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?
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 memory5 (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 Pavlov7 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-
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 developed 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. In the late 1960s, Atkinson and Shiffrin 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 non-meaningful 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 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. Tulving 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 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 implicit 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). 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 proposed an alternative to the STM store, using the term working memory. It consists of three components capable of both
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. 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 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 components of memory, up to the time of the establishment of stable LTM.

Eric Kandel, the American neurobiologist, 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). John Snow 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 and acetylene. 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 (1932) and Marshall (1937) advocated the use of nitrous oxide to study the psychology of memory. Steinberg et al. 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 information.
tion 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. and Hardy and Wakely in the 1960s on the amnesic properties of different premedications, 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. 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 (1959), Wolfe and Millett (1960), and Levinson (1965) in anesthetized patients preceded the reports of what we now know as implicit memory by Warrington and Weiskrantz (1968) and Milner et al. (1968) in amnesic patients and the distinction between implicit and explicit memory (1985). (For reviews, see Ghoneim. 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 and Curran.) 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. 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. Such impairments may also cause legal difficulties arising from not recalling one’s actions. 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.

Treatment with N-methyl-D-aspartate receptor antagonists, e.g., ketamine, produce cognitive and behavioral dysfunction similar to those of psychosis and dissociative disorders. 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 networking and organizational 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. 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

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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. 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-

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

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

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**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.**

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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.\(^2\),\(^6\),\(^7\),\(^8\) 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\(^6\),\(^9\)--\(^7\) 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,\(^7\) 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.\(^7\) For example, the more deeply or meaningfully information is processed, the more well retained it will be.\(^7\) 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.\(^7\)

**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.\(^{81,82}\)

### 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.\(^{5}\)

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**

<table>
<thead>
<tr>
<th>Task</th>
<th>Memory Type</th>
<th>Condensed Description</th>
<th>Stimulus</th>
<th>Response</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Digit span</td>
<td>STM (phonologic loop)</td>
<td>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.</td>
<td>Sequence of digits</td>
<td>Recall the digits in the same order</td>
<td>Maximum sequence length that can be correctly recalled</td>
</tr>
<tr>
<td>Spatial location span</td>
<td>STM (visuospatial sketch pad)</td>
<td>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.</td>
<td>Blackened cells</td>
<td>No. of blackened cells correctly reproduced</td>
<td>Maximum number of cells correctly reproduced</td>
</tr>
<tr>
<td>Multiple-trial free recall</td>
<td>Verbal learning</td>
<td>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.</td>
<td>Words</td>
<td>Correct words</td>
<td>No. of correct words recalled per trial</td>
</tr>
<tr>
<td>Free recall</td>
<td>Episodic memory (retrieval)</td>
<td>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.</td>
<td>Words</td>
<td>Correct words</td>
<td>No. of correct words recalled</td>
</tr>
<tr>
<td>Recognition</td>
<td>Episodic memory (retrieval)</td>
<td>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.</td>
<td>Words</td>
<td>Recognize old words</td>
<td>No. of old words; problems of guessing or chance success must be addressed</td>
</tr>
<tr>
<td>Category generation</td>
<td>Semantic memory</td>
<td>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.</td>
<td>Category or cue</td>
<td>Items that belong to a category or a cue</td>
<td>Nos. of correct items</td>
</tr>
<tr>
<td>Word completion</td>
<td>Implicit memory (repetition priming)</td>
<td>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.</td>
<td>Words</td>
<td>Completion of word fragments</td>
<td>Degree to which previous exposure to a word helps with its identification</td>
</tr>
<tr>
<td>Constrained associations</td>
<td>Implicit memory (conceptual priming)</td>
<td>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.</td>
<td>Specific categories</td>
<td>Exemplars of each category</td>
<td>Degree to which previous presentation of category exemplars facilitate their citations</td>
</tr>
</tbody>
</table>

STM = short-term memory.
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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. 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, 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. Curran and ourselves 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. 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. 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.

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.
than one correct completion with the asked to complete the word stems where there is more the idea of an incidental recognition tasks, we tell them laboratory, after the subjects perform the recall and are simply instructed to perform a new task (in our they are performing a memory test. Instead, they previous study phase, and subjects are not told that it is maximal when study phase and test stimuli are perceived in the same modality (visual or auditory). Priming is unaffected by modality manipulations. Priming is enhanced. Exemplified by category generation task.

Fig. 7. Characteristics of perceptual versus conceptual priming.

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. 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, 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. 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; 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. Priming may also decrease for visual material when details such as type font or type case are changed between study and test phases. 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
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. An additional method to dissociate explicit and implicit influences on memory performance is to use the process dissociation procedure introduced by Jacoby. 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.

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 conditioning.

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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 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?” or “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. Several 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.

**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. 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.

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2. The tasks may not be adequately related to current models of memory and do not provide complete measures of its functions.
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. 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. 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 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. Performance on the digit span test is not impaired by most drugs but is impaired by dementia and subanesthetic concentrations of inhalation anesthetics.

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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