Available online at www.sciencedirect.com
SCIENCE DIRECT®
Neurobiology of Learning and Memory 82 (2004) 230–242
Neurobiology of Learning and Memory
www.elsevier.com/locate/ynlme

Minireview

Coordination of multiple memory systems☆

Paul E. Gold*

Departments of Psychology and Psychiatry, Neuroscience Program and the Initiative on Aging, University of Illinois, Urbana-Champaign, IL 61820, USA

Received 1 July 2004; revised 8 July 2004; accepted 14 July 2004
Available online 11 September 2004

Abstract

On the basis of lesions of different brain areas, several neural systems appear to be important for processing information regarding different types of learning and memory. This paper examines the development of pharmacological and neurochemical approaches to multiple memory systems from past studies of modulation of memory formation. The findings suggest that peripheral neuroendocrine mechanisms that regulate memory processing may target their actions toward those neural systems most engaged in the processing of learning and memory. In addition, measurements of acetylcholine release in different memory systems reveals extensive interactions between memory systems, some cooperative and some competitive. These results imply that many neural systems, often characterized as relatively independent, may in fact interact extensively, blurring the dependencies of different memory tasks on specific neural systems.

Keywords: Memory systems; Interactions; Place learning; Spatial learning; Response learning; Strategy selection; Striatum; Hippocampus; Amygdala; Conditioned cue preference learning; Acetylcholine

1. Introduction

Research on memory in rodents has identified multiple memory processing systems by showing multiple dissociations of brain area by task, i.e., by showing that damage to one brain area impaired learning and memory for one task but not another, while damage to a second brain area impaired learning for the second but not the first task (e.g., Bussey, Muir, Everitt, & Robbins, 1997; Kesner, Bolland, & Dakis, 1993; McDonald & White, 1993), as reviewed in detail in many of the papers in this journal issue.

A second stage of this research came from the rather surprising findings that damage to some neural systems improved learning of tasks impaired by lesions of other brain areas. It is interesting to note that some of these experiments appeared well before the idea of multiple memory systems was established. For example, Isaacson, Douglas, and Moore (1961) found that lesions of the hippocampus enhanced active avoidance learning. These experiments were followed by others showing facilitation of learning in go/no-go tasks (e.g., Means, Walker, & Isaacson, 1970; Eichenbaum, Fagan, & Mathews, 1988). Most explanations for these unexpected results were based on non-mnemonic ideas. For example, increased locomotor activity might explain the enhanced learning evident in two-way active avoidance tasks after damage to the hippocampal formation. These findings received considerable attention (e.g., Zola & Mahut, 1973), largely because they seemed incompatible with a central role for the hippocampus in memory formation supported by studies of patients

☆ Supported by NIA (AG 07648), NINDS (NS 32914), USDA (00-35200-9839), and NIDA (DA 016951), the Alzheimer's Association, the University of Illinois Initiative on Aging and Office of the Vice-Chancellor for Research.
* Fax: +1 217 244 5876.
E-mail address: pgold@uiuc.edu.

1074-7427/$ - see front matter © 2004 Elsevier Inc. All rights reserved.
doi:10.1016/j.nlm.2004.07.003

with hippocampal damage (cf. Cohen, 1984; Squire, 1987). Initially, however, these examples of enhanced learning did not lead directly toward discussions of how independent learning and memory systems interact in a manner often characterized as competitive, as revealed during recall (cf. Gold, 2003; White & McDonald, 2002).

More recent findings showing that some brain damage can enhance learning have been viewed very differently. A key example is that, while lesions of the amygdala impair conditioned place preference learning, lesions of the hippocampal formation, i.e., of the fimbria–fornix or ventral hippocampus, facilitate conditioned place preference learning (Ferbinteanu & McDonald, 2001; McDonald & White, 1995). Similarly, rats with hippocampal lesions perform better than do non-lesioned rats on some tasks readily impaired by lesions of the dorsal striatum (Matthews & Best, 1995). In current formulations, these findings suggest that processing between different neural systems may compete for control over learning (Gold, 2003; Packard & Knowlton, 2002; White & McDonald, 2002). To the extent that competition is eliminated or reduced, i.e., by removing a system not associated with the task or by pharmacologically decreasing the contributions of a system, learning is enhanced.

For example, recent experiments examined the effects of lidocaine injections into the hippocampus and striatum while rats were trained on spatial or response versions of appetitive 4-arm mazes. In one experiment (Chang & Gold, 2003a), rats were trained to find food at the end of an arm either when start arms were varied and the goal was always in the same location of the room (place version), or when start arms were varied and the goal was always to the right (or left) of the starting location (response version). As shown in Fig. 1, when lidocaine was injected in the hippocampus, rats were severely impaired at acquiring the place version of the maze. However, lidocaine injections into the hippocampus facilitated learning the response version of the maze. These findings are similar to those obtained on similar tasks using bipuvicaine to induce reversible inactivation of the hippocampus (Schroeder, Wingard, & Packard, 2002), and suggest that the intact hippocampus is activated during training to attempt, unsuccessfully, to solve the maze using place strategies. When the hippocampus is inactivated, the unsuccessful learning strategy is removed, permitting a successful, perhaps striatal, response solution to emerge more quickly during training.

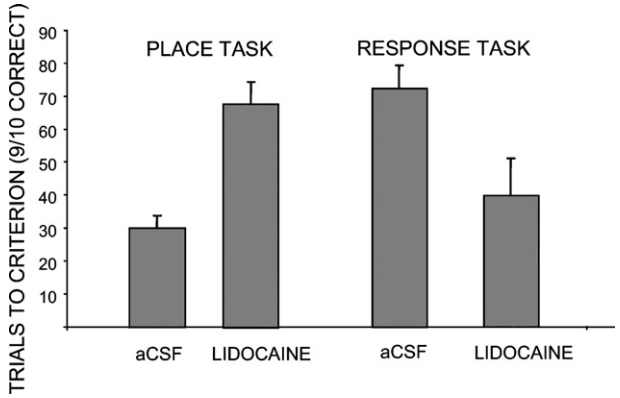

Fig. 1. Effects of lidocaine injections into the hippocampus on place and response learning in a 4-arm radial maze. Note that intrahippocampal injections of lidocaine impaired the rate of acquisition for the place task but enhanced the rate of acquisition in the response task. From Chang and Gold (2003a).

In viewing the interactions of neural systems involved in memory, one conclusion is that there are critical interactions between these systems that will determine, at least in part, the time it takes to learn a task. Moreover, these interactions may determine the content and the strength of particular memories. In studies using lesions of memory systems, the contribution of a neural area to memory is of course decreased from its normal proportional participation in memory processing to a value of zero. For example, if a rat is trained in a maze, there may be many cognitive strategies the rat might employ to learn the most efficient way to navigate the maze. The enhancement of learning seen when a brain area is damaged suggests that a neural system that contributes an efficient mode of learning is 'released' from competition by a system that contributes a less efficient mode of learning. Which system is most efficient will differ in different tasks.

A complication to the interpretation of studies of interactions between neural systems arises if the brain can successfully compensate for loss of a neural system. For example, Chang and Gold (2004) found that lidocaine injections into the striatum impair acquisition of response learning, as in the task above, but only in cue-deficient conditions. When typical room cues were available, rats learned to turn right or left to find food without evident impairments. However, when room cues were reduced, e.g., in a cue-poor room or in dim light, injections of lidocaine directly into the striatum significantly impaired learning. These findings suggest that alternate strategies, such as conditional discrimination learning, might be sufficient to support learning in this task using neural systems other than the striatum, thereby obscuring the contribution of the striatum to learning. Evidence for compensatory functions such as these reveals a limitation to the use of lesions to explore the relative contributions of different neural systems to learning and memory. Izquierdo and Medina (1998) have provided an excellent discussion of these issues.

A third level of analysis, derived heavily from lesion studies of multiple memory systems, involves examination of neurochemical changes in brain profiles associated with activation levels across memory systems.

These neurochemical changes appear to modulate the relative participation of the systems to learning and memory. Much of this research has involved measurement of acetylcholine (ACh) release in different neural systems during learning and memory testing and measurements of dynamic fluctuations in extracellular brain glucose concentrations during learning. These findings have led to observations of independence, competition, and cooperation of neural systems while the systems are intact. Before turning to the neurochemical experiments, this paper will proceed with a more general review of modulation of memory by many treatments, thereby providing a context for the findings of the neurochemical experiments presented later.

1.1. Modulation of memory: systemic injections, central effects

In contrast to the ability to use lesions and direct inactivation of neural systems to dissect cognitive attributes, the effects seen with systemic drugs often extend across many tasks and apparent cognitive domains (Gold, 1995). These findings lead to an interesting apparent paradox. If a single memory system is responsible for all of these tasks, the interpretation would be that the drugs act on that system to enhance memory in many tasks. However, in considering multiple memory systems that interact and often compete with each other, a systemic treatment might be expected to augment the processing of many systems including those that would have a positive relationship and those with a negative relationship with learning of the particular task employed. Yet most, if not all, systemic treatments that enhance or impair memory do both for many tasks; they do not enhance memory for one task and impair memory for another. Note that this situation is very different from findings showing that pharmacological modulation of different neural systems with direct brain injections can enhance or impair memory for different tasks that are generally consistent with evolving views of multiple memory systems.

Recent findings obtained with measurements of extracellular glucose during training offer a beginning toward reconciling the different task sensitivities seen with systemic and central drug treatments. Before describing those studies, it is useful first to examine the findings that led to them.

Much of the early research on memory consolidation was devoted toward identifying the time necessary for memory to be formed (cf. Cherkin, 1969; Dawson & McGaugh, 1971; Gold & McGaugh, 1975; McGaugh, 1966). By the early 1970s, however, it became clear that there was no single retrograde amnesia or retrograde enhancement gradient. Some of the key variables that led to multiple retrograde amnesia and retrograde enhancement gradients—tasks, time of day, species, strains of mice and rats—could readily be incorporated into memory consolidation theories. However, other findings indicated that retrograde amnesia gradients, as well as short-term memory decay curves, could extend from seconds to hours or even days when a treatment was administered at different intensities or doses. Findings consistent with this view were seen with electrical stimulation of the brain as well as with many drug treatments, including those impairing particular neurotransmitter functions and those interfering with protein synthesis.

The variable gradients led to a conclusion that, while memories take time to stabilize, the effects of these many treatments on memory did not reveal the time course of memory formation (Gold & McGaugh, 1975). The findings led to the consideration of this issue: If the temporal properties of memory formation are not assessed with these methods and designs, why do memories remain susceptible to modification in a time-dependent manner after an experience? One explanation for the phenomenon of retrograde effects on memory is that memories for new experiences might remain sensitive to post-experiential modifications so that endogenous modulators, such as hormones, responding to an experience could regulate the formation of new memories, augmenting memory formation for important events and permitting unimportant events to decay with time (cf. Cahill & McGaugh, 1998; Gold, 1992; Gold & McGaugh, 1975).

1.2. Epinephrine modulation of memory

It was thinking like this that led to tests of endogenous factors such as hormonal responses to training as potential modulators of the formation of memory for recent experiences. Studies of the effects of several hormones, most notably epinephrine for the purposes of this review, showed that these treatments could enhance and impair memory when administered or released shortly, but not long, after training. Epinephrine is one of the most reliable enhancers of memory formation, with evidence showing that the hormone can enhance memory not only in rats and mice but also, more recently, in humans. Moreover, with regard to issues of multiple memory systems, it is noteworthy that epinephrine enhances memory for a very wide range of tasks. In rodents, epinephrine enhances memory for inhibitory avoidance, active avoidance, spontaneous alternation, visual discrimination, and one-trial appetitive tasks (Gold & van Buskirk, 1975; Introini-Collison & McGaugh, 1986; Sternberg, Isaacs, Gold, & McGaugh, 1985; Talley, Kahn, Alexander, & Gold, 2000; Torras-Garcia, Costa-Miserachs, Portell-Cortes, & Morgado-Bernal, 1998). In humans, epinephrine also enhances memory for pictorial information presented in slides (Cahill & Alkire, 2003).

1.3. Glucose modulation of memory

Although a robust enhancer of memory processes, epinephrine does not readily enter the brain (Axelrod, Weil-Malherbe, & Tomchick, 1959). Therefore, peripheral actions of the hormone must contribute to the effects on memory. Several lines of evidence suggest that epinephrine may act on vagal afferents to the brain to regulate memory formation (Hassert, Miyashita, & Williams, 2004; Jensen, 2001). Also, considerable evidence suggests that epinephrine acts by increasing blood glucose levels, and that glucose then enters the brain to regulate memory. In addition to observing that systemic administration of glucose, like epinephrine, enhances learning and memory in rats, mice and humans (Gold, 2001), the evidence includes findings that epinephrine does not enhance memory if the increase in blood glucose is blocked (Gold, Vogt, & Hall, 1986; Talley et al., 2000). Moreover, direct injections of glucose into the brain modulate learning and memory and fluctuations in brain extracellular glucose levels decrease during learning and memory tests and these decreases are reversed by systemic glucose injections (cf. McNay & Gold, 2002). Together, the findings support the view that increases in circulating glucose after epinephrine release or administration mediate, at least in part, many of the effects of epinephrine on learning and memory.

Like epinephrine, systemic injections of glucose enhance memory for a remarkably wide range of tasks (Gold, 1995). For example, glucose enhances memory on several, primarily verbal, memory tasks in humans (cf. Benton et al., 2003; Gold, 2001; Korol, 2002; Messier, 2004; Watson & Craft, 2004), and enhances learning and memory in inhibitory and active avoidance and conditioned emotional response tasks (Gold, 1984; Messier & White, 1984, 1987; Pavone, Capone, Battaglia, & Sansone, 1998; Sansone, Battaglia, & Pavone, 2000), operant conditioning tasks (Benton et al., 2003; Messier & Destrade, 1988), visual discrimination and object recognition tasks (Hughes, 2003; Messier, 1997), spontaneous alternation tasks (Ragozzino, Unick, & Gold, 1996; Ragozzino, Pal, Unick, Stefani, & Gold, 1998; Talley et al., 2000), as well as in habituation (Kopf & Baratti, 1996) and extinction (Schroeder & Packard, 2003) tasks.

The breadth of tasks on which glucose enhances learning and memory suggests that the treatment might act on many neural systems that support multiple forms of memory processing. However, in the context of competition between memory systems, up-regulation of many memory systems by a peripherally administered treatment like glucose might be expected to up-regulate at once systems that are positively and negatively associated with a particular task, with results that might cancel each other in terms of learned performance. However, the results are clear in showing that this is not the case. Rather, systemically administered drugs like epinephrine and glucose enhance learning and memory for a broad spectrum of tasks. Epinephrine and glucose are two substances believed to enhance memory endogenously as well, raising the issue of how neural processing in systems apparently appropriate for some types of learning can be selectively enhanced without also enhancing other systems in competition.

Recent findings, described below, suggest that there may be some form of self-targeting of glucose actions toward particular neural systems important for a task at hand. By analogy, perhaps such targeting will be evident with other treatments as well. Several studies have examined the dynamic responses of extracellular glucose in the brain during learning and memory tests. Although it is generally presumed that available brain glucose saturates uptake processes (Lund-Andersen, 1979), more recent findings indicate that extracellular glucose levels in the brain are lower than previously thought and, especially important to understanding how glucose administration might influence brain functions, that the extracellular levels decrease in response to cognitive demand. We and others have coupled in vivo microdialysis with zero-net-flux procedures in which the glucose infused into the dialysis probe is varied to determine the concentration at which the glucose concentration in equals the glucose concentration out. The value at which there is no net transfer of glucose in or out of the brain is taken as the extracellular concentration of glucose. Using such methods, the glucose concentration of the striatum of freely moving rats appears to be between 0.35 and 0.7 mM (Fellows, Boutelle, & Fillenz, 1992; Forsyth et al., 1996; Fray, Boutelle, & Fillenz, 1997; McNay, McCarty, & Gold, 2001) and approximately 1 mM in the hippocampus (McNay & Gold, 1999). Moreover, extracellular glucose in the hippocampus is sensitive to behavioral testing and to systemic injections of glucose at doses that enhance learning and memory. Rats were tested for performance on a spontaneous alternation task on a 4-arm radial maze (McNay, Fries, & Gold, 2000). Consistent with previous findings (Ragozzino et al., 1996), alternation performance was enhanced by a systemic injection of glucose (Fig. 2). The extracellular glucose levels in the hippocampus of these rats obtained during testing are shown in Fig. 3. Note that in the saline and uninjected control rats, extracellular glucose concentrations in the hippocampus decreased by about 30% during testing. Administration of glucose fully blocked the decrease in hippocampal glucose. These glucose measurements were taken during collection of the behavioral data shown in Fig. 2. The depletion of extracellular glucose in the hippocampus during testing appears to reflect cognitive load and not simply movement; rats trained in an easier 3-arm maze travel about the same distance but do not exhibit depletion of hippocampal glucose. Additionally, the results in hippocampus do not passively reflect changes in blood

Fig. 2. Spontaneous alternation scores on a +-shaped maze. Note that injections of glucose (I.P.) enhanced alternation scores. From McNay et al. (2000).

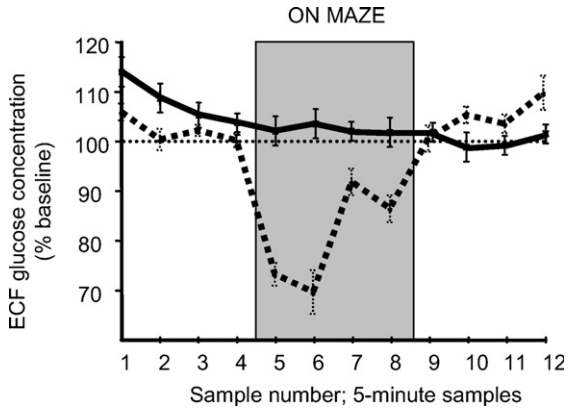

Fig. 4. Microdialysis measurements of extracellular glucose levels in the striatum and hippocampus during alternation testing (no treatment). Note that the glucose levels in the hippocampus (dotted line) but not in the striatum (solid line) declined significantly during maze testing. From McNay et al. (2001).

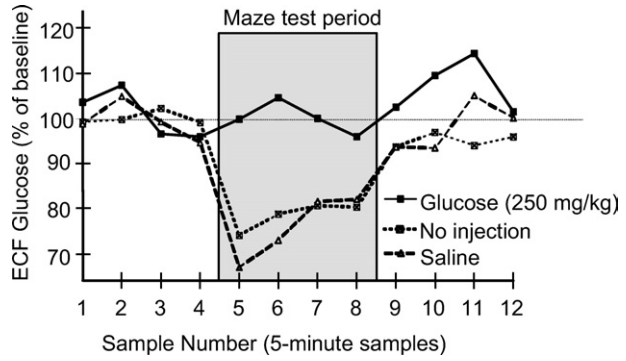

Fig. 3. Microdialysis measurements of glucose in the extracellular fluid of the hippocampus during testing of rats shown in Fig. 2. The groups that received either no injections or saline injections exhibited substantial drops in the extracellular glucose. However, the systemic injections of glucose that enhanced alternation performance blocked the depletion of extracellular glucose in the hippocampus. From McNay et al. (2000).

glucose levels. When blood and brain glucose levels are monitored together, there are several instances in which the levels do not change in parallel.

Moreover, if hippocampal extracellular glucose levels passively followed changes in blood glucose, similar effects would be expected throughout the brain. Excluding this possibility, glucose depletion did not occur in the striatum at the same time that glucose depletion was evident in the hippocampus. These latter results address a point potentially important to issues of multiple memory systems: The effects appear to be specific to brain regions important for the cognitive performance at the time of measurement. In this case, decreases in glucose were seen in the hippocampus but not striatum when rats were tested on a task for which performance is impaired by hippocampal, but not striatal, lesions (Fig. 4).

The significance of these findings for issues relating to multiple memory systems is that activation of particular neural systems needed to acquire and to store different types of information may direct the endogenous or exogenous substances that support memory processing to those brain areas in which the substances are needed. In this particular example, extracellular glucose levels in the hippocampus were depleted when rats performed a task sensitive to hippocampal manipulations but extracellular glucose levels in the striatum were unchanged. Thus, glucose might be viewed as a substrate for which availability is limiting for memory processing. However, glucose derived from injections or from physiological increases in circulating glucose levels can replete the hippocampus and enhance memory. At the same time, while rats are engaged in the hippocampus-sensitive alternation task, other neural systems such as the striatum where functions are not closely related to the task do not show the depletion of extracellular glucose levels during alternation performance and do not show increases in those areas after systemic injections of glucose.

While suggestive of the view outlined above, only minimal relevant data are now available. It will be important to have similar assessments of dynamic changes in extracellular glucose levels in many neural systems while rats perform a range of tasks. In addition, examination of whether other substances—e.g., hormonal and neural steroids and neurotransmitters—exhibit similar targeting of delivery in a manner associated with cognitive functioning.

1.4. Mechanisms underlying glucose modulation of memory

Although the mechanisms of delivery of glucose to different neural systems are not clear, some information

is available regarding the mechanisms by which glucose acts to enhance memory. One component of the mechanisms underlying glucose effects on learning and memory is that the treatment appears to act, at least in part, by closing potassium-ATP (K^+-ATP) channels. This mechanism of action is like that seen in pancreatic β-cells in which extracellular glucose levels regulate stimulus-secretion coupling associated with release of insulin into blood. Findings of several experiments show that systemic and central drugs that open K^+-ATP channels impair learning and memory while drugs that close the channels enhance learning and memory. Moreover, the effects of these drugs interact with glucose in a consistent manner in which glucose reverses the effects of channel opening treatments and augments the effects of channel closing treatments (Rashidy-Pour, 2001; Stefani & Gold, 1998, 2001; Stefani, Nicholson, & Gold, 1999).

A second component of the mechanisms by which glucose acts is by augmenting the release of ACh in the brain during times of learning and memory. Using in vivo microdialysis to collect extracellular fluid samples in behaving rats, Ragozzino et al. (1996) showed that release of ACh in the hippocampus increased when glucose was administered to rats during spontaneous alternation testing. The efficacy of glucose enhancing ACh release seems unlikely to be a direct one. For example, unilateral infusions of glucose into the hippocampus can augment training-related increases in ACh release in the contralateral hippocampus (Ragozzino et al., 1998).

While the mechanism linking glucose to ACh release is not yet understood, there is good evidence that glucose does not increase release of ACh at once in all neural systems but instead selectively increases the release of ACh in those systems with major participation in the behavioral task under study. Systemic injections did not increase release of ACh in the hippocampus of rats not engaged in spontaneous alternation tests and did not increase release of ACh in neighboring brain areas (misplaced dialysis probes) during the behavioral tests. Thus, ACh release in response to training and glucose injections appeared to exhibit specificity by neural system. The specificity appears to be based on the relative engagement of neural systems at the time of training, extending the view supported above by studies of extracellular glucose levels and memory.

The selective action of glucose on ACh release in different neural systems suggested that endogenous increases in blood glucose levels during training might regulate ACh release in a manner reflecting, and perhaps contributing to, the relative participation of multiple memory systems during learning and memory. This hypothesis led to tests of ACh release in different neural systems under different training conditions, summarized in the sections below.

1.5. ACh release in different memory systems: regulation of relative contributions to learning

The assessment of ACh release in different neural systems during different learning and memory tests was based heavily on the findings that lesions of specific neural systems impaired memory in some tasks but spared memory in other tasks. Although now 'commonplace,' the findings that damage to some brain areas can improve memory typically associated with different areas remains especially intriguing. It is these latter examples that provide the major evidence for competition between neural systems for control over learning. Examples of competition suggest that brain areas other than those on which learning is dependent, in the sense that damage impairs learning, must also be involved in memory processing for the training experiences revealing competition. Restated, some brain areas participate in a manner that promotes optimal performance on a task, while other brain areas participate to the detriment of optimal performance.

The experiments reviewed in this section assess ACh release in different neural systems during learning and memory procedures. The experiments use in vivo microdialysis to collect samples of extracellular fluid in different brain regions. Using high-performance liquid chromatography, the samples are later assayed for ACh content, which largely reflects release of ACh into an extracellular pool (Westerink & Timmerman, 1999; Westerink, 1995).

It is important to measure ACh release during behavioral tests not only by examining those brain areas for which the behavior is lost after damage but also by examining those neural systems in which damage does not interfere, or may enhance, performance on that task. The assessment of 'wrong' brain area by task is necessary if instances of competition or other types of interaction are to be seen 'on-line' during testing.

In measuring ACh release, the experiments in my laboratory have focused on the relative contributions of the hippocampus vs. amygdala on some tasks and of the hippocampus vs. striatum on other tasks. The experiments have used individual differences in performance to examine the engagement of these systems, as well as the interactions between these systems, in different learning and memory tasks.

1.5.1. Hippocampus vs. amygdala

Injections of drugs that decrease cholinergic functions in the hippocampus generally impair the performance of rats tested on spatial working memory tasks, including spontaneous alternation tests (cf. Gold, 2002). For example, injections of the γ-aminobutyric acid (GABA) agonist, muscimol, impair spontaneous alternation performance; the impairment can be reversed by injections of the indirect cholinergic agonist,

physostigmine (Degroot & Parent, 2000). Morphine injections into the medial septum reduce ACh release in the hippocampus (Ragozzino & Gold, 1995). The morphine injections also impair alternation performance; systemic injections of glucose reverse the block of ACh release in the hippocampus and also reverse the impairment of spontaneous alternation scores. In contrast, injections of morphine into the amygdala do not impair alternation scores (Ragozzino & Gold, 1994), showing task by brain area specificity for morphine impairments of spontaneous alternation performance.

ACh release in the hippocampus and other brain areas offers a way to assess the relative contributions of different neural systems to memory. In individual rats, the magnitude of release of ACh in response to alternation testing is positively related to the alternation scores (Ragozzino & Gold, 1995), supporting the idea that ACh release reflects the level of activation, and the relative participation, of the hippocampus in contributing to performance on this working memory task.

The evidence that hippocampal damage can enhance performance on some tasks suggests that ACh release may be inversely related to performance on tasks dependent on other neural systems. These were the results obtained when ACh release was measured during conditioned cue preference training, a task enhanced by hippocampal lesions but impaired by lesions of the amygdala or by injections of the muscarinic antagonist, scopolamine, directly into the amygdala (Ferbinteanu & McDonald, 2001; McDonald & White, 1993; McIntyre, Ragozzino, Williams, & Gold, 1998). In the conditioned cue preference task, rats are trained on a two-arm maze across several days. On alternate days, rats are placed on an arm that is baited with a large supply of highly palatable food or on an arm without food; only one arm is open on each training day. After several exposures to each arm, rats are tested on a probe trial in which both arms are open. Memory is assessed by the time the rats spend on the baited vs. unbaited arms. We tested the relationship between ACh release in the hippocampus and learning on a task readily enhanced by interference with hippocampus functions and readily impaired by interference with amygdala functions. As shown in Fig. 5, those rats exhibiting the best memory on the conditioned cue preference task had the lowest levels of training-related release of ACh in the hippocampus (McIntyre, Marriott, & Gold, 2003b). This negative relationship between ACh release in the hippocampus and memory for a task dependent on the integrity of the amygdala parallels well the findings that hippocampal damage enhances learning on this task. In particular, these findings demonstrate active competitive interactions between the hippocampus and amygdala when both systems are fully functional.

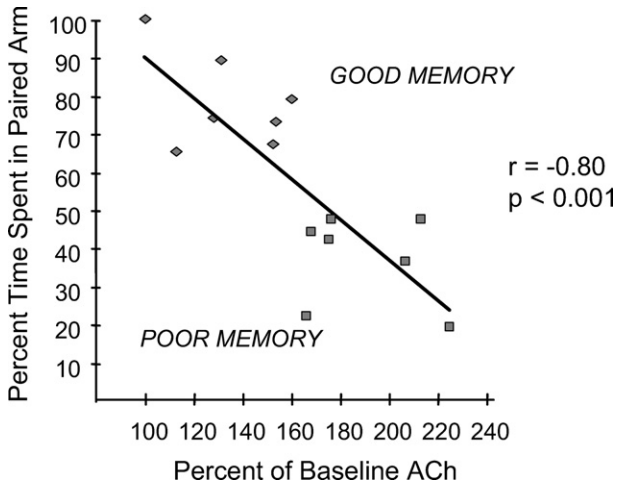

Fig. 5. Acetylcholine release measured in hippocampus during testing on a conditioned cue preference task impaired by amygdala lesions, but enhanced by hippocampal lesions. In measuring individual differences in acetylcholine release in the hippocampus and memory for the conditioned cue preference task, there was an inverse relationship between ACh release in the hippocampus and performance on this amygdala-sensitive task, suggesting that the extent of hippocampal participation in learning competed with the amygdala processing important for acquiring this task. From McIntyre et al. (2002).

A converse study examined the relationship between ACh release in the amygdala in individual rats tested for performance on a spontaneous alternation task which, as noted, depends on the integrity of the hippocampus. In this case, there again was a close relationship between ACh release and performance, but it was a positive relationship (Fig. 6): High levels of ACh release in the amygdala were associated with high alternation scores (McIntyre, Pal, Marriott, & Gold, 2002).

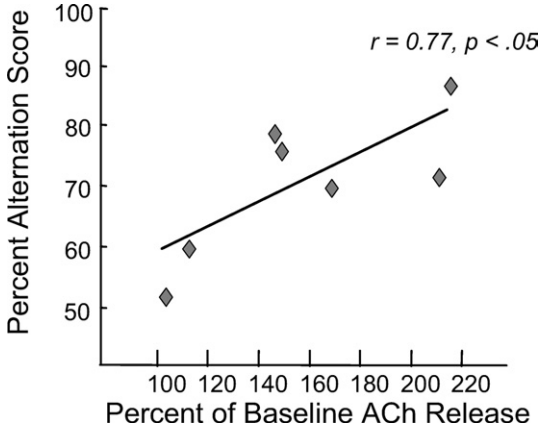

Fig. 6. Acetylcholine release in the amygdala while rats were tested for performance on a hippocampus-sensitive alternation task. Acetylcholine release in the amygdala was positively correlated with individual alternation scores, suggesting that the extent of amygdala participation in alternation testing cooperated with hippocampal processing important for good performance in this task. From McIntyre et al. (2003b).

Thus, there appear to be substantial differences in the nature of the interactions between the hippocampus and amygdala, depending on the direction of the interaction. The results obtained when ACh release in the hippocampus was measured during tests of memory for conditioned cue preference revealed a negative relationship consistent with competition between the hippocampus and amygdala. In contrast, the positive relationship between release of ACh in the amygdala and spontaneous alternation performance suggests a cooperative relationship. Note that a cooperative relationship was seen with methods that permit simultaneous assessment of the activation of both systems, but might not have been evident with lesion analyses. The evidence for a cooperative relationship of the amygdala with the hippocampus and other neural systems is consistent with a substantial set of findings showing that injections of memory-enhancing treatments into the amygdala enhance memory for tasks sensitive to lesions of many other brain areas. For example, glucose injections into the amygdala enhance spontaneous alternation scores (McNay & Gold, 1998), a task impaired not by amygdala lesions but by hippocampal lesions. Also, posttraining injections of amphetamine directly into the amygdala enhance memory for both the hidden (hippocampus-sensitive) and visible (striatum-sensitive) versions of the swim task (Packard & Teather, 1998). These findings are consistent with the view that the amygdala modulates memory processing in many neural systems (McGaugh, 2004; Packard & Wingard, 2004).

The finding of cooperative relationships adds a new level of complexity to understanding the dynamic relationships between neural systems. Of particular note, the relationships are apparently non-symmetrical, i.e., competitive in one direction and cooperative in the other. In addition, one interpretation of amygdala functions derived from these and other studies is that the amygdala may serve as a component of a neural system on which some types of learning are dependent (Davis, Walker, & Myers, 2003; LeDoux, 2000; McDonald & White, 1993, 1995; White & McDonald, 2002) and also serve as a neural system characterized as a positive modulator of memory processing in other systems (McGaugh, 2004).

1.5.2. Hippocampus vs. striatum

Packard and McGaugh (1996) provided evidence that the hippocampus and striatum control learned performance on a T-maze that can be solved successfully using either a place or response solution (Restle, 1957; Tolman, Ritchie, & Kalish, 1946). From a start arm (e.g., South), rats are trained to enter one arm (e.g., right = -east) to find food. After training in the T-maze, a probe trial is administered to determine the type of learning the rat expresses. On the probe trial, the start arm is rotated 180° and the selection of a place or response solution is based on whether the rat turns in the same direction (e.g., right, which is now west) or turns to the same room position (e.g., left, which is now east). During acquisition, there are no differences in trials to criterion (9/10 correct) or other measures identifying the solution a particular rat will prefer on the probe trial.

Whether trained within a single session (Chang & Gold, 2003b) or across days (Packard, 1999), rats typically express place solutions early in learning and response solutions later in learning. The rate at which the transition occurs is susceptible to pharmacological manipulations of the hippocampus and striatum. For example, when rats were trained across days on the T-maze, posttraining injections of glutamate into the hippocampus resulted in rats maintaining the place solution on probe trials after control rats would have made the change to response solutions. Conversely, posttraining injections of glutamate into the striatum resulted in more rapid expression of response solutions (Packard, 1999).

In untreated rats, the relative release of ACh in the hippocampus and striatum appears to be associated with the expression of place or response solutions on probe trials after T-maze training. McIntyre, Marriott, and Gold (2003a) examined simultaneously the release of ACh in the hippocampus and striatum of rats before and after single-session training in the T-maze. ACh release in all rats increased in both brain regions during training. Those rats that would later exhibit place solutions showed significantly higher release of ACh in the hippocampus than did those rats that would exhibit response solutions. The pattern of results was in the opposite direction in the striatum, but this relationship was not significant. Importantly, hippocampal ACh release predicted which rats would use place or response solutions not only when measured during training but also when measured at baseline, i.e., before the rats had any prior maze experience. Thus, there appeared to be a neurochemical bias established in individual rats prior to training that determined the neural system used during training.

A key question is what establishes this bias. While it is possible that the bias may be constant over time, it is also possible that the bias varies across days in individual rats. According to this view, the same rat might have, for example, high ACh release in the hippocampus and show a preference for place solutions to the T-maze on one day, and low ACh release and preference for response solutions on the next. Evidence supporting this view comes from a report showing that ACh release in the hippocampus fluctuates across the estrous cycle in a manner related to cyclical changes in preferred strategy for solving the T-maze (Marriott & Korol, 2003). It will be important to identify those experiential and genetic factors that establish the bias across neural systems.

In the past few years, the sensitivity of the assay has improved considerably, enabling measurements of ACh release in smaller samples. The improvements have led directly to the ability to measure ACh release in 5 min samples instead of earlier 20–30 min, a refinement that permits examinations of ACh release in samples collected with shorter time domains. Using these procedures, Chang and Gold (2003b) assessed ACh release in the hippocampus and striatum before and during training in a manner that enabled tests of changes of ACh release patterns during learning. As found by Packard and McGaugh (1996), male rats tend to use place solutions early in training and switch to response learning later in training when training is performed across several days. Using multiple probe trials (one after each 20 training trials, to 100 trials maximum), Chang and Gold (2003b) observed similar results when training was massed into a single session, with trials administered each minute.

There were two main elements of the neurochemical findings. First, as in the McIntyre et al. (2003a) report, about half of the rats used place and half used response solutions on the probe trial closest to the time each rat reached 9/10 correct (Fig. 7). Second, ACh release increased in both the hippocampus and striatum. Samples were collected every 5 min to match each 5 training trials. Using these methods, there was an important difference between the increases seen in the hippocampus and striatum during training. ACh release in the hippocampus increased to its asymptotic levels on the first set of 5 trials and remained elevated throughout the 100 trials. ACh release in the striatum increased more gradually, reaching its peak levels only after 40–50 trials. The more gradual increase in striatal ACh release corresponds roughly to the transition from place to response solutions, suggesting that the early activation of the hippocampus controls place solutions on the early probe trial, ceding control to the striatum as activation engages striatal functions as well. When both brain areas are engaged at the end of training, it appears to be the striatum that controls the learned response on late probe trials. Thus, the findings suggest that the competition between the hippocampus and striatum in this task changes with time and with continued training.

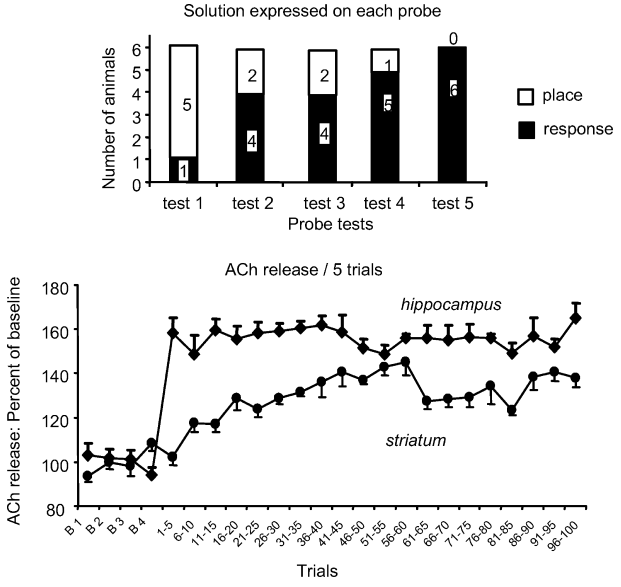

Fig. 7. Simultaneous measurement of acetylcholine release in the hippocampus and striatum during training in a T-maze. (Top) Place or response strategy expressed on probe trials administered after trials 20, 40, 60, 80, and 100. Note that most rats showed place solutions early in training and then switched to response solutions later in training. (Bottom) ACh release at baseline (B1–B4) and during each set of 5 trials throughout training. Note that ACh release in the hippocampus increased during the first 5 trials to its asymptotic level. In contrast, ACh release in the striatum increased more slowly, reaching its peak levels after about 50 trials. The increase in ACh release in the striatum roughly corresponds to the transition of performance on probe trials from place to response solutions.

Similar results were recently obtained in a different task, a rewarded spontaneous alternation task (Pych, Chang, Colon-Rivera, & Gold, 2004). Rats received food reward at the end of each arm of a Y-maze. There were no 'errors'; all arms were continually rebaited. In this task, rats initially show alternation scores comparable to those seen in unbaited tests (~70% alternation), but the scores increase during a 20-min session, surpassing 90% at the end of training. The change in scores reflects a gradual transition from alternation performance to persistent response-based right or left turning. As in the T-maze, ACh release exhibited training-related increases in both the hippocampus and striatum with ACh increases seen first in the hippocampus and increasing later in the striatum. As before, the change in relative release of ACh in the two brain areas corresponded to a change in the behavior used by the rats. These findings again suggest that the hippocampus controls expression of learning early in training and the striatum does so later in training.

2. Conclusions

The findings reviewed here show multiple examples of interactions between neural systems. First, the interactions are not only competitive but can also be cooperative. These relationships can be non-reciprocal, with the hippocampus apparently competing with the amygdala and the amygdala cooperating with the hippocampus during learning. Second there is apparent competition between the hippocampus and striatum, with a changing dominance during extensive training. Third, the relative contributions of different neural systems to learning and memory, marked by ACh release in the hippocampus and striatum, appear to exhibit individual differences that can be seen in terms of the rate at which rats make

transitions from place to response solutions to maze tasks.

While there are clearly important task distinctions to be made in ascribing functions to different memory systems, the findings of extensive interactions described here and in other papers in this issue make murky the extent to which the systems can be considered to be independent memory systems. For example, while place and response learning appear to be dependent on the functional integrity of the hippocampus and striatum, respectively, each is also dependent on the function of the other system in the sense that activation of the alternative system impairs learning. While much of the field of multiple memory systems has focused on positive dependencies, the role of negative dependencies need not be less important.

The interactions across systems are not necessarily direct in the sense that up-regulation of one brain area down-regulates another. In a retrospective analysis of ACh release in the hippocampus and striatum across studies, we found no evidence for a negative correlation (unpublished findings) indicating that, at least with this neural marker, a reciprocal relationship is not evident. One possibility is that the products of the processing in each system are collected by another, undefined, brain area to control output of learned responses. This logical possibility does not have direct empirical support, and tests of systems with an output function of this sort are needed.

There is also a need to identify the neurobiological bases by which neural systems are differentially activated during learning. Some of the findings presented here suggest that differences in ACh release in different neural systems reflect the relative engagement of those systems in learning and memory in some tasks. However, information is not available to explain what establishes the differential release of ACh across animals. One possibility is that there is an input system that regulates ACh release in the forebrain. While reasonable, note that ACh release in the hippocampus is derived from projection neurons from the basal forebrain cholinergic neurons, while that in the striatum is derived from intrinsic short-axon neurons. Thus, the regulation of differential release is not likely to come from a single (unknown) system projecting to cholinergic neurons, but might more likely be mediated by presynaptic regulation of release within each neural system involved in learning and memory processing.

A final issue to be considered is whether ACh release can be viewed as a participant in the neural plasticity underlying memory formation, as well as being a marker of activation of each neural system. In this regard, the evidence from other contexts suggests that ACh can regulate neural plasticity, e.g., during development (Gu, 2003), during induction of long-term potentiation (Centonze, Gubellini, Pisani, Bernardi, & Calabresi, 2003; Jerusalinsky, Kornisiuk, & Izquierdo, 1997; Segal & Auerbach, 1997), and perhaps most directly relevant, during plasticity of auditory cortex associated with conditioning (Weinberger, 2003, 2004). It will be very important to investigate the role of ACh release in regulating several forms of neural plasticity in hippocampus, striatum, and amygdala, among other brain regions. With the additional evidence that cell signaling mechanisms, (e.g., CREB, see Colombo, 2004) may be differentially activated during learning in the hippocampus and striatum, it may be useful to examine ACh effects on memory processing in different neural systems in terms of the activation of molecular pathways responsive to activation of ACh receptors.

References

Axelrod, J., Weil-Malherbe, H., & Tomchick, R. (1959). The physiological disposition of 3H-epinephrine and its metabolite metanephrine. *Journal of Pharmacological and Experimental Therapeutics, 127*, 251–256.

Benton, D., Ruffin, M. P., Lassel, T., Nabb, S., Messaoudi, M., Vinoy, S., Desor, D., & Lang, V. (2003). The delivery rate of dietary carbohydrates affects cognitive performance in both rats and humans. *Psychopharmacology, 166*, 86–90.

Bussey, T. J., Muir, J. L., Everitt, B. J., & Robbins, T. W. (1997). Triple dissociation of anterior cingulate, posterior cingulate, and medial frontal cortices on visual discrimination tasks using a touchscreen testing procedure for the rat. *Behavioral Neuroscience, 111*, 920–936.

Cahill, L., & Alkire, M. T. (2003). Epinephrine enhancement of human memory consolidation: Interaction with arousal at encoding. *Neurobiology of Learning and Memory, 79*, 194–198.

Cahill, L., & McGaugh, J. L. (1998). Mechanisms of emotional arousal and lasting declarative memory. *Trends in Neurosciences, 21*, 294–299.

Centonze, D., Gubellini, P., Pisani, A., Bernardi, G., & Calabresi, P. (2003). Dopamine, acetylcholine and nitric oxide systems interact to induce corticostriatal synaptic plasticity. *Reviews in the Neurosciences, 14*, 207–216.

Chang, Q., & Gold, P. E. (2003a). Intra-hippocampal lidocaine injections impair acquisition of a place task and facilitate acquisition of a response task in rats. *Behavioural Brain Research, 144*, 19–24.

Chang, Q., & Gold, P. E. (2003b). Switching from hippocampal to striatal memory systems during learning: Changes in patterns of acetylcholine release in rats. *Journal of Neuroscience, 23*, 3001–3005.

Chang, Q., & Gold, P. E. (2004). Inactivation of dorsolateral striatum impairs acquisition of response learning in cue-deficient but not cue-available conditions. *Behavioral Neuroscience, 118*, 383–388.

Cherkin, A. (1969). Kinetics of memory consolidation: Role of amnesic treatment parameters. *Proceedings of the National Academy of Sciences of the United States of America, 63*, 1094–1101.

Cohen, N. J. (1984). Preserved learning capacity in amnesia: Evidence for multiple memory systems. In L. R. Squire & N. Butters (Eds.), *The neuropsychology of memory* (pp. 83–103). New York: Guilford Press.

Colombo, P. (2004). Learning-induced activation of transcription factors among multiple memory systems. *Neurobiology of Learning and Memory* 82, 230–242.

Davis, M., Walker, D. L., & Myers, K. M. (2003). Role of the amygdala in fear extinction measured with potentiated startle. *Annals of the New York Academy of Sciences, 985*, 218–232.

Dawson, R. G., & McGaugh, J. L. (1971). Modification of memory storage processes. *Behavioral Science, 16*, 45–63.

Degroot, A., & Parent, M. B. (2000). Increasing acetylcholine levels in the hippocampus or entorhinal cortex reverses the impairing effects of septal GABA receptor activation on spontaneous alternation. *Learning and Memory, 7*, 293–302.

Eichenbaum, H., Fagan, A., & Mathews, P. (1988). Hippocampal system dysfunction and odor discrimination learning in rats: Impairment or facilitation depending on representational demands. *Behavioral Neuroscience, 102*, 331–339.

Fellows, L. K., Boutelle, M. G., & Fillenz, M. (1992). Extracellular brain glucose levels reflect local neuronal activity: A microdialysis study in awake, freely moving rats. *Journal of Neurochemistry, 59*, 2141–2147.

Ferbinteanu, J., & McDonald, R. J. (2001). Dorsal/ventral hippocampus, fornix, and conditioned place preference. *Hippocampus, 11*, 187–200.

Forsyth, R., Fray, A., Boutelle, M., Fillenz, M., Middleditch, C., & Burchell, A. (1996). A role for astrocytes in glucose delivery to neurons. *Developmental Neuroscience, 18*, 360–370.

Fray, A. E., Boutelle, M., & Fillenz, M. (1997). Extracellular glucose turnover in the striatum of unanaesthetized rats measured by quantitative microdialysis. *Journal of Physiology, 504*(Pt. 3), 721–726.

Gold, P. E. (1984). Memory modulation: Roles of peripheral catecholamines. In L. R. Squire & N. Butters (Eds.), *Neuropsychology of memory* (pp. 566–578). New York: The Guilford Press.

Gold, P. E. (1992). Modulation of memory processing: Enhancement of memory in rodents and humans. In L. R. Squire & N. Butters (Eds.), *Neuropsychology of memory* (2nd ed., pp. 402–414). New York: Guilford Press.

Gold, P. E. (1995). Modulation of emotional and non-emotional memories: Same pharmacological systems, different neuroanatomical systems. In J. L. McGaugh, N. M. Weinberger, & G. S. Lynch (Eds.), *Brain and memory: Modulation and mediation of neural plasticity* (pp. 41–74). New York: Oxford Press.

Gold, P. E. (2001). Drug enhancement of memory in aged rodents and humans. In M. E. Carroll & J. B. Overmier (Eds.), *Animal research and human health: Advancing human welfare through behavioral science* (pp. 293–304). Washington, DC: American Psychological Association.

Gold, P. E. (2003). Acetylcholine modulation of neural systems involved in learning and memory. *Neurobiology of Learning and Memory, 80*, 194–210.

Gold, P. E., & McGaugh, J. L. (1975). A single trace, two process view of memory storage processes. In D. Deutsch & J. A. Deutsch (Eds.), *Short term memory* (pp. 355–390). New York: Academic Press.

Gold, P. E., & van Buskirk, R. B. (1975). Facilitation of time dependent memory processes with posttrial epinephrine injections. *Behavioral Biology, 13*, 145–153.

Gold, P. E., Vogt, J., & Hall, J. L. (1986). Posttraining glucose effects on memory: Behavioral and pharmacological characteristics. *Behavioral and Neural Biology, 46*, 145–155.

Gu, Q. (2003). Contribution of acetylcholine to visual cortex plasticity. *Neurobiology of Learning and Memory, 80*, 291–301.

Hassert, D. L., Miyashita, T., & Williams, C. L. (2004). The effects of peripheral vagal nerve stimulation at a memory-modulating intensity on norepinephrine output in the basolateral amygdala. *Behavioral Neuroscience, 118*, 79–88.

Hughes, R. N. (2003). Effects of glucose on responsiveness to change in young adult and middle-aged rats. *Physiology and Behavior, 78*, 529–534.

Introini-Collison, I. B., & McGaugh, J. L. (1986). Epinephrine modulates long-term retention of an aversively motivated discrimination. *Behavioral and Neural Biology, 45*, 358–365.

Isaacson, R. L., Douglas, R. J., & Moore, R. Y. (1961). The effect of radical hippocampal ablation on acquisition of avoidance response. *Journal of Comparative and Physiological Psychology, 54*, 625–628.

Izquierdo, I., & Medina, J. H. (1998). On brain lesions, the milkman and Sigmunda. *Trends in Neurosciences, 21*, 423–426.

Jensen, R. A. (2001). Neural pathways mediating the modulation of learning and memory by arousal. In P. E. Gold & W. T. Greenough (Eds.), *Memory consolidation essays in honor of James L McGaugh: A time to remember* (pp. 129–140). Washington, DC: American Psychological Association.

Jerusalinsky, D., Kornisiuk, E., & Izquierdo, I. (1997). Cholinergic neurotransmission and synaptic plasticity concerning memory processing. *Neurochemical Research, 22*, 507–515.

Kesner, R. P., Bolland, B. L., & Dakis, M. (1993). Memory for spatial locations, motor responses, and objects: Triple dissociation among the hippocampus, caudate nucleus, and extrastriate visual cortex. *Experimental Brain Research, 93*, 462–470.

Kopf, S. R., & Baratti, C. M. (1996). Effects of posttraining administration of glucose on retention of a habituation response in mice: participation of a central cholinergic mechanism. *Neurobiology of Learning and Memory, 65*, 253–260.

Korol, D. L. (2002). Enhancing cognitive function across the life span. *Annals of the New York Academy of Sciences, 959*, 167–179.

LeDoux, J. E. (2000). Emotion circuits in the brain. *Annual Review of Neuroscience, 23*, 155–184.

Lund-Andersen, H. (1979). Transport of glucose from blood to brain. *Physiological Reviews, 59*, 305–352.

Marriott, L. K., & Korol, D. L. (2003). Short-term estrogen treatment in ovariectomized rats augments hippocampal acetylcholine release during place learning. *Neurobiology of Learning and Memory, 80*, 315–322.

Matthews, D. B., & Best, P. J. (1995). Fimbria/fornix lesions facilitate the learning of a nonspatial response task. *Psychonomic Bulletin and Review, 2*, 113–116.

McDonald, R. J., & White, N. M. (1993). A triple dissociation of memory systems: Hippocampus, amygdala, and dorsal striatum. *Behavioral Neuroscience, 107*, 3–22.

McDonald, R. J., & White, N. M. (1995). Information acquired by the hippocampus interferes with acquisition of the amygdala-based conditioned-cue preference in the rat. *Hippocampus, 5*, 189–197.

McGaugh, J. L. (2004). The amygdala modulates the consolidation of memories of emotionally arousing experiences. *Annual Review of Neuroscience, 27*, 1–28.

McGaugh J.L (1966). Time-dependent processes in memory storage. *Science, 153*, 1351–1358.

McIntyre, C. K., Marriott, L. K., & Gold, P. E. (2003a). Patterns of brain acetylcholine release predict individual differences in preferred learning strategies in rats. *Neurobiology of Learning and Memory, 79*, 177–183.

McIntyre, C. K., Marriott, L. K., & Gold, P. E. (2003b). Cooperation between memory systems: Acetylcholine release in the amygdala correlates positively with good performance on a hippocampus-dependent task. *Behavioral Neuroscience, 117*, 320–326.

McIntyre, C. K., Pal, S. N., Marriott, L. K., & Gold, P. E. (2002). Competition between memory systems: Acetylcholine release in the hippocampus correlates negatively with good performance on an amygdala-dependent task. *Journal of Neuroscience, 22*, 1171–1176.

McIntyre, C. K., Ragozzino, M. E., Williams, L., & Gold, P. E. (1998). Intra-amygdala infusions of scopolamine impair performance on a conditioned place preference task but not a win-shift task. *Behavioural Brain Research, 95*, 219–226.

McNay, E. C., Fries, T. M., & Gold, P. E. (2000). Decreases in rat extracellular hippocampal glucose concentration associated with

cognitive demand during a spatial task. *Proceedings of the National Academy of Sciences, 97*, 2881–2885.

McNay, E. C., & Gold, P. E. (1998). Memory modulation across neural systems: Intra-amygdala glucose reverses deficits caused by intra-septal morphine on a spatial task, but not on an aversive task. *Journal of Neuroscience, 18*, 3853–3858.

McNay, E. C., & Gold, P. E. (1999). Extracellular glucose concentrations in the rat hippocampus measured by zero-net-flux: Effects of microdialysis flow rate, strain and age. *Journal of Neurochemistry, 72*, 785–790.

McNay, E. C., & Gold, P. E. (2002). Food for thought: Fluctuations in brain extracellular glucose provide insight into the mechanisms of memory modulation. *Behavioral and Cognitive Neuroscience Reviews, 1*, 264–280.

McNay, E. C., McCarty, R. M., & Gold, P. E. (2001). Fluctuations in glucose concentration during behavioral testing: Dissociations both between brain areas and between brain and blood. *Neurobiology of Learning and Memory, 75*, 325–337.

Means, L. W., Walker, D. W., & Isaacson, R. L. (1970). Facilitated single-alternation go, no-go acquisition following hippocampectomy in the rat. *Journal of Comparative and Physiological Psychology, 72*, 278–285.

Messier, C. (1997). Object recognition in mice: Improvement of memory by glucose. *Neurobiology of Learning and Memory, 67*, 172–175.

Messier, C. (2004). Glucose improvement of memory: A review. *European Journal of Pharmacology, 490*, 33–57.

Messier, C., & Destrade, C. (1988). Improvement of memory for an operant response by post-training glucose in mice. *Behavioural Brain Research, 31*, 185–191.

Messier, C., & White, N. M. (1984). Contingent and non-contingent actions of sucrose and saccharin reinforcers: Effects on taste preference and memory. *Physiology and Behavior, 32*, 195–203.

Messier, C., & White, N. M. (1987). Memory improvement by glucose, fructose, and two glucose analogs: a possible effect on peripheral glucose transport. *Behavioral and Neural Biology, 48*, 104–127.

Packard, M. G. (1999). Glutamate infused posttraining into the hippocampus or caudate-putamen differentially strengthens place and response learning. *Proceedings of the National Academy of Sciences of the United States of America, 96*, 12881–12886.

Packard, M. G., & Knowlton, B. J. (2002). Learning and memory functions of the basal ganglia. *Annual Review of Neuroscience, 25*, 563–593.

Packard, M. G., & McGaugh, J. L. (1996). Inactivation of hippocampus or caudate nucleus with lidocaine differentially affects expression of place and response learning. *Neurobiology of Learning and Memory, 65*, 65–72.

Packard, M. G., & Teather, L. A. (1998). Amygdala modulation of multiple memory systems: Hippocampus and caudate-putamen. *Neurobiology of Learning and Memory, 69*, 163–203.

Packard, M. G., & Wingard, J. C. (2004). Amygdala and "emotional" modulation of the relative use of multiple memory systems. *Neurobiology of Learning and Memory,* in this issue.

Pavone, F., Capone, F., Battaglia, M., & Sansone, M. (1998). Shuttle-box avoidance learning in mice: Improvement by combined glucose and tacrine. *Neurobiology of Learning and Memory, 69*, 204–210.

Pych, J., Chang, Q., Colon-Rivera, C., & Gold, P. E. (2004). *Acetylcholine release in hippocampus and striatum during training on a rewarded spontaneous alternation task.* Presented at Society for Neuroscience, 2004, San Diego, CA.

Ragozzino, M. E., & Gold, P. E. (1994). Task-dependent effects of intra-amygdala morphine injections: Attenuation by intra-amygdala glucose injections. *Journal of Neuroscience, 14*, 7478–7485.

Ragozzino, M. E., & Gold, P. E. (1995). Glucose injections into the medial septum reverse the effects of intraseptal morphine infusions on hippocampal acetylcholine output and memory. *Neuroscience, 68*, 981–988.

Ragozzino, M. E., Unick, K. E., & Gold, P. E. (1996). Hippocampal acetylcholine release during memory testing in rats: Augmentation by glucose. *Proceedings of the National Academy of Sciences of the United States of America, 93*, 4693–4698.

Ragozzino, M. E., Pal, S. N., Unick, K., Stefani, M. R., & Gold, P. E. (1998). Modulation of hippocampal acetylcholine release and of memory by intrahippocampal glucose injections. *Journal of Neuroscience, 18*, 1595–1601.

Rashidy-Pour, A. (2001). ATP-sensitive potassium channels mediate the effects of a peripheral injection of glucose on memory storage in an inhibitory avoidance task. *Behavioural Brain Research, 126*, 43–48.

Restle, E. (1957). Discrimination of cues in mazes: A resolution of the "place-vs. response" question. *Psychological Review, 64*, 217–228.

Sansone, M., Battaglia, M., & Pavone, F. (2000). Shuttle-box avoidance learning in mice: Improvement by glucose combined with stimulant drugs. *Neurobiology of Learning and Memory, 73*, 94–100.

Schroeder, J. P., & Packard, M. G. (2003). Systemic or intra-amygdala injections of glucose facilitate memory consolidation for extinction of drug-induced conditioned reward. *European Journal of Neuroscience, 17*, 1482–1488.

Schroeder, J., Wingard, J., & Packard, M. G. (2002). Post-training reversible inactivation of hippocampus reveals interference between memory systems. *Hippocampus, 12*, 280–284.

Segal, M., & Auerbach, J. M. (1997). Muscarinic receptors involved in hippocampal plasticity. *Life Sciences, 60*, 1085–1091.

Squire, L. R. (1987). *Memory and brain*. New York: Oxford University Press.

Stefani, M. R., & Gold, P. E. (1998). Intra-septal injections of glucose and glibenclamide attenuate galanin-induced spontaneous alternation performance deficits in the rat. *Brain Research, 813*, 50–56.

Stefani, M. R., & Gold, P. E. (2001). Intra-hippocampal infusions of K-ATP channel modulators influence spontaneous alternation performance: relationships to acetylcholine release in the hippocampus. *Journal of Neuroscience, 21*, 609–614.

Stefani, M. R., Nicholson, G. M., & Gold, P. E. (1999). ATP-sensitive potassium channel blockade enhances spontaneous alternation performance in the rat: A potential mechanism for glucose-mediated memory enhancement. *Neuroscience, 93*, 557–563.

Sternberg, D. B., Isaacs, K., Gold, P. E., & McGaugh, J. L. (1985). Epinephrine facilitation of appetitive learning: Attenuation with adrenergic receptor antagonists. *Behavioral and Neural Biology, 44*, 447–453.

Talley, C. E. P., Kahn, S., Alexander, L., & Gold, P. E. (2000). Epinephrine fails to enhance performance of food-deprived rats on a delayed spontaneous alternation task. *Neurobiology of Learning and Memory, 73*, 79–86.

Tolman, E. C., Ritchie, B. F., & Kalish, D. (1946). Studies in spatial learning: II. Place learning versus response. *Journal of Experimental Psychology, 36*, 221–229.

Torras-Garcia, M., Costa-Miserachs, D., Portell-Cortes, I., & Morgado-Bernal, I. (1998). Posttraining epinephrine and memory consolidation in rats with different basic learning capacities. The role of the stria terminalis. *Experimental Brain Research, 121*, 20–28.

Watson, G. S., & Craft, S. (2004). Modulation of memory by insulin and glucose: Neuropsychological observations in Alzheimer's disease. *European Journal of Pharmacology, 490*, 97–113.

Weinberger, N. M. (2004). Specific long-term memory traces in primary auditory cortex. *Nature Reviews Neuroscience, 5*, 279–290.

Weinberger, N. M. (2003). The nucleus basalis and memory codes: Auditory cortical plasticity and the induction of specific, associative behavioral memory. *Neurobiology of Learning and Memory, 80*, 268–284.

Westerink, B. H., & Timmerman, W. (1999). Do neurotransmitters sampled by brain microdialysis reflect functional release. *Analytica Chimica Acta, 379*, 263–274.

Westerink, B. H. (1995). Brain microdialysis and its application for the study of animal behaviour. *Behavioural Brain Research, 70*, 103–124.

White, N. M., & McDonald, R. J. (2002). Multiple parallel memory systems in the brain of the rat. *Neurobiology of Learning and Memory, 77*, 125–184.

Zola, S. M., & Mahut, H. (1973). Paradoxical facilitation of object reversal learning after transection of the fornix in monkeys. *Neuropsychologia, 11*, 271–284.