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How do memory systems interact? Evidence from human classification learning

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Abstract

Studies of human classification learning using functional neuroimaging have suggested that basal ganglia and medial temporal lobe memory systems may interact during learning. We review these results and outline a set of possible mechanisms for such interactions. Effective connectivity analyses suggest that interaction between basal ganglia and medial temporal lobe are mediated by prefrontal cortex rather than by direct connectivity between regions. A review of possible neurobiological mechanisms suggests that interactions may be driven by neuromodulatory systems in addition to mediation by interaction of inputs to prefrontal cortical neurons. These results suggest that memory system interactions may reflect multiple mechanisms that combine to optimize behavior based on experience.

1. Introduction

The last two decades saw the widespread acceptance of the multiple memory systems theory as a framework for understanding the neural basis of learning and memory in both humans and other animals (Cohen, 1984; Cohen & Eichenbaum, 1993; Cohen & Squire, 1980; Gabrieli, 1998; Squire, 1992). Dissociations between memory tasks in neuropsychological patients suggested that these memory systems operated in a relatively independent manner. Particularly strong evidence came from demonstrations of double dissociations between patient groups, suggesting that the underlying substrates must operate independently. However, much of the work described in this special issue suggests that this strong independence hypothesis goes too far, and argues instead that memory systems in the intact brain can interact, and even compete, during the course of behavior. In this paper, we describe a set of neuroimaging and neuropsychological studies that have motivated the concept of interactive memory systems in humans.

As a preview, it is useful to clarify the operational distinctions between independent, interactive, and competitive memory systems. Like others, we claim that procedural and declarative memory systems are independent in the sense that their specific representations and processes can function normally even when the other is compromised. Furthermore, depending on behavioral demands, the systems may be competitive in the sense that they drive the organism toward different behaviors. One working hypothesis is that competition at this level could be implemented at a decision making stage separate from the memory systems themselves (cf. White & McDonald, 2002). In this case the memory systems are independent and autonomous, and the interaction takes place elsewhere. We propose a level of interaction beyond this, in which neural activity in each of the competing systems in modulated based on task demands and behavioral success. The mechanisms by which such an interaction could occur are still a matter of speculation; below we outline one possible framework through which such an interaction could occur.

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2. Classification learning and the striatum

Classification learning has proven an important paradigm in the study of memory system interactions in humans. This paradigm has a long history in cognitive psychology (e.g., Medin & Schaffer, 1978; Shepard, Hovland, & Jenkins, 1961), but the neural systems underlying classification learning have only recently been identified (cf. Keri, 2003). In a commonly used classification task known as the "weather prediction task" (Knowlton, Squire, & Gluck, 1994; Knowlton, Mangels, & Squire, 1996), subjects are presented on every trial with a set of cards depicting abstract shapes, and are asked to decide whether that set of cards predicts one of two outcomes ("rain" or "sunshine"). Following each decision subjects are given feedback, and the subject acquires the classification based on this feedback. The feedback is probabilistic, such that different outcomes will be given as feedback for the same set of cards on different trials (with a given probability). Strategy analyses have shown that individual subjects learn this task using a variety of strategies, but generally move from the use of relatively simple strategies based on single features to the (more optimal) use of multiple features (Gluck, Shohamy, & Myers, 2002).

Work by Knowlton and colleagues has demonstrated that this form of probabilistic classification learning relies crucially upon the basal ganglia. In particular, neuropsychological investigation of the weather prediction task has demonstrated that patients with Parkinson's and Huntington's diseases are impaired at learning the classification (Knowlton, Mangels et al., 1996; Knowlton, Squire et al., 1996). Patients with amnesia due to medial temporal lobe (MTL) damage, on the other hand, are not significantly impaired early in training but are impaired later in training relative to controls (Knowlton et al., 1994; Knowlton, Mangels et al., 1996).

These results suggested that classification learning should be associated with activation of the basal ganglia in normal subjects using functional neuroimaging. Confirmation of this was first reported by Poldrack, Prabakharan, Seger, and Gabrieli (1999). During fMRI acquisition, subjects received alternating blocks of weather prediction trials and baseline trials. On baseline trials, subjects decided whether the number of cards on the screen equaled two, equating the essential perceptual and motor demands of the weather prediction task. Comparison with the baseline task showed a large set of brain regions that were more active during weather prediction, including bilateral prefrontal and parietal regions. Consistent with the impairments of Parkinson's disease (PD) and Huntington's disease (HD) patients on the task, activity was observed in the caudate nucleus, confirming the importance of the basal ganglia for this task. Subsequent studies have replicated this result, showing activation throughout the striatum as well as in midbrain regions that putatively correspond to the substantia nigra (SN)/ventral tegmental area (VTA) (Aron et al., 2004; Moody, Bookheimer, Vanek, & Knowlton, 2004; Poldrack et al., 2001).

3. Imaging memory system interactions

The finding of basal ganglia activation during classification learning is fully consistent with the notion of independent memory systems, with a striatal system engaged in "habit learning" (e.g., Mishkin, Malamut, & Bachevalier, 1984). However, other results from Poldrack et al. (1999) provided a suggestion that the striatum and MTL might interact during learning. In particular, one analysis examined whether any other brain regions exhibited negative signal change (also called "deactivation") during weather prediction compared to baseline. Such negative activations often go unreported in brain imaging studies, and when they are reported there is a consistent set of regions that exhibit task-related negative signal change across studies, including medial prefrontal and medial parietal cortex (Shulman et al., 1997). In the weather prediction task, these brain regions showed negative signal change, but in addition significant negative signal change was also found in the MTL. Further examination of the individual subject data showed that 6 of 8 subjects had negative signals in the left hippocampus, 5 in the right hippocampus, and 2 had additional negative signals in the medial temporal (parahippocampal/perirhinal) cortex. Analysis of the time course of this negative signal change showed that it became more pronounced over the first 48 trials, and then appeared to dissipate by 96 trials (the length of the study). It should be noted that these negative signal changes reflect decreased net synaptic activity, and thus are unlikely to solely reflect local inhibitory potentials, though they may reflect the results of inhibition acting on other upstream regions (Hershey et al., 2003; Lauritzen, 2001). The dissipation of MTL negative signal relatively late in the course of learning suggested that MTL might become active with further training, consistent with neuropsychological studies suggesting later impairment of amnesics on the weather prediction task (Knowlton et al., 1994).

A subsequent set of studies (Poldrack et al., 2001) examined whether the negative signal change extended out to 144 training trials on the weather prediction task using a blocked design similar to the initial study. Interestingly, the negative signal change in the MTL was maintained through 144 trials with no sign of abatement, suggesting that the MTL does not become engaged later in training. Note that 144 trials is well beyond the point at which MTL amnesics have become impaired relative to controls. Results from a second

experiment using event-related fMRI confirmed the persistence of MTL deactivation through 96 trials.

Poldrack et al. (2001) also examined whether the negative signal change was specific to a feedback-driven version of the task, by comparing performance on that version with performance of another group of subjects on an observational learning version of the task. In this version, subjects were presented with the same stimuli and probabilistic outcomes, but they were simply asked to learn through observation the relationship between cue and outcome without actually making responses (predictions) on each trial. Although a subsequent behavioral test showed that these subjects learned the classification as accurately as those subjects in the standard feedback-driven version of the task, there was significantly greater negative signal change in MTL during the feedback-based version of the task, demonstrating that the negative signal change is driven by particular task demands (i.e., feedback-driven vs. observational learning). These findings were subsequently investigated in a group of patients with Parkinson's disease (PD) and matched controls. This study (Shohamy et al., 2004) found that while the PD patients were impaired on the feedback-based version of the task, they performed as well as normal controls on the observational learning version of the task. These results converge with our imaging findings to implicate the basal ganglia in the feedback processing aspects of classification learning.

4. Functional interactions between memory systems

Another question raised by the finding of negative signal in MTL was whether there were other brain regions whose activity was negatively correlated with MTL activity, which would suggest a negative functional relationship. To examine this question, the level of task-evoked signal from the MTL was extracted for each subject in the blocked-design study (including subjects in both feedback-based and observational learning conditions) and re-entered into a correlational analysis with all other voxels in the brain (Poldrack et al., 2001). This analysis found that activity in the caudate nucleus was negatively correlated with activity in the MTL across subjects, providing evidence that the concurrent striatal activation and negative signal in MTL was not coincidental. However, because this is a correlational analysis it cannot definitively demonstrate that this relationship is causal, or that some other brain region does not drive it. Another analysis examined changes in activity over the course of learning, and found that the caudate nucleus and MTL also showed a reciprocal relationship in activity across trials. The MTL was activated and the caudate deactivated early in training, but the MTL signal became negative and the caudate became positive as learning progressed. Thus, both across subjects and across time there was a negative relation between activity in the MTL and caudate nucleus, consistent with competition between these regions.

A number of other neuroimaging results are also consistent with a negative relationship between the MTL and basal ganglia. First, beyond the studies of cognitive skill learning described above, other studies of both motor skill learning (Jenkins, Brooks, Nixon, & Frackowiak, 1994) and perceptual skill learning (Poldrack & Gabrieli, 2001) have found increasing activation in the striatum (putamen and caudate, respectively) that was accompanied by increasingly negative signal change in the MTL. Second, PET imaging during performance of a planning task (the Tower of Toronto) showed that normal subjects exhibited increasing striatal activity and decreasing MTL activity as task difficulty increased, whereas patients with Parkinson's disease showed neither of these changes even though their level of performance was equivalent to the controls (Dagher, Owen, Boecker, & Brooks, 2001). This finding suggests that this particular task can be performed equivalently using either brain system, but that the two systems trade off in their activity. Third, Rauch et al. (1997) have presented evidence suggesting that the interaction between MTL and striatum may also be disrupted in patients with obsessive–compulsive disorder (OCD). Using an implicit motor sequence learning task, they found that normal controls showed activation in the striatum during learning with no activity in the MTL, whereas OCD patients showed no activation in the striatum, but instead exhibited activation in the MTL bilaterally. Finally, a recent report using fMRI (Moody et al., 2004) replicated our findings of striatal activation and negative MTL signal change in normal subjects during the weather prediction classification task, and further showed that both of these responses were attenuated in patients with Parkinson's disease. Together these results provide increasing evidence that in particular learning situations, there is a negative relationship in activity between the striatum and MTL.

5. Connectivity analysis of fMRI data

The interactions between brain regions can be evaluated through connectivity analysis methods (Friston, 1994; Mcintosh et al., 1994). *Functional connectivity* refers to analysis of interactions based on correlation measures. *Effective connectivity* refers to methods that go beyond correlations by deriving measures of causal influences. One method for effective connectivity analysis is path analysis using structural equation modeling (SEM). SEM is a multivariate regression technique that models the covariance structure of a set of variables

based on a subset of possible paths (or factors) connecting those variables. In the context of fMRI, each variable is one representative time series extracted from brain regions involved in the task of interest (Buchel, Coull, & Friston, 1999). To the extent that the model fits the data, one can say that the path coefficients are indices of causal influence between variables (cf. Bollen, 1989; Pearl, 2001).

To further examine the nature of interactions between striatum and MTL, Rodriguez and Poldrack (2003) implemented a path analysis for each subject in the classification learning study of Poldrack et al. (2001, experiment 2). Time series were extracted from eight brain regions that were activated in the task. The regions were centered at the following locations: midbrain (SN/VTA), MTL (anterior hippocampus), ventral striatum, dorsal striatum, prefrontal cortex, anterior cingulate, superior parietal, and fusiform gyrus. The last two regions represented the dorsal (superior parietal) and ventral (fusiform gyrus) visual processing streams. All paths between the regions were selected using an automated search procedure (Bollen, 1989; Bullmore et al., 2000), which resulted in a different set of paths for each subject. Paths from the visual system were only allowed to serve as input to the other regions (exogenous variables), and anatomical knowledge was used to constrain some paths from being selected. In particular, paths from dorsal striatum to MTL, dorsal striatum to ventral striatum, and striatum to frontal cortex areas were not allowed. Otherwise, bidirectional paths were allowed later in the search procedure to avoid unsolvable models (Bollen, 1989).

The main issue we hoped to clarify with the connectivity analysis concerned the causal influences that could account for MTL and striatum competition. In particular, we were interested in direct connections between MTL and striatum as well as subcortical–cortical connections. Also, because MTL activity was decreased relative to baseline, we attempted to determine where the negative paths would be that could mediate this effect.

The results are shown in Fig. 1 for the left hemisphere. The figure summarizes path coefficients for all subjects that were significant according to a Z-score based on estimated parameter covariances (Bollen, 1989). Nine out of 11 subjects had paths with significant negative path coefficients to or from the hippocampus. Moreover, most of the negative paths involving the hippocampus were to or from PFC regions, where across subjects the majority of the significant connections were negative (e.g., 5/8 for DLPFC and 4/6 for ACC). Interestingly, the paths to and from the striatal regions to both MTL and PFC were mostly significantly positive and relatively few were negative (e.g., only 2/8 negative paths between MTL and vStr, 2/8 negative paths between MTL and dorsal striatum).

As a further test we reran the analysis without any anatomical constraints. The results were very similar (not shown)—negative paths mostly involved the MTL and PFC, and direct connections between MTL and dorsal or ventral striatum were mostly positive. We also ran an analysis for the right hemisphere and both hemispheres combined into a single model. The right hemisphere analysis showed fewer negative paths overall; 4/11 subjects had negative paths into or out of the MTL and only 1 of those involved dorsal striatum. With both hemispheres connected the general pattern of connections within left or right do not change and cross hemisphere connections are almost all significantly positive. This means that mediating effects of cross hemisphere connections do not account for left hemisphere negative paths. Taken all together, the connectivity analysis re-

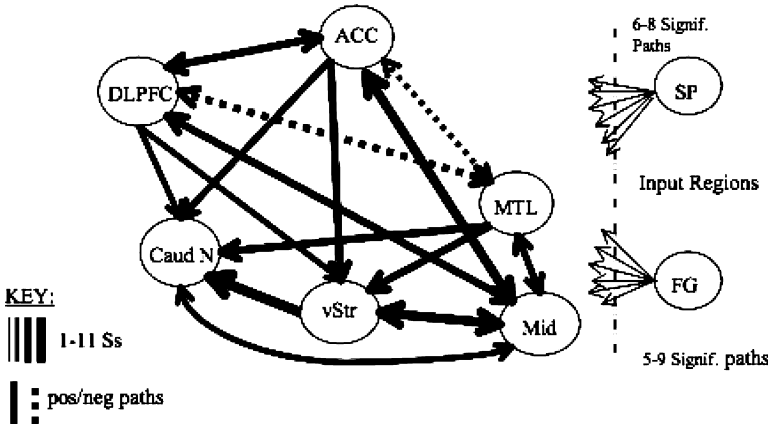

Fig. 1. Results from a path analysis show that significant negative paths are primarily found between MTL and PFC structures. The figure summarizes the analyses across subjects in the left hemisphere. The line thickness indicates the number of subjects that had significant coefficients for that path ($p > 1.96$ or $p < -1.96$). The solid/dashed line indicates that the majority of connections were primarily positive/negative. The lines with double sided arrows indicate that bidirectional connections were allowed for that path. The lines with one sided arrows indicate that uni-directional connections were allowed according to known anatomical constraints.

sults provide substantial evidence in favor of prefrontal mediation of memory system interactions, and against direct interactions between the striatum and MTL.

6. Why might memory systems compete?

The results presented here and throughout this volume provide substantial empirical evidence for competition between striatal and hippocampal memory systems under particular task conditions. It is interesting to ask from an evolutionary standpoint why competing memory systems might have arisen. There are a number of ways in which it seems that different learning situations have incompatible functional demands, and these competing demands may have led to the development of separate memory systems. Sherry and Schacter (1987) have suggested that the evolution of memory systems may have been driven by the incompatible needs to learn invariant features across events versus learning specific (variable) features of events. Examination of the computational characteristics of striatum and MTL suggests that their roles in learning and memory are consistent with this characterization.

The striatum appears to be specialized for the learning of invariant stimulus–response relationships, culminating in the development of "habits" in which a response is automatically triggered by a particular stimulus (Packard & Knowlton, 2002). The well-known cortico–striato–thalamo–cortical loop structure (Alexander, DeLong, & Strick, 1986) provides an architecture for the association of stimuli with responses through plasticity at cortico–striatal synapses. The initial phases of habit learning seem to require dopaminergic feedback signals, most likely because plasticity at cortico–striatal synapses is modulated by DA (Wickens & Kotter, 1995). However, later in learning habits appear to be insensitive to the presence or absence of rewards. For example, reinforcer devaluation does not seem to affect striatally mediated habits (Sage & Knowlton, 2000). The firing characteristics of striatal neurons may also be responsible for the invariance-sensitivity of the striatum. Striatal medium spiny neurons, which receive the principal input to the striatum, exhibit two states: a "down" state in which the neuron is hyperpolarized, and an "up" state in which the neuron is near threshold and exhibits burst firing. These neurons also have a high convergence ratio, with each spiny neuron receiving input from hundreds of afferent neurons (Wilson, 1995). These features combine such that substantial input from a large number of afferent neurons is necessary to bring the neuron into the "up" state; this convergence provides an explanation for the highly context-dependent nature of striatal habit learning.

The hippocampus and medial temporal cortices, on the other hand, appear to be specialized for the representation of variant features across episodes. The CA1, CA3, and dentate gyrus regions of the hippocampus are thought to engage in pattern separation and pattern completion, creating highly sparse representations of the input space to allow the greatest degree of later discrimination between representations and then later reconstructing those representations based on a subset of features (Levy, 1996; Marr, 1971; McNaughton & Morris, 1987; Mizumori, McNaughton, Barnes, & Fox, 1989; O'Reilly & McClelland, 1994). The recurrent connections in the CA3 region in particular are thought to perform a pattern completion function, retrieving episodic representations based on partial information. The ability to successfully retrieve a specific episodic representation requires that the common features across representations be ignored and that the variant features be exaggerated, and the computational machinery of the hippocampus is well-designed to do exactly this.

7. How do the striatum and MTL interact?

The foregoing results provide substantial evidence in favor of interaction between the striatum and MTL during classification learning, raising the more fundamental question of how this interaction might be mediated. It should be noted that there may be multiple mechanisms of interaction, so the possibilities outlined here are not necessarily exclusive. One alternative is that there are direct connections between these regions that mediate direct effects; in particular, an explanation of signal decreases in MTL would require direct connections from striatum to MTL that could plausibly decrease net MTL activity. There is little evidence for direct connections from striatum to hippocampus in primates (cf. Poldrack & Packard, 2003). There is ample evidence of anatomical connectivity from MTL to ventral (rather than dorsal) striatum, but it is not clear how such connections could mediate the effects observed in the aforementioned imaging studies.

It is also possible that functional connectivity between MTL and striatum is mediated by some other region, with a prominent candidate being the prefrontal cortex (PFC). PFC is a particularly good candidate because it is frequently associated with executive control functions involving the scheduling and optimization of lower-level functions implemented in subcortical and posterior cortical regions (e.g., Miller & Cohen, 2001; Norman & Shallice, 1986). Under such an account, both MTL and striatum would be independently engaged in processes related to task performance, and the role of the prefrontal cortex would be to select among these sources of information for the purposes of response selection (cf. White & McDonald, 2002). Supervised learning mechanisms could then potentiate the "winner" and suppress the "loser" of the competition (cf. Houk &

Wise, 1995), resulting in the patterns of positive and negative signal change observed in neuroimaging. It is critical to note that such a mechanism does not require positing a homunculus to control behavior; rather, selection of behavior by the prefrontal cortex emerges from the dynamic interactions between the cortex and subcortical structures including hippocampus and striatum. This interaction involves the modulation of subcortical inputs to prefrontal cortex by synaptic plasticity, possibly driven by dopaminergic signals. This architecture is compatible with the actor–critic architecture for reinforcement learning (e.g., Barto, 1995) often used in basal ganglia models (for a review see, Joel, Niva, & Ruppin, 2002). In the context of multiple memory systems, however, MTL would be more like another actor and the critic would also be involved in gating. The mechanisms by which local activity in MTL and striatum could be modulated by PFC remain to be fully characterized. Although future work is required to characterize the putative mechanisms of PFC modulation of memory system function, it is noteworthy that PFC modulates processing in lateral amygdala via projections to inhibitory interneurons (Rosenkranz, Moore, & Grace, 2003). This provides a candidate mechanism by which the PFC may also project similarly to the MTL. Although direct inhibition would not lead to decreased fMRI signal, it could lead to net decreases indirectly by dampening activity throughout the hippocampal circuit.

A third possible mechanism for interaction between MTL and striatum is through the action of neuromodulatory systems, particularly the mesencephalic dopamine (DA) system. The mesencephalic DA system originates in substantial nigra pars compacta (SNpc) and ventral tegmental area (VTA) and is known to project to striatum and widespread prefrontal targets (Haber & Fudge, 1997; Williams & Goldman-Rakic, 1998). DA is released by neurons in the SNpc/VTA in response to unpredicted rewards, cues that predict subsequent rewards, and other salient events (Horvitz, 2000; Schultz, 2000). The DA system also projects to the hippocampus in the rat (Gasbarri, Sulli, & Packard, 1997) and presumably in primates (given the expression of DA receptors in primate hippocampus: Bergson et al., 1995). Although long-term potentiation in both the striatum (Wickens & Kotter, 1995) and the hippocampus (Huang & Kandel, 1995; Otmakhova & Lisman, 1996) is known to be modulated by DA, the functional significance of DA projections to hippocampus are less well understood. In rats, for example, it has been shown that DA suppresses the perforant path input to CA1, increasing the influence of CA3 inputs to CA1 (Lisman & Otmakhova, 2001). There are also substantial differences in how hippocampus and striatum may respond to dopaminergic signals; for example, whereas neuronal activity in the striatum is sensitive to reward magnitudes (Cromwell & Schultz, 2003), neural activity in the hippocampus does not seem to be (Gilbert & Kesner, 2002; Tabuchi, Mulder, & Wiener, 2003). Studies of schizophrenia provide evidence from humans for the importance of the DA system in classification learning; patients on typical antipsychotic agents (which block D2 receptors in the dorsal striatum, in addition to actions elsewhere) are impaired at classification learning, whereas patients on atypical antipsychotics (which do not block DA in the dorsal striatum) are not impaired relative to controls (Beninger et al., 2003).

8. Multiple mediators of memory system interactions

Based on the foregoing review, we propose that interactions between MTL and striatal memory systems are mediated by the prefrontal cortex and modulated by input from dopaminergic and perhaps other neuromodulatory systems. In support of this proposal, and by way of explanation, we briefly discuss some specific findings that identify possible sites of interactions.

Direct inputs from MTL and striatum (via pallidum/thalamus) impinge on common prefrontal regions, providing a critical substrate for competition. Furthermore, there is evidence that these projections may have modulatory effects on one another. Floresco and Grace (2003) have demonstrated that stimulation of mediodorsal (MD) thalamic inputs to PFC can result in inhibition of subsequent responses to PFC inputs from hippocampus, and stimulation of hippocampal inputs can result in inhibition of subsequent response to MD inputs. Although it is unknown whether the specific MD neurons stimulated in this study received striatal input, this nucleus is a target of striatal outputs as part of the associative and limbic corticostriatal loops (Joel & Weiner, 2000).

In addition to this direct interaction by prefrontal afferents, it also appears that the DA system may gate hippocampal inputs to PFC. Floresco and Grace (2003) showed that hippocampal inputs to PFC are inhibited by concurrent stimulation of the VTA. This effect was reduced in the presence of D2/D4 receptor antagonists, and enhanced in the presence of D1 antagonists, demonstrating the critical role of DA. Dopaminergic regions of the midbrain may in turn be modulated by both cortical and subcortical structures, with a particularly important role for the nucleus accumbens. The accumbens, as well as the entire dorsal striatum, project extensively to the SNpc/VTA. There is also evidence that the hippocampus (ventral subiculum in rats) may modulate activity in the VTA via its projection to the nucleus accumbens (Floresco, Todd, & Grace, 2001). Sesack and colleagues (Sesack, Carr, Omelchenko, & Pinto, 2003) have found that PFC projections to the midbrain are anatomically segregated between mesofrontal and

mesoaccumbens DA systems, with PFC innervating mesoaccumbens GABA cells but not DA cells and innervating mesofrontal DA but not GABA neurons. These results suggest a complex set of interactions between cortical, striatal, and dopaminergic systems that may mediate the interaction between memory systems.

Memory system interactions may also be modulated by the cholinergic system. Gold and colleagues (McIntyre, Marriott, & Gold, 2003) have recently shown that the use of place versus response strategies in a maze learning task in rats can be predicted by the relative levels of acetylcholine (ACh) in the striatum and hippocampus determined using microdialysis. However, Bizon, Han, Hudon, and Gallagher (2003) found that depletion of hippocampal ACh promoted rather than impaired the use of hippocampally dependent strategies in a water maze task. These findings suggest that ACh may correlate with some other modulator of memory system interactions, rather than being causal in those interactions. Other work by Hasselmo (1999) has suggested that acetylcholine can bias the hippocampus into an encoding or retrieval mode, which could have important effects on memory system modulations. It is important to note that neuromodulatory systems are highly interactive, which could underlie some of the empirical discrepancies noted above. For example, dopaminergic cells from VTA project to medial septum, which is a major source of cholinergic activity in hippocampus, and DA inhibits the release of acetylcholine (Levin & Rose, 1992).

Another region that is likely to be involved in modulation of MTL–striatal interactions is the amygdala. It appears that stress responses in the amygdala can modulate the use of hippocampal-dependent learning strategies on the Morris water maze task (Kim, Lee, Han, & Packard, 2001). The role of amygdala in modulating memory system interactions in humans has yet to be established, but this should soon become an area of active research. Together, the foregoing results suggest that a full account of memory system interactions must take into account the complex effects of neural dynamics and neuromodulatory effects. We expect that other neuromodulatory systems (e.g., the noradrenergic system) are likely to be involved as well, either independently or through their interactions with the DA system.

9. Conclusions

Neuroimaging in humans has provided evidence for interactive memory systems that converges strongly with evidence from non-human animal studies. Analyses of functional connectivity suggest that the interaction between basal ganglia and medial temporal lobe may be mediated by the prefrontal cortex, with dopamine as a critical modulator of these interactions. A number of open questions remain regarding these interactions. First, does competition between memory systems reflect a strategy by which organisms might minimize energy utilization while maximizing gains? Analyses using economic frameworks may provide added leverage on this question. Second, what are the functional implications of negative signal change in the MTL? In particular, is memory encoding impaired under conditions of reduced MTL activity? Third, is it possible for MTL and striatum to cooperate under certain circumstances? These questions suggest that there is still a substantial amount of work to be done in characterizing how memory systems interact. Future studies should continue to focus on how the complex interactions between cortical, subcortical, and neuromodulatory systems give rise to the seamless behavioral expression of memory system interactions.

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