

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 Learning	Drug State during Recall	
	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 endog-

enous 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

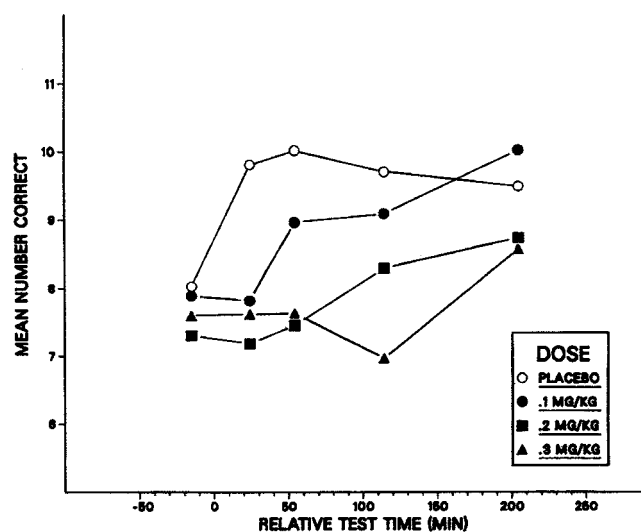


Fig. 10. Mean number of digits recalled at intervals before and after diazepam and placebo treatments. Zero was the time of drug administration. A different random 15-digit number was presented each time. The score represents the mean of three trials. From Ghoneim *et al.*⁹⁵; used with permission.

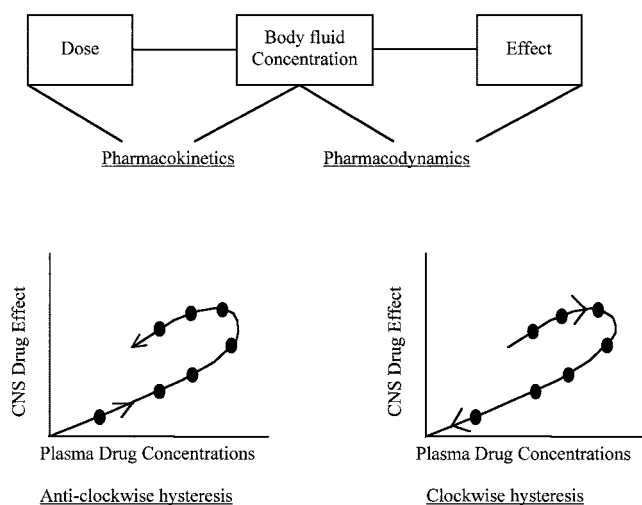


Fig. 11. Definitions of pharmacokinetics and pharmacodynamics and types of hysteresis.

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 per-

formed 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 <i>et al.</i> ¹⁴⁷ (1996), Curran <i>et al.</i> ¹⁴⁸ (1998)
Assess the development of tolerance to sedative and memory effects	Tolerance to sedation develops before tolerance to memory effects.	Ghoneim <i>et al.</i> ¹⁴⁹ (1981), Lucki <i>et al.</i> ¹⁵¹ (1986), Curran <i>et al.</i> ¹⁵⁰ (1994), Tata <i>et al.</i> 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 <i>et al.</i> 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 <i>et al.</i> 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 <i>et al.</i> ¹⁴⁸ (1998), Veselis <i>et al.</i> 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 <i>et al.</i> ¹³⁸ (1997)

From Curran⁴⁹; 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 compartment¹⁴⁶ 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 model¹⁴² 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

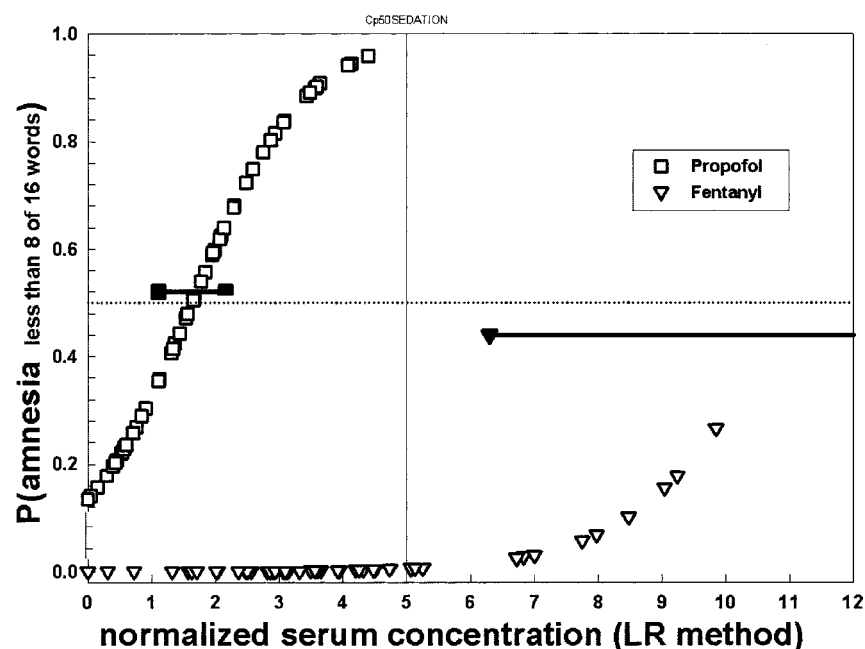


Fig. 12. Probability of amnesia being present as a function of normalized serum concentration using a logistic regression (LR) model. Amnesia is defined as recognition of fewer than half of the words presented. Confidence intervals for $Cp50_{AMN}$ are given as horizontal bold lines for each drug. The 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 patients¹⁵⁰ 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 flumazenil¹⁵³ or pretreatment with flumazenil before administration of a benzodiazepine¹⁵⁴ 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 equiseda-

tive 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 animals¹⁶¹⁻¹⁶³ 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 laboratory¹⁷¹ 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 regard-

ing 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

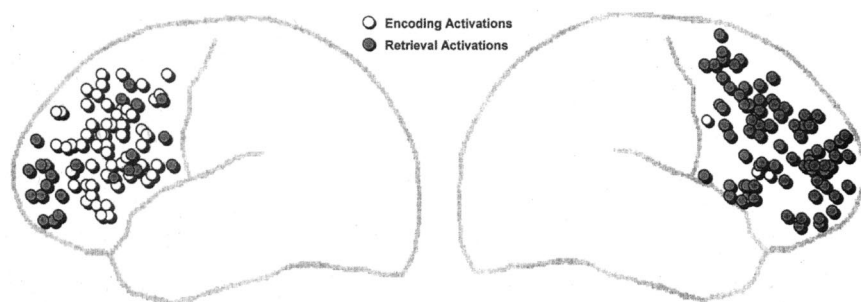


Fig. 13. Hemispheric asymmetrical involvement of left and right prefrontal cortex during episodic encoding and episodic retrieval. From Nyberg and Cabeza¹⁷³; used with permission.

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

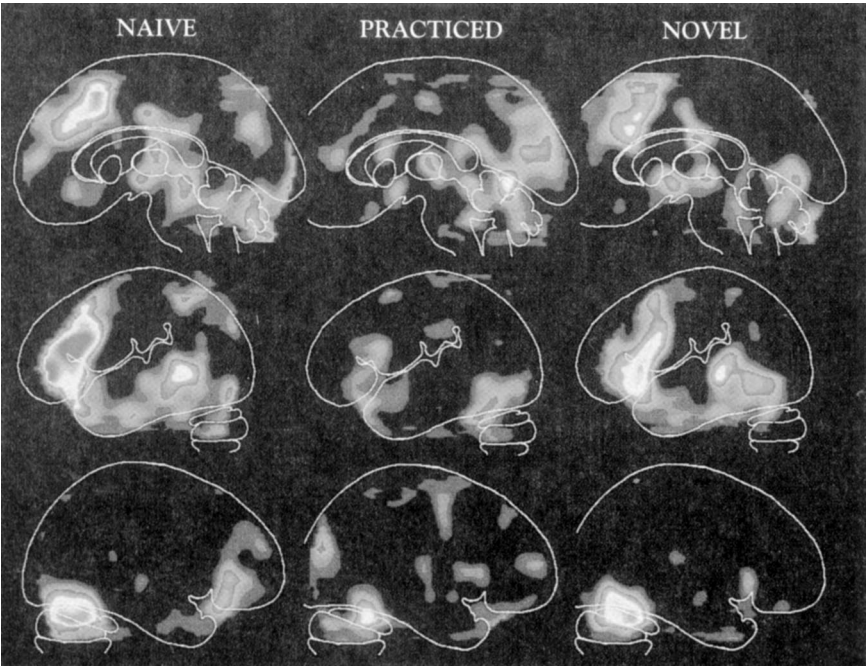
Tulving *et al.*¹⁸⁰ proposed the hemispheric encoding/retrieval asymmetry model. According to this model, the prefrontal regions in the left hemisphere tend to be differentially activated during episodic encoding and semantic retrieval, whereas the right prefrontal regions tend to be differentially involved 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 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 Raichle¹⁹⁶; 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 Cabeza¹⁷³; 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 Warburton²⁰⁸ 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 Ehling²⁰⁹ 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

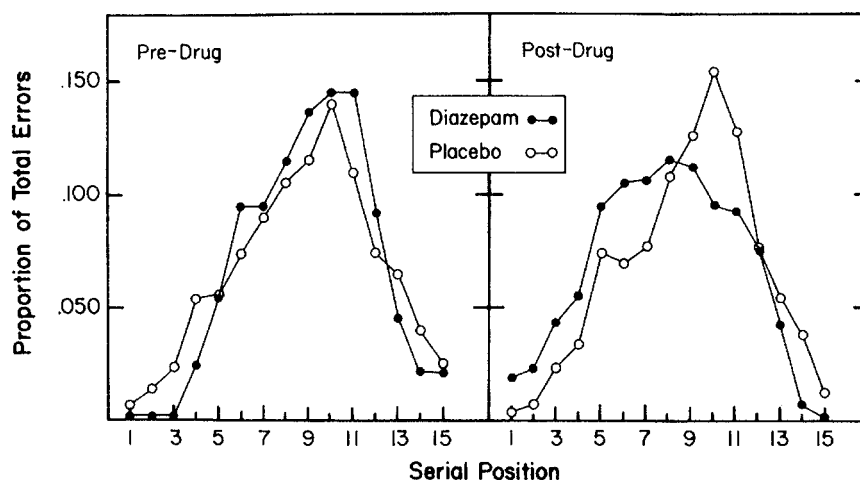
Effects on Explicit versus Implicit Memory

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 Morgan²²⁹ 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. Tulving¹² proposed that the two states reflect autoecic 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 alcohol²³³ 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 may be 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 Schacter²⁴⁷ 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 Griffiths²³² 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, vigabatrin) 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 myelination 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, multi-infarct 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-hydroxy-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. Pardridge³⁷¹ 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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