreased activation bilaterally in occipitotemporal cortical areas is usually associated with perceptual priming, and the left inferior frontal cortex is usually associated with conceptual priming.[191,195,196] Last, *aversive conditioning* is associated with activation of the amygdala.[197,198] Table 9 summarizes these results. It should be emphasized, however, that there are discrepancies and uncertainties about precise anatomic localization of various memory processes. For example, in a review of verbal working memory by Ivry and Fiez,[199] Broca area activation was found in only 9 of 12 data sets by different groups of investigators. Neuroimaging is a "noisy" technique, and results obtained in one study may not be replicated in a second. Assumptions that the cognitive tasks used in different studies evaluate the same memory processes may not be certain, and teasing apart the different operations involved in complex mental functions is far from easy.

Network Analyses

The standard subtraction approach to analyzing functional neuroimaging data can be used to identify the brain regions active in certain tasks. However, it does not indicate the functional interrelations between such regions and regions that do not show differential activity but may still be part of the specific functional network. The network approach complements the subtraction approach in characterizing the functionally specialized brain regions and their interactions.[200–202] Several procedures have been used to identify the different brain regions and how they interact in a given network model. A commonly used procedure is *structural equation modeling* or path analysis.[203] Briefly, the following steps

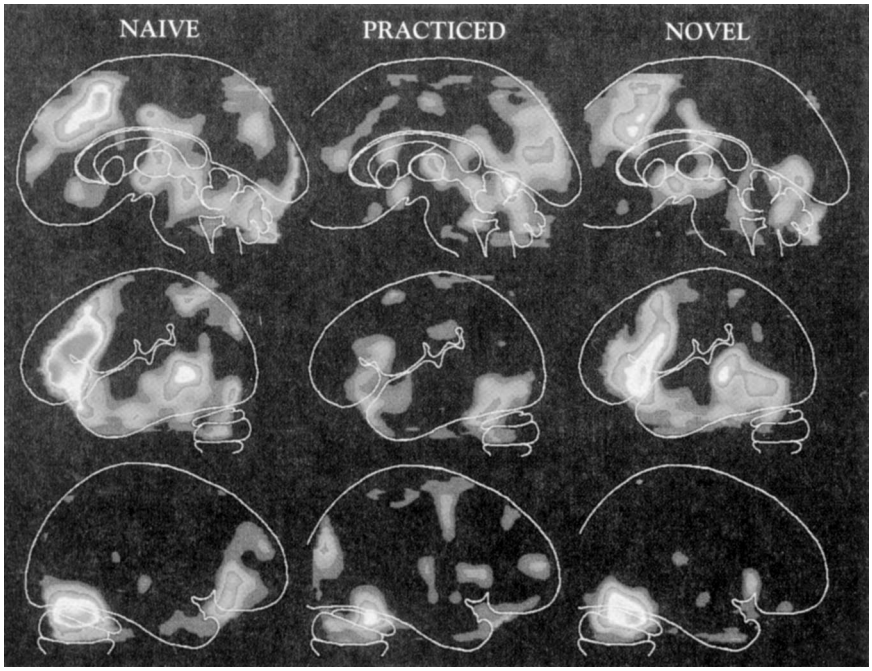

Fig. 14. Positron emission tomography scans of three vertical slices through the brain revealed the areas of activation (*whitened*) during administration of lists of words. In the unpracticed or naive subject (*left column*), the anterior cingulate (*top row*), temporal and frontal lobes (*middle row*), and right cerebellum (*bottom row*) are active, but the practiced subject performs the task with no activation of these areas (*middle column*). Introduction of a new list of words reverses these practice-induced changes (*right column*). (The reader should refer to the original reference for reviewing the colored pictures). From Posner and Raichle[196]; used with permission.

are involved: (1) Brain regions differentially activated through subtraction analysis are identified. (2) The regions are linked to each other on the basis of neuroanatomy to create an anatomic network model. (3) Regional cerebral blood flow correlations among the regions are calculated. (4) Structural equation modeling is applied to the regional cerebral blood flow correlations among the regions. The values or weights for the different connections are calculated.

Conclusions

Functional neuroimaging has been used to investigate the normal operations of memory with considerable success. The scope of this work has not been matched by studies in subjects with drug-induced memory changes. Future investigations will no doubt define the neural substrates associated with memory impairment (or enhancement), differentiate between the substrates of sedative–hypnotic effects and amnesic effects, and determine the neuroanatomic signatures of each drug. Potential or currently accepted therapeutic interventions in pathologic states might also be closely examined using neuroimaging.

Overview of Memory-impairing Drugs

A wide variety of drugs impair memory. These include the benzodiazepines, anticholinergic agents, alcohol, anesthetics, barbiturates, cannabis derivatives, β-adrenergic blockers, and others. The benzodiazepines and the anticholinergics have been investigated more than the others. These drugs have a wide diversity of chemical structures, which vary from the monoatomic xenon and the biatomic nitrous oxide to the more complex structure of a benzodiazepine, a barbiturate, or a halogenated

Table 9. Brain Regions Activated during Learning and Memory

Memory Operations	Typical Activation Patterns
Working memory	
Phonologic loop	Left frontoopercular (Broca area), premotor and parietal cortex
Sketch pad	Ventral (object information) and dorsal (spatial information) visual pathways
Central executive	Prefrontal cortex (ventrolateral and middorsal)
Episodic memory	
Encoding	Left prefrontal and temporal cortex, anterior cingulate, hippocampus*
General retrieval	Right prefrontal cortex, anterior cingulate, cerebellum, precuneus, thalamus
Successful retrieval	Prefrontal cortex, precuneus, hippocampus*
Semantic memory	Left prefrontal and temporal cortex, anterior cingulate
Priming	
Perceptual priming	Bilateral occipitotemporal cortex†
Conceptual priming	Left inferior frontal cortex†

From Nyberg and Cabeza[173]; modified with permission.

* Hippocampus refers to hippocampus proper as well as nearby cortex. † Decreased activation.

Table 10. General Characteristics of Amnesic Drugs

A wide variety of molecular structures and biochemical pathways but similar profiles of impairments exist.
The acquisition of new information is impeded, producing anterograde amnesia.
Retrieval processes are only impaired by anesthetics.
Short-term memory is only impaired by anesthetics.
Episodic but not semantic memory is impaired.
Learning of skills or procedures usually remains intact.
Explicit memory is much more impaired than implicit memory.
The degree of amnesia is related to the dosage, additive effects of other drugs, and aging.
Tolerance and cross-tolerance to memory impairment are usually modest.
Amnesia is independent of sedation.
State-dependent effects are controversial.

volatile anesthetic. Benzodiazepines, barbiturates, and volatile anesthetics act at the γ-aminobutyric acid type A ($GABA_A$) receptors potentiating chloride currents. Xenon, nitrous oxide, and ketamine seem to have their major effects at the *N*-methyl-D-aspartate receptors. Cholinergic antagonists act at muscarinic receptors. β Blockers act at β-adrenergic receptors. Marijuana acts on cannabinoid receptors. Drugs such as ethanol act on receptors for serotonin, acetylcholine, GABA, glutamate, glycine, and dopamine. Differentiating which receptor is mediating amnesia, subjective experience (sedation, hypnosis, anxiolysis), or other behavioral effects is difficult to assess. However, despite the disparity in molecular structure, selective targets, chemical transmitters, and specific binding areas in the brain, these diverse agents seem to produce similar profiles of memory impairment. It seems that there are multiple pathways to the final effects on memory. This kind of commonality agrees with the current view that memory is a distributed property of cortical systems rather than exclusive to specific areas.[204,205] Thus, one brain region may be part of more than one neural network subserving different memory abilities. The general characteristics of drug impairments are displayed in table 10.

Effects on STM versus *LTM and Components of Working Memory*

Drugs, with the exception of general anesthetics,[35,206] spare short-term memory (STM) but impair long-term memory (LTM).[49,159] Therefore, sensitive memory tasks are those that minimize the contribution of STM and maximize the contribution of LTM, *e.g.*, a test that examines the delayed retention of a relatively long list of items. If immediate recall is tested, the position of the items in the list should be analyzed to exclude those whose performance relies more on STM.

A gradual increase in a general anesthetic dose produces a progressive impairment of STM or working memory until events occurring only 1–2 s before cannot be remembered.[206] Learning ceases before loss of consciousness and STM function. A small further increase in anesthetic dose is associated with loss of consciousness.[207] Few studies have examined the effects of drugs on components of working memory. Rusted and Warburton[208] used dual-task paradigms to investigate the effects of scopolamine. The drug produced impairments of the central executive component, which confirmed earlier observations with the drug.[33] Gorissen and Ehling[209] also used dual-task experiments to test the effects of benzodiazepines. Although dividing attention reduced memory performance, this manipulation was no more disruptive in those given diazepam *versus* those given placebo. Both groups of investigators agree that reduced attentional resources due to impairments of the central executive are not sufficient to explain the effects of the drugs on memory.[210]

Effects on Explicit versus *Implicit Memory*

Drugs act prominently on explicit memory. The effects on implicit memory have not been studied as extensively as with explicit memory, and their results have been conflicting. Most of the studies have investigated the effects of priming. Some studies showed preservation of implicit memory through performance on perceptual tasks such as the word-generation test,[67,153,211–215] whereas others found impairment.[216–220] There are some studies on the effects of drugs on procedural learning as exemplified by motor skill acquisition tasks. The majority suggest preservation,[159] but others do not.[61] It should be remembered that areas of the brain involved in attention and explicit memory may be needed early in skill learning and that these areas become less important as learning proceeds.[221,222] Also, a drug effect may be caused by a general slowing of performance related to the sedative effect of the drug.[67,153,159] In general, it is possible to conclude that impairment of explicit memory usually is more pronounced than that of implicit memory, effortful cognitive processes are much more impaired than automatic ones, there is usually diminished contamination of indirect test performance by explicit memory, and impairments are usually milder in forced-choice recognition than in yes–no recognition.[223] (Subjects in a forced-choice recognition, unlike yes–no recognition, where they may not respond if they are not sure, may be guided by the sensation of familiarity and guessing, which may fall within the domain of implicit memory.)

Effects on Explicit Memory

Pharmacologic agents act on episodic memory by impeding the acquisition of new information (this is described by some authors as impairment of encoding or the related components of storage or consolidation of the material to be learned or its transfer from STM to LTM).[49,159,224,225] How drugs impair acquisition remains to be elucidated. The effects on learning can be easily demonstrated when looking at the shape of the serial

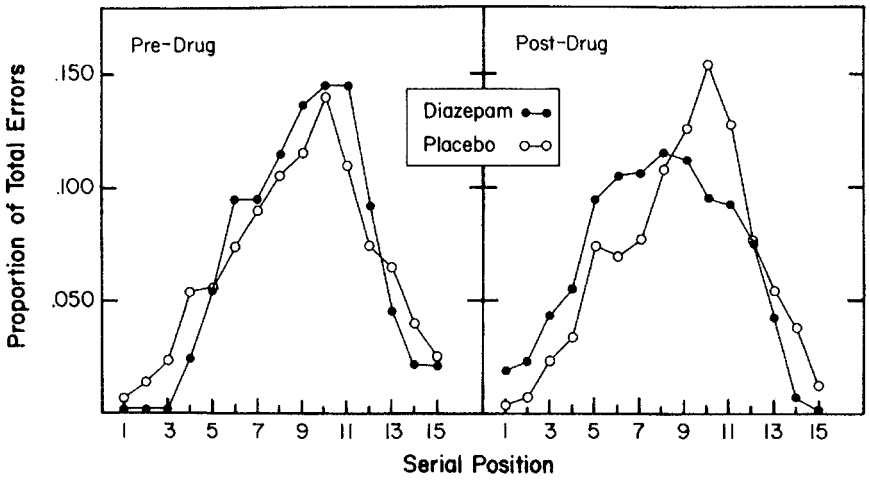

Fig. 15. Relative proportion of errors across serial position in volunteers treated with placebo or diazepam before and after treatment. From Hinrichs *et al.*[226]; used with permission.

position curves of the items being learned.[226] One of the most stable characteristics of human learning is the skewed serial position function observed in serial list learning (*e.g.*, learning a 15-digit sequence over three trials). Under the influence of drugs, the curve becomes perfectly symmetrical (fig. 15). Drugged subjects are forced to rely more on STM (which is not usually impaired) to aid performance, producing an increase in recall of the last few items of the list with the reduced recall from the primary region of the curve, which is obtained from LTM.[226] Sometimes the drug effect may not be manifested by a decrease in number of items learned, but a failure to benefit from previous practice.[95] Therefore, such a performance decrement would be missed if subjects were not repeatedly tested (fig. 12). A performance decrement could also be missed if the subjects are required to attain a specific criterion of learning, thus equating learning between drugged and undrugged subjects. Then, a later recall would be similar for the two groups.

Drugs reduce learning and memory of information presented after their administration (anterograde amnesia) but do not alter retrieval of previously stored material.[159] Indeed, some drugs produce retrograde enhancement of recall of material acquired before the drug intake. The most probable cause for the latter is that drugged subjects learn so little while under the influence of the drug that there is less interference and therefore less forgetting of the material learned before drug administration.[227] Retrieval processes remain intact except with subanesthetic concentrations of general anesthetics.[35,36,117,228]

Semantic Memory

Retrieval of semantic information is generally intact as to be expected from testing preexperimental memory.[3,159] In the common task that assesses semantic fluency, *e.g.*, "list as many animals as you can in 1 min or as many words beginning with the letter T in 1 min," drugged subjects often provide lower correct responses compared with a placebo group. However, impairment of semantic memory can only be inferred with confidence if it can be demonstrated that slowing of performance on the task is not due to drowsiness or psychomotor impairment. Better evidence for impairment of semantic memory is a drug-induced increase in the number of incorrect responses. For example, Curran and Morgan[229] recently reported that habitual abusers of ketamine made semantic errors while performing a category-generation task (*e.g.*, for the category *fruit*: oranges, *juice*, *vitamins*, . . .). Such effects are very uncommon. Remembering and knowing are two subjective states of awareness associated with memory. Tulving[12] proposed that the two states reflect autonoetic and noetic consciousness that respectively characterize episodic and semantic memory systems.[230] When subjects are asked to make remember/know judgments indicating whether they have a specific recollection of the presentation of a word during the study phase (*remember*; recollection-based recognition) or the word seems familiar (*know*; familiarity-based recognition), remember responses are more reduced by drugs as compared with familiarity.[49,231,232]

Dose–Effect Functions

Drugs produce *dose- and time-related decrements* in episodic memory.[95] The impairments are also additive, *e.g.*, taking a benzodiazepine with alcohol[233] or with a subanesthetic concentration of an inhalation anesthetic.[217] *The elderly are more sensitive* to the behavioral effects of drugs, including memory. The cause may be pharmacokinetic (*e.g.*, altered rates of distribution or elimination) or pharmacodynamic (*e.g.*, changes at the receptor or transmitter sites). A third cause is a lower baseline performance of the elderly. Table 11 summarizes the memory changes in healthy older adults.[234–237] These changes may make equal cognitive decrements in the young and the old more noticeable and more serious in the latter. A modest decline in the cognitive abilities of a young person may have little or no effect on that

Table 11. Memory Changes Associated with Aging

Memory performance declines with aging. However, not all aspects of memory are impaired.[234]
There is diminished encoding and retrieval of episodic memories. When retrieval is facilitated by the provision of cues at the time of testing, *e.g.,* recognition tasks, age differences often disappear.[235,236]
Implicit memory is relatively less affected.[237]

person's activities. The same loss in an older individual who is already performing at a lower level or exerting more effort to maintain comparable behavior may have serious objective and clinical consequences.[238] As with other CNS-active drugs, *tolerance and cross-tolerance* to the effects of the drugs may occur. However, although marked tolerance to the sedative and attentional effects of the benzodiazepines occurs with continued administration, only minor tolerance to the memory effects occurs.[149–152] The same pattern has been produced in animals.[239,240] There was also no cross-tolerance for memory impairment between ethanol and benzodiazepines.[233] *State-dependent drug effects* in humans are controversial. Some studies show state dependency,[79,80,228,241] but the majority show asymmetrical state-dependent memory effects or equivocal results at best.[117,242]

Subjective Assessment of Memory Function, Real-life Memory, and Memory for Emotional Events

It is not uncommon for subjects' performance on memory tasks to vary sharply from their own subjective evaluations of their behavior. Patients may not notice or be appropriately concerned about even fairly large impairments in learning and cognitive abilities.[226] In the few studies in which tasks involving "everyday memory" demands were used, impairment was found.[243] It is expected that amnesia for emotionally significant and stressful events, such as those related to surgery, accidents, or crimes, would be less than those for standard presentations of neutral verbal and visual stimuli. Real-life events maybe subject to a greater encoding elaboration because they are likely to be represented in several sensory modalities and/or evoke release of stress hormones during and after emotionally arousing events, which interact with the amygdala complex to modulate the storage of these events.[244] Affective reactions could also take place in the absence of conscious awareness of stimuli.[245] Some drugs may produce selective impairments of cognitive functions. For example, in a series of studies by Cahill *et al.*,[246] propranolol impaired subjects' recall of emotionally arousing but not neutral elements of a story. Using the same task with two patients who had bilateral damage to the amygdala, they found a similar pattern of memory, suggesting that adrenergic function in the amygdala mediates memory for emotional material.

Distortions of Memory

Daniel Schacter[247] recently wrote a fascinating book about the errors and imperfections of normal memory, what he called "the seven sins of memory": transience, absentmindedness, blocking, misattribution, suggestibility, bias, and persistence. The effects of drugs on these normal memory malfunctions have yet to be systematically explored. A recent study by Mintzer and Griffiths[232] found that triazolam, in addition to reducing rates of true recognition of studied words, reduced rates of false recognition to nonstudied words. This was consistent with reports of reduced false-recognition rates in patients with organic amnesic syndromes.[248] It is possible to conclude that false recognition relies on normal memory mechanisms that are impaired in drug-induced and organic amnesias. Some drugs, such as methamphetamine, benzodiazepines, and marijuana, also produce an increase in intrusions, *i.e.*, false recall of words that were not on the presented lists.[249–251] The drugs may impair formation of new associations between distinct items or between an item and its context,[251] may cause irrelevant associations from semantic memory,[250] or, as in the case of stimulant drugs, may lead the subjects to adopt a strategy of little inhibition in their recall, "recalling" every word that occurs to them. Nondrugged subjects typically filter their responses, and some correct responses may be inhibited because of a much stricter confidence criterion.[249]

Disease, Drugs, and Memory

Most studies of the behavioral effects of drugs have been conducted using healthy volunteers, but there may be some differences in drug actions related to the pathology in patients. Several diseases are associated with cognitive deficits that may affect the patients' independence and quality of life. Factors that may influence the level of impairment include the severity of the disease, age at onset, duration, interaction with the effects of aging, and adequate therapeutic interventions preventing and/or controlling further cognitive impairments. Major *depression* is associated with memory impairments. Noradrenergic tricyclic antidepressants and serotonergic drugs may be equally effective in treating the depression, but the improvement of memory performance is significantly greater with the latter type of drugs.[252,253] This is consistent with the literature on serotonergic neurotransmission and memory.[254] In *epilepsy,* declarative memory functions show characteristic patterns of impairment when mediotemporal and associated neocortical structures are affected by lesions, ongoing epileptic activity, or the undesired side effects of drugs or operative treatment. The "new" antiepileptic drugs (*e.g.*, oxcarbazepine, vigabatrim) seem to have no or minor cognitive effects as compared with "older" drugs (*e.g.*, phenytoin, phenobarbital).[255,256]

Cognitive dysfunction, particularly memory loss, is

common in *schizophrenia*.[257,258] Optimal pharmacologic treatment may lead to more effective treatment of the cognitive deficits.[258,259] Newer antipsychotic drugs (*e.g.*, risperidone, olanzapine) ameliorate the cognitive deficits better than conventional agents (*e.g.*, haloperidol, clozapine).[260] *Parkinson disease* is associated with subtle but widespread cognitive impairment. Dopaminergic agents may enhance cognitive functions in some patients and impair them in others, according to the level of dopamine depletion in different parts of the brain. The cognitive changes may also be task specific.[261–263] Patients with *diabetes mellitus* may have cognitive deficits including those of memory. Although the peripheral neuropathy is widely known, involvement of the CNS is much less recognized in diabetes.[264–267] Bent *et al.*[268] recently compared three groups of subjects, insulin-dependent diabetics, non–insulin-dependent diabetics, and a control group, using a battery of cognitive tasks including memory tests. The diabetic patients (combined together) scored at a lower level than the control group, but most of the impairment occurred in the non–insulin-dependent diabetics (particularly those controlled by oral hypoglycemic drugs), perhaps emphasizing the need for effective management of the disease or a deleterious effect of the latter drugs.

Two other endocrine dysfunctions and therapies are associated with cognitive disturbances. In Cushing syndrome, hypersecretion of *cortisol* is associated with a high incidence of impairment of memory, hippocampal atrophy, and depression. Pharmacologic use of glucocorticoids is similarly productive of mood change and memory deficit. Reduction of glucocorticoid concentrations, either through discontinuation of steroid treatment or through use of agents that block glucocorticoid synthesis, ameliorates the adverse behavioral effects.[269] *Estrogens* have been used to treat some menopausal symptoms such as hot flashes as well as osteoporosis. Studies suggest some beneficial effects on learning and memory in postmenopausal women, although clinical trials in dementias have not been successful.[270–272] On the other hand, the use of luteinizing hormone-releasing hormone analogs to treat patients with carcinoma of the prostate has been associated with impaired memory.[273]

Patients with *anxiety disorders* may show reductions in cognitive and psychomotor functions. Adequate therapeutic interventions may cause improvements in performance,[274,275] contrary to the effects observed in healthy subjects given same drugs.[276] However, other investigators found the same effects of drugs in patients and healthy volunteers, with two exceptions. First, the anxiolytic effects of drugs were easily perceived by the patients but have rarely been reported in healthy volunteers. This dimension of feeling is probably too stable in healthy subjects to be affected by these drugs. The second difference was the slower rate of learning to perform the various behavioral tasks by the patients. This necessitates longer practice sessions than those used for healthy volunteers to achieve a stable performance before drug administration.[277,278] The recent discovery of metabotropic glutamate receptors, which modulate the function of the glutamatergic system, offers an additional avenue for development of a new generation of anxiolytics free from cognitive side effects.[279] Also, the discovery that α_2-$GABA_A$ receptors mediate anxiolysis, whereas α_1-$GABA_A$ receptors mediate sedation and amnesia, may fulfill the same promise.[280]

Sleep difficulties affect approximately one third of adults. Untreated sleep disturbances are associated with increased risk for the development of psychiatric disorders (specifically major depression), memory impairment, reduced work performance, increased rate of accidents, and a compromised quality of life.[281,282] Treatment with benzodiazepines may also lead to memory impairment and residual sleepiness affecting daytime performance.[283] Zaleplon, a novel nonbenzodiazepine drug, is rapidly eliminated from the body and does not produce cognitive impairment or residual sedation the next day.[284,285] In addition, it does not produce rebound effects.[286] It is almost unique in these respects.[281]

Memory Function in the Perianesthetic and Perisurgical Periods

The gradual *loss of STM and LTM memory* with an increase in anesthetic dose until loss of consciousness is achieved has been described above.[206] However, 0.1–0.2% of patients in general surgical cases (with potentially higher numbers during cardiac, obstetric, and trauma surgical procedures) may recall intraoperative memories or experience what is referred to in the anesthesia literature as *awareness*.[287] It is mostly caused by too-light anesthesia, particularly when muscle relaxants are used. Its most feared sequela is posttraumatic stress disorder.[288] *Implicit memory* for events during general anesthesia may occur in a few patients, only some of the time and particularly after light levels of anesthesia. Learning may be more perceptual than engaging in elaborate processing of information, and it may be more evident if patients are tested soon after the end of surgery.[289]

Memory Impairment during Postoperative Recovery. Memory impairment *in the early recovery phase* after general anesthesia is common. In a recent study by Rundshagen *et al.*,[290] 53% of the patients did not recall this period when they were asked 24 h later. Hence, giving written instructions and information to escorts of patients returning home on the same day of surgery is important. The results of memory and cognitive tests usually return to the preoperative values approximately 1–4 days after surgery.[291–293] In addition to the variable sensitivities of the tests, it is possible that some patients, even while experiencing severe fatigue or aftereffects of sedation, may muster sufficient resources

to perform satisfactorily for short periods.[294] Also, individual variation in recovery is often masked when results are expressed in terms of group means.[295] There are anecdotal reports of patients reporting forgetfulness or inability to concentrate for several days after general anesthesia. These *residual impairments* may be due to the residual effects of the anesthetics or increased metabolic demands induced by the endocrine responses to surgery.[296,297] Patients who are admitted to an *intensive care unit* may experience memory problems while there. They frequently have little or no recall of their stay in the unit and may remember only nightmares, hallucinations, or paranoid delusions. Some of the contributing factors are the illness and treatment with sedative–hypnotics that may impair memory as well as the physical constraints, the social isolation, and the life-threatening nature of the illness, which may lead to the hallucinations and delusions.[298]

Transient global amnesia (TGA) has been reported in few cases after general anesthesia.[299,300] Patients with TGA have sudden onset of severe memory impairment, including both anterograde and retrograde amnesia, which lasts 2–12 h. Clinical examination during TGA shows a relatively isolated amnesic syndrome with an otherwise normal neurologic examination. TGA generally occurs in persons aged older than 50 yr and resolves spontaneously after several hours. After the attacks, patients remain unable to recall the period of TGA, and they occasionally exhibit a period of permanent retrograde amnesia before the onset of TGA. Kritchevsky *et al.*[301] studied 11 patients with TGA. During the episode, the patients had severe anterograde amnesia for verbal and nonverbal material and retrograde amnesia that typically covered at least two decades.

Prolonged Postoperative Problems. Psychological distress may become apparent 2–3 months after surgery as a result of factors such as slower-than-anticipated recovery and progression of disease.[302] Patients may report more memory problems during this period, which may reflect general psychological distress more than actual deficits in memory performance.[302,303] It is not uncommon for subjective evaluations and objective measures of memory to show poor association.[304] CNS *complications of cardiac surgery* have been the subject of considerable research.[305] Cognitive impairment is common, affecting as many as 80% of patients a few days after surgery and persisting in one third. Millar *et al.*[306] stress the importance of a patient's preexisting cognitive and emotional states, in addition to age and other factors, for increasing the risk of an adverse outcome. Pharmacologic neuroprotection may, in the future, offer an improved outcome.[307]

Electroconvulsive therapy is effective in the treatment of patients with depression, bipolar disorders, schizophrenia, and catatonia.[308] Adverse effects on memory are the most common side effects and are the most distressing to many patients.[309] Owing to a combination of anterograde and retrograde effects, many patients may manifest persistent loss of memory for some events that transpired in the interval starting several months before and extending to several weeks after the electroconvulsive course. Some patients experience persistent amnesia extending several years before electroconvulsive treatments. Profound and persistent retrograde amnesia may be more likely in patients with preexisting neurologic impairment and patients who receive large numbers of treatments, using methods that accentuate short-term cognitive side effects (*e.g.*, sine wave stimulation, bilateral electrode placement, high electrical stimulus intensity).[310] The deficits in memory are largely restricted to episodic declarative memory and involve consolidation and retrieval processes.[311]

Drugs of Abuse

There is evidence that compulsion to repetitive drug intake and its persistence are based on a pathologic usurpation of molecular mechanisms that are normally involved in learning and memory.[312–314] Progress in understanding these mechanisms may lead to more effective therapies for addiction than are currently present. The drugs have detrimental effects on memory and cognition. Although the short-term effects are similar to those of other drugs,[225,229,315,316] studies of their long-term effects have yielded inconsistent findings.[40] Some studies have found deficits in memory, attention, abstraction, decision making, and visuospatial abilities.[317–325] Others failed to find deficits in some of the same functions, and a few studies of stimulant abusers (cocaine and amphetamine) even suggested improved performance.[326–328] Methodologic flaws account for many of these inconsistencies, as explained in the section on design of experiments. However, the evidence is persuasive that long-term regular recreational use of some drugs may be associated with persistent impairment of memory and cognition and may not be reversed by prolonged abstinence, which is an important and worrisome concern. Also, the concomitant use of more than one drug may have additive negative effects.[40,229,318,329–332]

Developmental Memory Deficits

Some drugs administered to fetuses and infants may induce apoptotic neurodegeneration in the developing brain and persistent learning and memory deficits. The period of peak brain growth occurs in humans between the last month of gestation and first 6 months after birth.[333,334] Ethanol; marijuana; phenobarbital; phenytoin; nitrous oxide; a combination of midazolam, nitrous oxide, and isoflurane; and other drugs that block *N*-methyl-D-aspartate receptors or hyperactivate $GABA_A$ receptors may be neurotoxic in young animals.[335–338] Other than the effects of alcohol,[339] the neurobehavioral disturbances produced by other drugs must be evaluated

in humans. Perhaps the technology of brain imaging can be adapted to infants to study human development. Subtle changes in learning and memory in the absence of dysmorphogenic effects may be easily overlooked.[334] Significant brain development also occurs during adolescence.[340] Changes in cerebral blood flow and metabolic rate are associated with increases in myelinization and decreases in gray matter, which reflect maturation and remodeling of the brain.[341,342] Effects of drugs during this period may be due to direct neurotoxicity or indirect hormonal changes. Wilson *et al.*[343] found significant effects correlating the age of first use of marijuana to brain morphology. Subjects who started using marijuana early (before the age of 17 yr) had a smaller percent of cortical gray matter and increased white matter compared with subjects who started later. Animal data also showed greater histologic changes in peripubertal animals *versus* young adults exposed to cannabinoids.[344]

Effects of Drugs in a Hyperbaric Environment

Nitrogen narcosis (euphoria and cognitive and motor dysfunctions) may be precipitated when compressed air is breathed by a scuba diver. Narcosis may occur at depths of 66 ft of water (3 atm) or greater and significantly increase the risks of the underwater environment.[345] Depth results in a significant impairment of memory, which contributes to the dangers of diving.[346] Drugs taken by some divers to combat nausea and vomiting, *e.g.*, scopolamine and dimenhydrinate, may add to the cognitive impairments of diving.[347] It is sound advice that people avoid all drugs, particularly psychoactive drugs, before diving.

Drugs and Neuroanatomy of Memory

Two main areas of the brain that play important roles in pathologic dysfunctions of memory, the medial temporal lobes and frontal lobes, have been recognized. Damage to each one of these areas produces its characteristic profile of memory deficits. The medial temporal lobe memory system refers to the hippocampal formation together with the adjacent perirhinal and parahippocampal cortices.[348] It is necessary for establishing long-term explicit or declarative memory, which can be assessed by tests of recall and recognition. The frontal lobes are essential for STM or working memory and when accurate memory depends on organization, search, selection, and verification in the retrieval of stored information. Damage to the frontal cortex does not typically involve recollection *per se* unless some organizational component is needed to facilitate performance.[349] Frontal lobe–sensitive tests include the Wisconsin Card Sorting Test, the Stroop test, tests for confabulation,[350] word fluency tests, and tests for source memory.[351] Generally, the effects of drugs on memory result from functional disruption of the medial temporal lobe system. Frontal lobe involvement may be restricted to a few drugs, such as ketamine.[63]

Memory-enhancing Drugs

As the world population ages, the incidence and prevalence of various dementias (Alzheimer disease, multiinfarct dementia, senile dementia, and others) will increase in the absence of effective treatments for alleviating symptoms and preventing progression of these ailments. Successful drugs should have a great impact on individuals, their families, and society. A cure for established symptomatic disease may not be feasible because of the apparent irreversibility of cerebral lesions, but prevention and slowing or arresting the progress of the disease are reasonable goals. This highlights the importance of current attempts to define the criteria for assessment of memory associated with mild cognitive impairment,[352] a stage of cognitive dysfunction beyond normal aging (people who are more forgetful than they ought to be for their age and education) but of insufficient magnitude to qualify for the diagnosis of clinically probable Alzheimer disease. Several studies have shown that subjects diagnosed as having mild cognitive impairment progress to Alzheimer disease at a much higher rate than age-matched controls.[353] This stage of cognitive impairment is becoming an important target for potential therapeutic intervention and has recently been approved by the U.S. Food and Drug Administration for clinical treatments.

Cholinesterase inhibitors (*e.g.*, donepezil, rivastigmine, galantamine) are the first line of treatment of Alzheimer disease and the only drugs of proven benefit.[354,355] The rationale for their use is based on evidence in patients with Alzheimer disease of deficits in the enzymes responsible for synthesis of acetylcholine in postmortem studies,[356] loss of cholinergic projection neurons in other autopsies,[357] and declines of cerebral acetylcholinesterase activity in imaging studies *in vivo*.[358] Unfortunately, the effects of cholinesterase inhibitors are modest, and the disease eventually progresses despite treatment. There is some preliminary evidence that antioxidant therapy, specifically with vitamin E or selegiline, may delay the time to clinical worsening of the disease. The strategy is based on evidence for increased oxidative stress and free radical injury in the Alzheimer diseased brain.[354,355] Despite the publications of some epidemiologic studies that suggest associations between the use of antiinflammatory drugs (nonsteroidal antiinflammatory agents and prednisone) or estrogen with a lower incidence of Alzheimer disease, clinical trials have not shown any beneficial effects.[270,271,359,360]

The amyloid hypothesis of Alzheimer disease holds that cerebral deposition of insoluble β-amyloid peptide is critical for the pathogenesis of the disease.[361] Agents

that interfere with β-amyloid production or aggregation are therefore being developed. Such drugs theoretically could reduce β-amyloid burden and may confer protection against the development of the disease.[355,360] The fate of the β-amyloid protein is determined by the actions of secretases that cleave it into different fragments. Several researchers demonstrated that immunization with amyloid peptide in transgenic mice prevented cognitive dysfunction.[362–364] These significant advances in knowledge about the disease at the molecular level remain to be translated into effective therapies in humans. Other new strategies include the use of glutamatergic agonists and serotonergic antagonists based on the hypothesis that synaptic transmission at cortical neurons represents a balance between cholinergic, glutamatergic, and serotonergic influences. New findings indicate that treatment with lipid-lowering drugs may also be associated with a reduced risk for the disease.[365–368]

Novel drugs are also being developed based on the molecular changes that occur at memory-related synapses. Encoding involves activation of α-amino-3-hyroxy-5-methyl-4 isoxazole propionic acid (AMPA)–type glutamate receptors, which then depolarize the postsynaptic region and unblock *N*-methyl-D-aspartate–type glutamate receptors.[369] Consolidation involves new protein synthesis. The CREB (cAMP–response element binding proteins, which switch on and off the genes needed to form LTM) family of transcription factors are important for the gene signaling.[370] Biotechnology companies are introducing compounds that modulate the AMPA compounds, with preliminary encouraging results.[353] If these new pharmacologic agents and others prove to be devoid of serious adverse effects, they may also be used for treatment of the normal decline of memory produced by aging. Pardridge[371] recently drew attention to the fact that the majority of newly developed drugs do not cross the blood–brain barrier. If progress with development of new drugs for the brain is to keep pace with progress in the molecular neurosciences, drug-delivery strategies based on endogenous blood–brain barrier transport systems must be explored.

Conclusions

Memory is a critical mental function. The history of drug effects on memory is as old as the history of its systematic study. There are three aims for studying the psychopharmacology of memory: evaluating drugs, modeling memory deficits in pathologic disorders, and contributing to a comprehensive account of memory.

Memory tests should be theoretically driven rather than components of a fixed battery of neuropsychologic tests. A memory experiment usually has three stages: a study phase, a retention interval, and a test phase. We propose a battery of tests that may include tests for working memory, episodic LTM, semantic LTM, and implicit memory. We favor free recall and recognition tests for episodic memory and a priming task for implicit memory. The contents of the battery can be changed to fit the aims of a specific investigation. It is important when investigating memory-impairing drugs to separate the effects on memory from impairments in attention, arousal, or mood. It is also important to separate the effects on memory from enhancement of alertness and attention, and decreased fatigue when investigating memory-enhancing drugs. The accepted standard for the design of an experiment is the randomized, prospective, concurrent assignments of subjects to the drug and placebo groups under double-blind conditions. Two comparison groups are usually necessary: pretreatment and posttreatment, and experimental and control groups. In the study of drug abusers, measurement of premorbid cognitive function, inclusion of a control group, and use of a large sample size are necessary.

Two major techniques, PET and fMRI, are used for functional neuroimaging. However, an explosion of new methods that promise to improve temporal and spatial resolutions and allow studies of the brain from infancy to old age are on the horizon. It is possible to identify the neural networks serving each memory function by combining the anatomic model and interregional correlations. A fundamental change from localizing memories in specific areas to viewing memory as distributed cortical networks that support specific mnemonic processes is rapidly evolving.

A wide variety of drugs impair memory. The amnesia is independent of sedation. In general, drugs produce a similar profile of memory impairment. They impair acquisition. With the exception of general anesthetics, they do not impair STM. They produce anterograde but not retrograde amnesia. Retrieval processes remain intact except with subanesthetic concentrations of general anesthetics. Drugs usually do not impair semantic memory, automatic processes, or learning of skills and procedures. Impairment of implicit memory is less than that of explicit memory. Amnesia for emotionally significant and stressful events is also less than that for neutral stimuli. Amnesia is dose and time related. Impairments are additive with those produced by other drugs, and the elderly are more impaired. Tolerance and cross-tolerance may be less for memory than for the other behavioral effects. Much remains to be investigated. For example, the specific encoding operations that are involved in drug impairments must be elucidated. Dose–response curves for drugs acting at different receptors and through different neurotransmitters or on different forms of memory may provide valuable insight into this vital behavior. Factors that contribute to altered sensitivity to drug effects are largely unknown. The question of possible irreversibility of memory and cognitive prob-

lems associated with long-term abuse of some drugs must be answered.

Development of memory-enhancing drugs is of great concern to a progressively aging population. Attempts to diagnose mild cognitive impairment before progression to an established disease are also equally important. Several new strategies for drug development seem to be promising. These include the use of glutamatergic agonists, serotonergic antagonists, and new pharmacologic agents of exquisite selectivity involved in the molecular changes that occur at the memory-related synapses. Development of strategies for breaching the blood–brain barrier will ensure the delivery of these drugs to their desired sites. All of these developments promise rapid advances in the therapeutics of memory and are important contributions to its understanding.

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