

The Competitive Nature of Declarative and Nondeclarative Memory Systems: Converging Evidence from Animal and Human Brain Studies

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Evidence from experimental animal studies as well as human neuroimaging studies has led researchers to agree that memory is not unitary in nature, but is actually subserved by multiple memory systems localized in different regions of the brain. Further research of the neurobiological basis of memory supports a clear distinction between the declarative (hippocampal dependent) and nondeclarative (striatal dependent) memory systems. Moreover, evidence indicates that the two memory systems may, in actuality, interact with one another during learning; however, the level at which this interaction occurs, either during acquisition or response, remains unknown. Investigation of the multiple memory systems and the mechanisms of interaction is not only important for what it reveals about the evolution and adaptive function of the brain, but for its clinical applications as well.



INTRODUCTION

Converging evidence from animal experiments and human neuroimaging studies has led to the agreement that memory is not unitary in nature, but better explained by multiple systems that subserve different types of memory (Poldrack, 2003). Extensive research of the neurobiological basis of memory further supports the distinction between the two types of long-term memory systems: declarative and nondeclarative. While declarative knowledge is characterized as flexible memory for past events and facts, nondeclarative memory is characterized by relatively inflexible knowledge for habitual and procedural behaviors (Cohen and Squire, 1980; Figure 1). The key distinction between the two memory systems lies in the differential capacity to recall stored information. While declarative memory is subject to conscious recollection, nondeclarative memory is expressed through performance and is not accessible through conscious faculties (Squire and Zola, 1996). Additionally, multiple studies reveal a specialization between the two memory systems in that the declarative system appears to be responsible for rapid learning of information about individual trials, whereas the nondeclarative learning system seems to be involved in gradual learning across many trials (Poldrack et al., 2001).

Neurobiological studies have identified multiple brain systems that differ in terms of the types of memory they subserve: declarative memory relies on the hippocampus of the medial temporal lobe whereas nondeclarative memory relies on the striatum of the basal ganglia (Squire, 1992; Figure 2, 3). The hypothesis that multiple brain systems mediate different types of memory was originally derived from the results of several studies that examined spared learning abilities after hippocampal damage. Cohen and Squire (1980) report that preserved learning skills in amnesiacs are broader than reported in previous studies as amnesiacs seem to have impaired declarative knowledge, but spared nondeclarative or procedural abilities. From the synthesis of evidence from experimental animal and human brain studies, a biological perspective emerges further supporting the dissociation between declarative and nondeclarative memory and proposes that the different functions rest on the distinct anatomical organization of the memory systems (Squire, 1992; Figure 3). Additionally, several dual-memory theories examining the characteristics of declarative (hippocampal dependent) and nondeclarative (striatal dependent) memory have been proposed. One such theory suggests that the effects of a dual-task (a task which includes both declarative and nondeclarative components) on the measures of nondeclarative sequence learning may

be partly due to the intrusion and disruption of declarative knowledge (Jimenez and Vasquez, 2005). As evidenced by studies of both animals and humans, current research demonstrates the existence of multiple memory systems and more specifically, the fundamental differences between declarative and nondeclarative memory systems.

While evidence for a single dissociation within the hippocampal-dependent declarative memory system indicates the existence of multiple memory systems, double dissociation studies more clearly support the functional independence between the declarative and nondeclarative systems. Double dissociation studies, performed by creating irreversible and reversible lesions of the hippocampus and striatum in experimental animals, provide the most powerful evidence for the necessity of multiple memory systems. Packard et al. (1989) examined the differential effects of lesions to the hippocampus and caudate nucleus of the striatum in experimental rats while performing two radial maze tasks in order to behaviorally demonstrate a double dissociation of the mnemonic functions of the two memory systems. Additionally, Knowlton et al. (1996) utilized a probabilistic classification task, designed to separate the function of the two memory systems by relying on procedural skills, during neuroimaging of patients with amnesia (due to hippocampal damage) and patients with Parkinson's disease (due to striatal damage), further demonstrating a double dissociation within the long-term memory systems. Amnesic patients exhibited normal learning of the task, but had no declarative knowledge of the training event, whereas Parkinson's disease patients exhibited no procedural learning, but had intact, declarative memory for the training episode. Additionally, Tranel and colleagues (1994) found that while patients with lesions to the hippocampus exhibited impaired declarative memory,

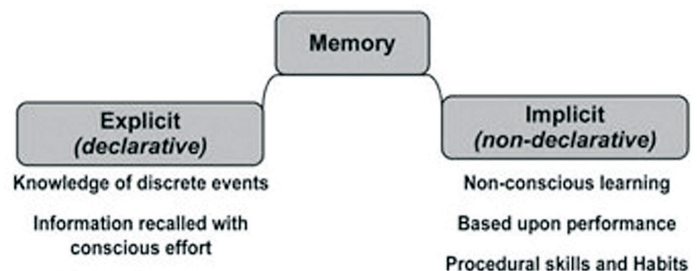


Figure 1. Functions of Declarative and Non-declarative Long-Term Memory. Declarative or explicit memory is knowledge of facts and events, usually recalled with a conscious effort. Examples include one's knowledge of the capital of France, the date of a historical event, or a sibling's date of birth. Nondeclarative or implicit memory is procedural learning, usually recalled through performance without conscious effort. Examples include one's ability to ride a bicycle or drive a manual transmission automobile. Typically, non-declarative memory is not accessible through verbal description.

they did not exhibit impaired nondeclarative motor skill learning. Moreover, Heindel et al. (1989) found that those with damage to the striatal system showed impaired nondeclarative skill learning, but intact declarative memory. Multiple studies of animals and humans provide converging evidence for the double dissociation of the two memory systems, further supporting the differentiation of declarative and nondeclarative memory systems as they act independent of one another to support learning.

Despite the apparent independence of the declarative and nondeclarative memory systems, many studies indicate that multiple memory systems in the brain may, in actuality, interact with one another (Poldrack, 2003). These studies indicate that the interaction is cooperative in that more than one system can provide the solution in a learning situation as subjects can use both their declarative and nondeclarative memory. As one might hypothesize, using both systems in a cooperative manner may optimize learning and performance; however, in light of our evolutionary existence, another theory suggests a more competitive interaction between the memory systems in that when one system is unable to provide an adequate solution, the other system is recruited to provide the answer (Sherry and Schacter, 1987). Converging evidence across species supports the competitive nature of the two memory systems: non-human animal studies reveal that damage to a given memory system actually results in enhanced learning and, more recently, human neuroimaging studies provide further evidence supporting the competitive nature of the systems as well (Poldrack and Packard, 2003). The most recent findings favor this theory as it more completely explains the interaction of the two memory systems, while challenging the previously held hypothesis of memory systems only working independently of one another.

This review serves to outline converging evidence from both experimental animal studies and from more recent human neuroimaging studies, which indicate that memory mechanisms in the hippocampus and striatum competitively interact with one another during learning. Multiple studies provide evidence that the competition occurs between the hippocampal and striatal memory systems at the level of acquisition. However, the most current findings indicate that the competition occurs not at the level of acquisition, but at the response level after learning has already occurred.

COMPETITIVE INTERACTION OCCURRING AT THE LEVEL OF ACQUISITION

EXPERIMENTAL ANIMAL STUDIES Experimental studies within animal models report a clear dissociation between

the hippocampal and striatal memory systems, proving that they are functionally separate. Many animal studies have shown that the hippocampus and the striatum acquire different types of information during learning; specifically, flexible, relational knowledge by the hippocampus and inflexible stimulus-response associations by the striatum (Squire and Zola, 1996). Selectively inactivating the hippocampal or striatal system with lidocaine was used to examine the involvement of the two memory systems during a place and response learning task that utilized a cross-maze. The rats were categorized according to their response as either “place” learners (i.e., animals going to the place where the food was located during training) or “response” learners (i.e., animals making the same turning response as during training) (Packard and McGaugh, 1996). Packard and McGaugh found that hippocampal and striatal learning occurred simultaneously when rats were studied in this cross-maze experimental setup. Initially, the rat was taught to run to a particular arm of the maze from a given starting point and was rewarded. The rat was then immediately positioned in a different starting location and was tested on its ability to find the previously rewarded location.

Packard and McGaugh (1996) reported that the hippocampus was activated during place learning, in which the rat was challenged to find the previously rewarded location starting from a new position; and, that the striatum was activated during response learning to aid in making the previously rewarded motor response from the new starting location. Under certain conditions, the two systems could interfere with one another and lead to different behavioral responses. Healthy control rats exhibited a more gradual transition as they initially relied upon hippocampal-dependent place learning strategies and then later upon striatal-dependent response learning strategies. Pharmacological suppression of a given memory system resulted in facilitation of the other system, suggesting that these structures are involved in competition at the level of place and response learning.

Such findings support the theory of competitive interaction between the hippocampal and striatal memory systems and favor competition occurring at the level of learning (Packard and McGaugh, 1996). The present findings can be interpreted to suggest that the hippocampal lesion induced experimentally reduces the cognitive interference between the two memory systems and improves the function of the striatal system to learn and perform in certain situations. According to this interpretation, when a lesion is experimentally induced and one memory system is impaired, the spared memory system is able to take over

and mediate learning and task performance, leading to a different behavioral response. Moreover, when one system is impaired, it is less able to interfere in the actions of the other system, resulting in an enhanced behavioral response as well.

HUMAN NEUROIMAGING STUDIES Recent studies have provided evidence for altered patterns of brain activity in healthy subjects and patients with Parkinson's and Huntington's disease. A recent positron emission tomography (PET) study using the Tower of London task, which assesses executive functions such as planning through problem-solving, reported that mildly affected Parkinson's disease patients performed as well as the control group, but showed a different pattern of neuronal activity (Dagher et al., 2001; Figure 4). Parkinson's disease patients showed enhanced activation of the right hippocampus as compared to healthy control subjects. The data suggest that normal frontal lobe activation can occur in Parkinson's disease patients despite abnormal striatal processing, as this task directly relies on this the frontal lobe, and that right hippocampal activity is enhanced in these patients while suppressed in normal control subjects.

Dagher et al. (2001) suggest that a shift to dependence on declarative memory structures during the Tower of London task may be a result of abnormal striatal processing and an insufficient working memory capacity within the frontal lobe in Parkinson's disease patients. Moreover, the authors suggest that the enhanced activation of the right hippocampus and failed activation of the right caudate nucleus during the Tower of London task represents recruitment of the hippocampus to overcome the striatal defect within Parkinson's disease patients. As a result of striatal dysfunction, the hippocampus must be recruited to perform the frontostriatal task and to partially overcome the striatal deficits. Dagher and colleagues interpret the recruitment of the spared hippocampus within Parkinson's disease patients as evidence to support competition at the level of acquisition or learning.

Additionally, striatal and hippocampal lesions can impair performance on certain spatial memory tasks as investigated in the PET study of abnormal basal ganglia function in Parkinson's disease patients (Owen et al., 1998). Owen et al. examined the effects of striatal dopamine depletion on cortical and subcortical blood flow changes during a frontostriatal-dependent task. While performing three variations of a Tower of London planning task ((1) an easy and difficult version, (2) a variant task requiring short-term retention, and (3) a control condition involving identical visual stimuli and motor response), regional

cerebral blood flow was measured in six patients with moderate Parkinson's disease and six control subjects. An inverse relationship of regional cerebral blood flow was observed between control subjects and Parkinson's disease patients, in that there was an increase in blood flow in the right striatum in control subjects and a decrease in the same region in Parkinson's disease patients. Only when the mnemonic components were increased was the hippocampal system recruited to mediate task performance. These findings are consistent with the previous animal studies in that hippocampal recruitment in Parkinson's disease patients could be the result of striatal dysfunction. The current findings are interpreted to support competition at the level of learning in that the two competing memory systems act independently of one another and only mediate task performance if one of the other systems is unable.

COMPETITIVE INTERACTION OCCURRING AT THE LEVEL OF RESPONSE

EXPERIMENTAL ANIMAL STUDIES Previous research reveals that pre-training lesions of a given system can result in enhanced acquisition of a task, relative to brain-intact animals performing the same task, and this is mostly due to the reduction of competitive interference between the two memory systems (Poldrack and Packard, 2003). In a study examining the acquisition of striatal-dependent active avoidance behavior, the enhanced behavioral response following a hippocampal lesion was suggested to be the result of cognitive interference reduction (O'Keefe and Nadel, 1978). Similarly, striatal system lesions have been reported to facilitate learning of a spatial discrimination task dependent upon the declarative memory system by disrupting the ability of a potentially interfering nondeclarative strategy (Mitchell and Hall, 1988).

Additionally, Packard and McGaugh (1996) showed that the two systems can compete with one another on certain tasks and that the performance of a striatal-dependent task can be enhanced if the hippocampal system is lesioned or temporarily inactivated. Conversely, inactivation of the striatal memory system allowed for a response strategy that depended on the hippocampus, proving that the knowledge was still accessible even when it was not the dominant pathway applied. This study proved that even though one system governed the performance of the animals in the cross-maze task, multiple representations still exist within both memory systems.

Furthermore, recent findings indicate that post-training reversible inactivation of the hippocampal system can further enhance striatal-dependent response learning,

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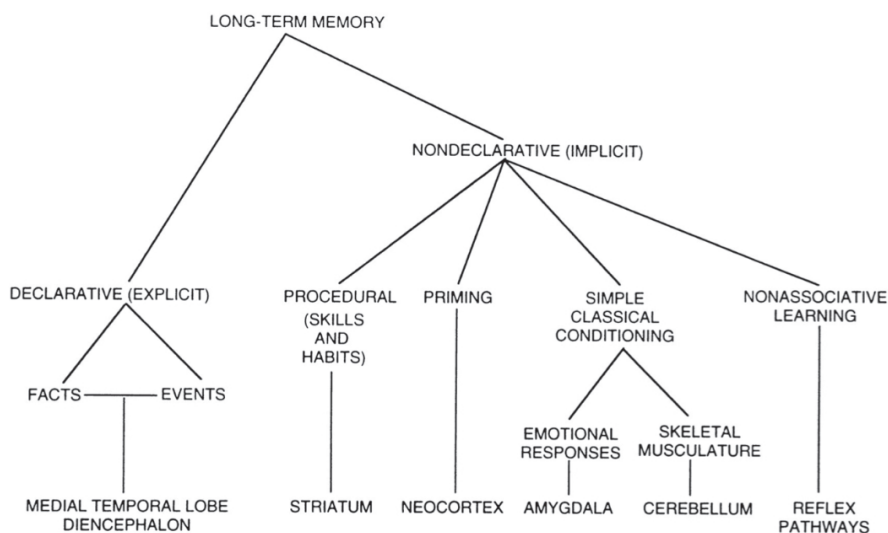


Figure 2. Long-Term Memory Systems. Categorization of declarative and nondeclarative long-term memory systems and the specific brain structures subserving each process. While declarative memory is subserved by the hippocampus or medial temporal lobe, nondeclarative or procedural learning is subserved by the striatum (adapted from Squire and Zola, 1996).

suggesting that multiple memory systems compete during the memory reformation or reconsolidation period as well (Schroeder et al., 2002). According to this interpretation of the competitive interaction, pre-training lesions act to eliminate competition among multiple memory systems by removing the ability of a given memory system to process, learn, and mediate a behavior during task performance at the response level.

HUMAN NEUROIMAGING STUDIES Consistent with the idea that there is an interaction between the hippocampal and striatal memory systems, numerous studies have investigated this interaction when one system is compromised by a neurological disorder such as Parkinson's or Huntington's disease. Using functional magnetic resonance imaging (fMRI), one study investigated the neural activity associated with performing a habit-learning task in healthy control subjects and Parkinson's disease patients (Moody et al., 2004). Parkinson's disease patients exhibited less activation in the striatal memory system and greater activation in the prefrontal cortex, which had been previously determined to be associated with declarative memory retrieval. Moreover, Parkinson's disease patients showed altered activation in the probabilistic classification task. The pattern of fMRI signal during performance indicated that there was greater activation of the hippocampal memory system, usually involved in declarative memory processing, and less activation in the basal ganglia, as is expected from the disease.

The present findings suggest that patients with Parkinson's disease may rely on their declarative memory

system for tasks that are usually learned implicitly using the striatal circuitry (Moody et al., 2004). In this task, declarative memory for individual trials, while less beneficial than information gained across trials, was used by Parkinson's disease patients to make decisions regarding the cue-outcome associations. The increased activation in the hippocampal system and prefrontal cortex reflects the ability of the Parkinson's disease patients to recollect previous trials in order to make their responses. When the nondeclarative circuitry is unable to mediate learning and task performance in Parkinson's disease patients, the declarative circuitry is recruited and is able to mediate task performance. These findings reveal that in normal subjects, competition is occurring at the level of response. Both systems are able to acquire redundant information and it is only through the competitive interaction between both systems that one system is able to mediate performance. Moreover, these findings reveal that in control subjects with intact memory systems, the striatal circuitry serves to inhibit the hippocampus during this task, as it recognizes its probabilistic nature. However, when the striatal system is impaired as in Parkinson's disease patients, only the spared system is able to mediate task performance and the competitive interaction is broken down.

A similar fMRI study of healthy subjects investigated the extent to which these two memory systems are engaged to optimize learning and behavior (Foerde et al., 2006). This study involved a distracting secondary task, which was used to investigate the degree to which a subject solves a problem using either declarative or nondeclarative memory. These results demonstrated a fundamental difference

in the two memory systems in that they greatly differ in their sensitivity to concurrent distraction during dual-task conditions. While the dual-task condition did not reduce accuracy, it did reduce the amount of declarative learning about the task. Moreover, performance was correlated with striatal activity under the dual-task condition, whereas task performance and declarative knowledge was correlated with hippocampal activity under the single-task condition. While either system could support learning and performance in these healthy subjects, the nature of what was learned by each system differed in terms of their sensitivity to distraction. This was further evidenced by the fact that the striatum may have been activated during the task, but did not influence the behavioral response when declarative knowledge was readily available.

While the current findings are consistent with the competing memory systems hypothesis, they extend the current theory and prove that concurrent distraction can bias the competition (Foerde et al., 2006). Thus, the current findings reveal that separate memory systems acquire redundant information and competitively interact not at the level of learning, but when the knowledge is applied at the level of response.

LOCUS OF THE COMPETITIVE INTERACTION BETWEEN MEMORY SYSTEMS

While it is difficult to interpret the level at which the interaction occurs between the hippocampal and striatal memory systems, the previously mentioned studies provide distinct interpretations and biologically plausible explanations for both loci. While many studies interpret such findings as evidence for competition at the level of learning, more recent research suggests that separate

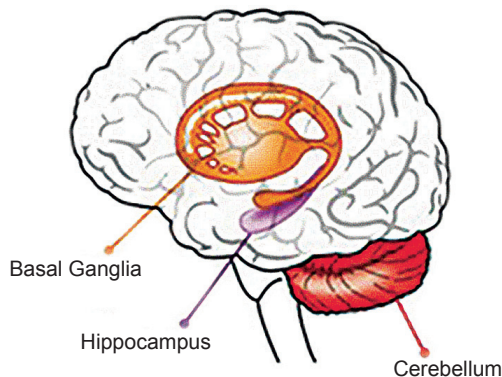


Figure 3. Anatomical localization of the structures subserving the two memory systems. The striatum (labeled here as the basal ganglia) subserves nondeclarative or procedural memory while the hippocampus subserves declarative memory.

memory systems acquire redundant information and it is only when a potential competitor is eliminated that a given system is allowed to freely mediate what was previously dominated by the other memory system.

Recently, Foerde et al. (2006) demonstrated that equivalent levels of learning on the probabilistic classification task can be mediated by both the hippocampus and the striatum and that concurrent distraction by a secondary task modulated the engagement of such memory systems. These systems differ not only in the locus of competitive interaction, but also in their ability to be modulated by external factors such as distraction. This suggests that the locus of competition, be it at the level of acquisition or response, can be subject to influence by external factors as well. Through evolution and natural selection, species evolved to have multiple memory systems and neural substrates mediating different learning abilities, but fully capable of subserving multiple behaviors should one system fail. Not only does this appear to be consistent across species, but it makes sense in light of our evolutionary existence and biological function.

COSTS OF THE COMPETITIVE INTERACTION BETWEEN MEMORY SYSTEMS Because redundant information can be acquired and mediated by the declarative memory system, the costs associated with impaired nondeclarative function are challenged (Moody et al., 2004). However, upon closer examination, the costs associated with Parkinson's and Huntington's disease become very clear. Nondeclarative habitual memory, subserved by the striatal system, is characterized as automatic responses to cued stimuli. In the previously mentioned studies, the findings proved that healthy control subjects were able to automatically perform such tasks using their nondeclarative knowledge whereas Parkinson's disease patients were able to use their spared, declarative knowledge. Using their declarative retrieval processes to perform habitual tasks may account for the decreased availability of cognitive resources for other processes, therefore explaining the cognitive slowing exhibited by Parkinson's disease patients. Even though the declarative memory system can mediate such behaviors, the loss of the cognitive ability to perform automatic, habitual activities could certainly be considered an impact in the lives of Parkinson's disease patients.

ADAPTIVE FUNCTION OF INTERACTING MEMORY SYSTEMS

Experimental evidence suggests that the hippocampal and striatal memory systems work independently, together,

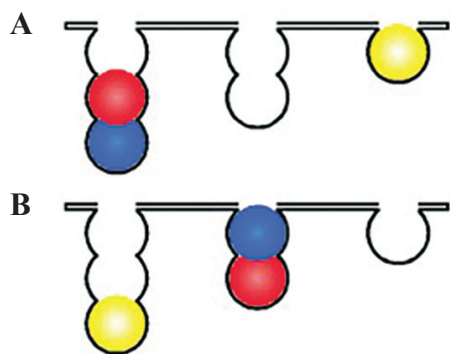


Figure 4. Tower of London Task. The Tower of London paradigm assesses executive functions such as planning through problem-solving tasks. Typically, the set-up consists of three pouches, which can hold one, two and three balls, respectively. The task is to move the differently colored balls, one at a time in a minimum number of moves, between the pouches in the lower panel (B) so that the resulting pattern matches that of the upper panel (A).

or interfere with one another in different situations. While extensive evidence indicates that the multiple memory systems can function independently in some learning paradigms, the findings reviewed here delineate the conditions by which an interaction occurs between the two memory systems and reveal the competitive nature of such an interaction. With the relatively recent development of fMRI in conjunction with earlier evidence provided by experimental animal models, investigation into the interaction between the two memory systems has revealed more detail regarding the competitive nature of the two systems.

The competition between memory systems reflects an adaptive mechanism for optimizing behavior depending upon the learning situation (Poldrack and Packard, 2003). Learning involves competition between hippocampal-dependent and striatal-dependent memory systems in the animal and human brain. The competitive nature of such an interaction may serve to arbitrate between the two fundamentally different requirements of learning, specifically the need for flexibly accessible knowledge and the need for automatic responses.

FUTURE DIRECTION

Many questions remain regarding the nature of the interaction between the hippocampal and striatal memory systems. The current findings suggest that multiple memory systems acquire redundant information and apply such information at the level of response when a pre-training lesion is experimentally induced. Further research should be conducted in order to delineate the experimental conditions that determine the locus of competition. While

multiple studies suggest that the competition occurs at the level of response rather than at the level of acquisition, further research should address this discrepancy, as it will provide a better understanding of the two competing memory systems and their interaction.

With regard to human neuroimaging studies, one central question centers on the nature of the neurophysiological deactivations that have been observed in nondeclarative learning situations engaging the striatum (Poldrack et al., 2001). There is ongoing debate concerning increased fMRI signal and it is unknown whether both excitatory and inhibitory synaptic activity results in this increased activation. Further investigation is necessary in order to fully understand the synaptic correlates of these signals and to better understand the deactivation associated with implicit learning situations and the striatum.

While it is clear that multiple memory systems exist and interact within the mammalian brain, little research has been conducted as to the neurobiological connections mediating such an interaction. One central question regarding animal studies centers on the neurobiological and neuropharmacological bases of the interactions observed. Possible mechanisms may include direct anatomical projections or indirect neuromodulatory influence of the brain structures within these systems (Poldrack and Packard, 2003). There has been some research of the direct anatomical projections between the hippocampus and the striatum. Using electrophysiological techniques in rats, stimulation of the entorhinal cortex of the hippocampus resulted in responses in the striatum of the basal ganglia (Finch et al., 1995). Moreover, Finch and colleagues found that the majority of the striatal responses to stimulation were inhibitory. The data are consistent with neuropsychological and behavioral findings in that a negative influence between these two structures is observed. Additionally, one indirect influence between the two systems could be that of neuromodulatory control. It is possible that neuromodulatory influence from structures other than the hippocampus and striatum is mediating the activity of these two memory systems. Further investigation into the direct anatomical projections and indirect neuromodulatory influence between the two systems may enhance our understanding of the hippocampus and striatum and provide a better understanding of the observed behavioral responses.

However, attributing the interaction between these two memory systems to direct anatomical or indirect neuromodulatory control may not provide full understanding of the interaction (Poldrack and Packard, 2003). It is quite possible that the interaction between the

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hippocampal and striatal memory systems is guided by top-down modulation (from cortical to subcortical structures) through connections from structures that are involved in response selection (Alexander et al., 1986). Extensive evidence for top-down attentional modulation effects can be seen in animals using electrophysiological techniques and in humans using neuroimaging. According to this theory, a higher order system could exert its effects on the hippocampal and striatal memory systems and modulate the output. This higher order modulatory system could be that of the frontostriatal circuit, previously demonstrated to be involved in other cognitive processes.

In order to examine the effects of declarative memory systems serving nondeclarative functions within Parkinson's disease patients, further investigation should be conducted into the behavioral manifestations and costs associated with a shift in dependence. Because nondeclarative, implicit learning is responsible for the automaticity of daily activities, research of the behavioral consequences associated with implicit memory loss should be conducted in order to better understand this shift in dependence and the competitive interaction associated with it (Moody et al., 2004). Understanding the shift in dependence between memory systems and the associated behavioral consequences may provide insight into the loss of cognitive functions within Parkinson's disease patients.

Finally, current research is limited in that it does not explain how various social, environmental, and physiological parameters influence the interaction between the two competing memory systems (Poldrack and Packard, 2003). Addressing these parameters will provide a better understanding of the factors underlying learning and memory and enhance our understanding of the interaction among multiple memory systems within the mammalian brain. Developmental factors have proven to have a great influence over the interaction of systems within the brain and investigation of these effects should be investigated in order to more fully understand the multiple memory systems that subserve our everyday behavior.

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