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COMMENTARY

Integrating Associative Learning Signals Across the Brain

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ABSTRACT: Associative learning is defined as the ability to link arbitrary stimuli or actions together in memory. The neural correlates of this fundamental form of plasticity were first described in the hippocampus during delay eye blink conditioning and have since been examined using a variety of tasks in both rats and monkeys. In monkeys, the neural correlates of associative learning have been studied using conditional motor learning tasks where animals learn to associate particular visual stimuli with particular motor responses (i.e., touch left or touch right). Similar tasks have also been used to examine learning-related plasticity in motor-related areas throughout the frontal lobe and striatum. Here, we review the patterns of learning-related activity seen in these diverse brain areas during conditional motor learning. While each of these areas exhibits strong associative learning signals, the differential patterns and time courses of these signals provides insight into the unique contribution of each area to associative learning. © **2007 Wiley-Liss, Inc.**

KEY WORDS: hippocampus; striatum; prefrontal cortex; SEF; FEF; premotor cortex

INTRODUCTION

The hippocampus and related structures of the medial temporal lobe have long been linked to the ability to learn and retain new long-term memories for facts and events. This ability is termed declarative memory in humans (Squire et al., 2004) and relational memory in animals (Eichenbaum and Cohen, 2001). A large body of evidence suggests that the medial temporal lobe in general and the hippocampus in particular are critically involved in the ability to form fast new associations in memory. For example, amnesic patients with medial temporal lobe damage are impaired in forming fast new associations between stimuli in multiple sensory modalities (Vargha-Khadem et al., 1997; Bayley and Squire, 2002; Stark et al., 2002; Stark and Squire, 2003). The importance of the hippocampus for the ability to form fast new associations is also a key feature of recent theories of hippocampal function (Eichenbaum and Cohen, 2001). Given these convergent findings, an important question becomes, how does the hippocampus signal the formation of new associative memories?

One of the earliest and most dramatic demonstrations of dynamic learning-related neural signals in the medial temporal lobe came in the 1970's when Berger et al. (Berger et al., 1976; Berger and Thompson, 1978) recorded multiunit activity in the hippocampus in rabbits during a delay eye-blink conditioning task. Compared to the responses in unpaired control animals, hippocampal neurons in conditioned animals developed enhanced responses, first to the air-puff US and subsequently to the CS tone, such that the enhanced response to the US appeared to shift forward gradually in time towards the CS presentation with learning. While delay conditioning is not dependent on hippocampal function, similar changes in neural activity were subsequently reported in trace conditioning that is known to be dependent on the integrity of the hippocampus (Solomon et al., 1986; Moyer, et al., 1990; Kim et al., 1995; McEchron et al., 2000). While many previous studies have shown fast development of place cell activity in a novel environment (Wilson and Mcnaughton, 1993) only a handful of studies have attempted to examine the dynamics of place cell activity during learning of various spatial memory tasks (Fyhn et al., 2002; Frank et al., 2004).

One particularly useful task that has been used to examine both the pattern and timing of associative learning signals in the hippocampus has been the conditional motor associative learning task. In this task, monkeys are required to associate a particular visual stimulus with a particular motor response (i.e., touch right or touch left). Because monkeys are able to learn multiple new conditional motor associations each day this allows direct comparison between changes in single neuron activity and changes in behavior over the course of the session. Strong associative learning signals have been seen in the monkey hippocampus using this task. Because this task involves a motor learning component, it has also been used to study motor learning throughout the frontal lobe including premotor cortex, supplementary eye field (SEF), frontal eye field (FEF), prefrontal cortex as well as in the striatum. Like hippocampal lesions (Rupniak and Gaffan, 1987; Murray and Wise, 1996; Wise and Murray, 1999; Murray et al., 2000; Brasted et al., 2002; Brasted et al., 2003), lesions of premotor areas disrupt learning of conditional motor associations (Petrides, 1982; Halsband and Passingham, 1982, 1985) but lesions of the prefrontal cortex cause only mild learning impairment (Petrides, 1982). While SEF, FEF, and striatum have been implicated in motor learning, the

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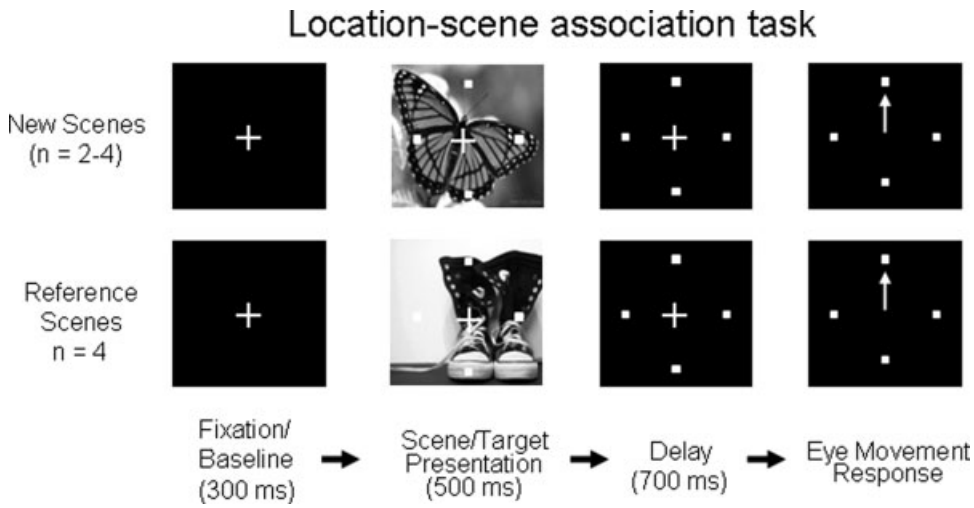

FIGURE 1. Schematic illustration of the location-scene association task from Wirth et al., (2003). Animals initiated each trial by fixating a central fixation point on the computer screen for 300 ms (fixation/baseline). Then four identical targets (small white squares located north, south east and west on the computer monitor) superimposed on a complex visual scene were presented for 500 ms (scene/target presentation). This was followed by a 700 ms delay interval in which the scene disappeared but the targets remained on the screen (delay). The trials ended with the fixation point disappearing which was the monkeys cue to make an eye movement response to one of the targets. Animals typically learned two–four new scenes randomly intermixed with two–four highly familiar reference scenes. Each of the four possible reference scenes was associated with a different rewarded target location.

effects of damage to these areas on tasks of conditional motor learning have not been examined. The use of the same learning task across these different brain areas provides a unique opportunity to examine, compare, and contrast how associative learning is represented across a wide range of different brain areas. Here, we review the patterns of learning-related signals in these different structures. Both the similarities as well as differences in the learning-related activity seen provide insight into how these areas may work together to signal different aspects of new conditional motor learning.

ASSOCIATIVE LEARNING IN THE HIPPOCAMPUS

Two groups have examined the patterns of hippocampal activity in monkeys as they learned novel conditional motor associations (Cahusac et al., 1993; Wirth et al., 2003). Conditional motor learning requires animals to associate a given sensory stimulus, typically a visual image presented on a computer screen, with a motor response (i.e., look right). Post-training lesions to the medial temporal lobe in monkeys impairs the ability to learn novel conditional motor associations, while well-learned associations remain unaffected (Rupniak and Gaffan, 1987; Murray and Wise, 1996; Wise and Murray, 1999; Murray et al., 2000; Brasted et al., 2002; Brasted et al., 2003), emphasizing the importance of the medial temporal lobe in new associative learning per se.

In the study by Wirth et al. (2003), animals were first shown four identical target stimuli superimposed on a complex visual scene that filled the video monitor (Fig. 1). Following a delay interval, during which the scene disappeared but the targets remained on the screen, the animal was cued to make a single eye movement to one of the peripheral targets on the screen (Fig. 1). For each visual scene, only one of the four targets was associated with reward. Each day, the animals learned two–four new scenes by trial and error. These new scenes were also randomly intermixed with well-learned "reference" scenes that the animals had seen for many months before the recording experiments began. Responses to the reference scenes were used to control for motor-related activity in the hippocampal cells. A similar task was used by Cahusac (1993), except only two possible response choices instead of four were given.

Wirth et al. (2003) reported that 61% of the hippocampal cells examined responded selectively (i.e., differentially) to the different scenes shown in the task during the scene period, the delay period or both periods. Selectively responding cells with learning-related activity were identified by correlating a moving average of the raw neural activity with a moving average of the raw behavioral performance during learning. Using this criterion, 28% of the selectively responding cells showed a significant positive or negative correlation with learning. These cells were termed "changing cells." Two categories of changing cells were described by Wirth et al. (2003; Table 1). Sustained changing cells (54% of the population of changing cells) signaled learning with a change in neural activity that was maintained for as long as the cell was held (Fig. 2A). A second category was termed baseline sustained changing cells that made up the remaining 45% of changing cells. These cells started out with a scene-selective response during either the scene or delay period of the task even before the animal learned the associa-

TABLE 1.

Learning Signals Across the Brain

Learning signal	Response to familiar conditions	Task period with max activity	Reference frame
Hippocampus			
Sustained	No response	Scene/delay	Not directional
Baseline sustained	No response	Scene/delay	Not directional
Transient	Not tested	Object period	Not directional or object-based
SEF/FEF[a]			
Learning-dependent	Same as for new	Scene/delay/response	Motor/ direction-based
Learning-selective	No response	Scene/delay/response	Motor/ direction-based
Learning static	Different from new	Scene/delay response	Not clear
Prefrontal[b]			
Earlier direction selectivity with learning	Decreased rsp	Scene/delay/response	Motor/ direction-based
Striatum			
Changes with learning rate	No changing signal	Feedback	Not clear
Changes with learning state	No changing signal	Feedback	Not clear

[a]Note that Brasted and Wise (2004) reported similar patterns of activity in striatum.
[b]Note that Pasupathy and Miller (2005) reported similar, though faster signals in the striatum.

tion and signaled learning by returning to baseline activity (Fig. 2B). This return to baseline activity was anticorrelated with the animal's learning curve for that particular scene. The changing cells in this study were only examined in the scene and delay periods of the task. Preliminary and unpublished analyses suggested relatively few changing signals in the motor response period of the task. While Cahusac et al. (1993) described sustained-like changing cells, they did not observe baseline sustained-type cells. Instead, they described another population of hippocampal learning-related cells that only showed differential activity to the two visual stimuli transiently, near the time of learning before returning to baseline levels of response (transient cells; Table 1).

To test the hypothesis that changing cells may provide a pure motor-based signal (i.e., cells respond anytime the animal moves its eyes north), Wirth et al. (2003) examined the response of each changing cell to the reference scene with the same rewarded target direction. In no case did either the sustained or baseline sustained cells respond similarly to the reference scene with the same rewarded target location suggesting

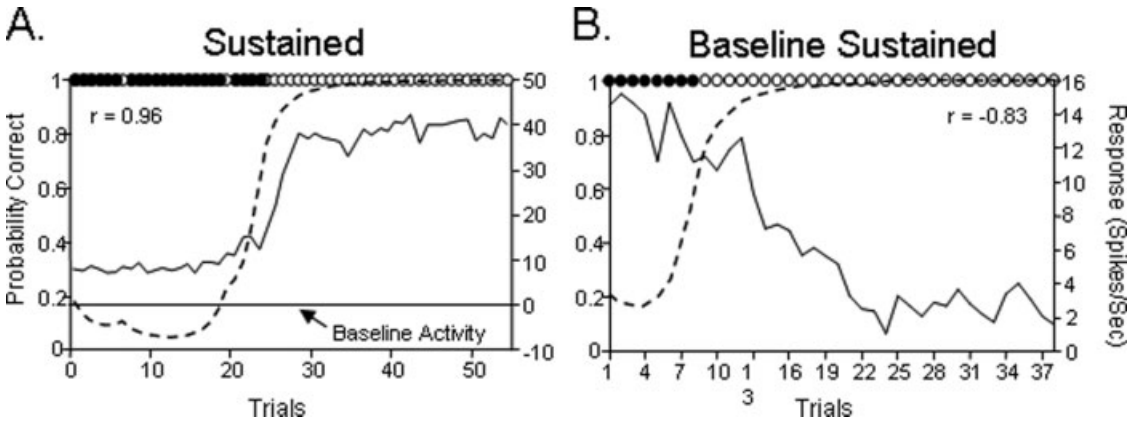

FIGURE 2. Panel A shows an example of a sustained changing cell and panel B shows an example of a baseline sustained changing cell. In both panels, neural activity is shown on the right *Y*-axis while probability correct is shown on the left *y*-axis. Black and white circles at the top of the graph indicate incorrect and correct trials, respectively. The *r*-values refer to the correlation between the behavioral learning curve and the neural activity across trials. Taken from Wirth et al., 2003.

that these cells did not exhibit a motor-based or direction-based learning signal. To test the hypothesis that changing cells signal any new learning associated with a particular response direction (i.e., changing activity anytime a new association to the east is learned), after first identifying a changing cell selective for a particular location-scene combination (i.e., Scene A, go south), they then gave the animal a second set of new associations to learn. The changing cells never signaled learning of the second novel scene with the same rewarded target location (i.e., Scene E, go south). These findings suggest that the hippocampal changing cells do not signal new learning in a motor-based or direction-based frame of reference. Moreover, findings from reversal experiments (Miyashita et al., 1989; Cahusac et al., 1993) suggest that hippocampal neurons exhibit no obvious dependence on the particular sensory stimulus involved in the association. Taken together with, these findings suggest that hippocampal cells signal random new associations between visual stimuli and targets/movements.

Another key question concerns whether hippocampal changing cells actually drive new associative learning or are downstream to other brain areas that drive learning. To address this question, Wirth et al. (2003) examined the temporal relationship between the changing cell activity and changes over time. For each new learning condition for which neural activity changed, comparisons were made between the estimated trial number of neural change and the estimated trial number of learning. This comparison showed that hippocampal cells can signal learning before ($n = 18$), at the same time ($n = 1$) as well as after ($n = 18$) learning. Hippocampal cells signaled learning starting from as much as 13 trials before learning to 15 trials after learning (Fig. 3). Similar to the Wirth et al. (2003) study, Cahusac et al. (1993) reported that the learning-related signals could occur within a wide range of lag or lead times relative to behavioral learning ranging mainly between 30 trials before learning to 40 trials after learning.

To summarize so far, these studies have demonstrated that hippocampal neurons signal new associative learning with dramatic changes in their firing rate. A detailed analysis of the timing of these learning-related signals suggests that hippocampal neurons participate at all stages of the learning process from several trials before behavioral learning is expressed, when the observed activity may be involved in driving the learned behavior to several trials after learning, when the activity may be involved in a strengthening process. These findings are consistent with findings from lesion studies showing that damage to the medial temporal lobe impairs learning of new conditional motor associations. However, these impairments, while significant do not completely prevent new conditional motor learning. Instead, learning is significantly slowed compared to normal control animals (Rupniak and Gaffan, 1987; Murray and Wise, 1996; Wise and Murray, 1999; Murray et al., 2000; Brasted et al., 2002; Brasted et al., 2003). These latter findings are consistent with a recent convergence of neurophysiological data showing other brain areas that also signal new learning of conditional motor associations. We next examine these other candidate brain areas implicated in learning new conditional motor associations.

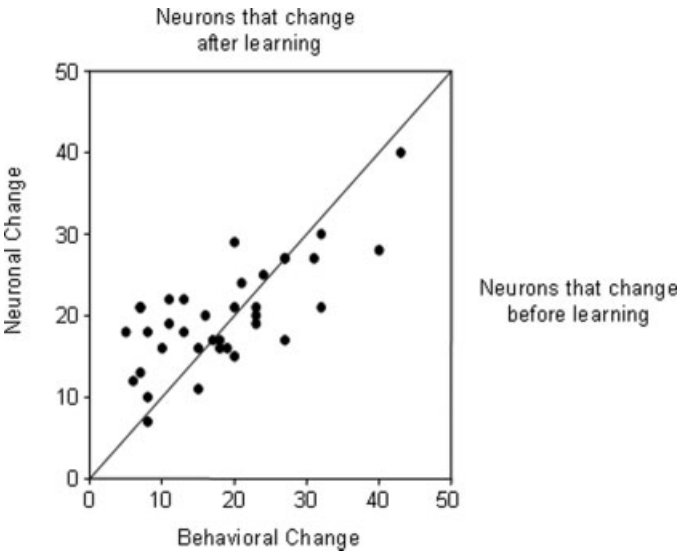

FIGURE 3. The estimated relationship between neural activity and learning for the population of sustained and baseline sustained cells. On the *X*-axis is shown the trial number of learning and the *Y*-axis shows the trail number when the neuron changed activity as estimated using a change point test. This graph shows that a similar proportion of hippocampal cells change before and after learning. Taken from Wirth et al., 2003.

ASSOCIATIVE LEARNING IN MOTOR REGIONS OF THE FRONTAL LOBE

Learning-related neural activity during conditional motor association tasks has been examined extensively throughout several motor related areas of the frontal lobe. For example, Wise and coworkers (Chen and Wise, 1995a,b; Brasted and Wise, 2004) described learning-related activity in the supplementary eye field (SEF), frontal eye field (FEF) during the performance of a conditional motor task with eye movement responses similar to the task used by Wirth et al. (2003; Fig. 1). Parallel studies have been done in the premotor cortex (Mitz et al., 1991; Brasted and Wise, 2004). These reports describe three major categories of learning-related cells (Table 1). The largest subcategory of learning-related cells was termed "learning-dependent." These cells exhibited significant changes in their neural activity during learning of new associations, and these changes were maintained for as long as the neuron was studied (Fig. 4A). Learning-dependent cells were also characterized by having significant task-related activity on familiar trials (analogous to the reference scenes trials in Wirth et al., 2003). Typically, activity during the novel conditions came to resemble activity in the familiar conditions with the same rewarded target location, suggesting a motor-based or direction-based learning signal. Note that motor-based learning signals were not seen in the hippocampus. Additional analyses showed that for a subset of the learning-dependent cells, the change in neu-

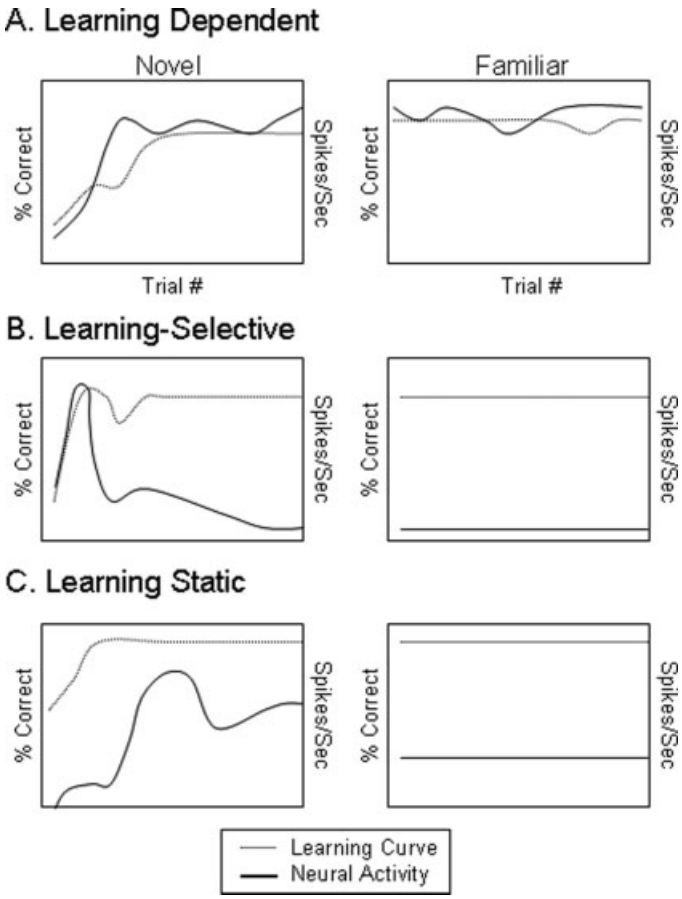

FIGURE 4. Schematic representation of learning dependent (A) learning selective (B) and learning static (C) responses described in the SEF, FEF, and premotor cortex. Shown in the left had column are schematic responses of learning-related cells to novel conditional motor associations and shown on the right is the corresponding response of the same cell to highly familiar associations with the same motor response. Note that the responses of learning dependent cells on novel associations come to resemble the responses to familiar associations with the same rewarded target. Learning selective cells decrease their responses anticorrelated with behavioral learning like the hippocampal baseline sustained cells while the learning static cells resemble the sustained changing cells in the hippocampus. Adapted from Chen and Wise (1995a,b).

ral activity associated with the novel condition corresponded with a shift in the cell's preferred direction during the learning process (Chen and Wise, 1996).

A second category of learning-related cells described in the SEF and FEF and premotor cortex was termed "learning-selective" (Fig. 4B; ~24.5% of the learning-related cells in the SEF). Unlike the learning-dependent cells, these cells did not respond to the familiar conditions, but signaled learning for the new conditions with a transient response around the time of learning. A typical pattern of learning-selective activity was an early initial increase in activity, followed by a decrease back down to baseline levels of activity. While some of these cells resembled the transient hippocampal cells described by Cahusac et al. (1993), others appeared to resemble more the baseline sustained cells of Wirth et al. (2003). Control experiments in which the learning-selective cells were examined during a second new learning set showed a similar transient, direction-selective response. Thus, the learning-selective cells in the SEF and FEF signal new learning in a direction-selective frame of reference. This direction-based response in SEF and FEF differentiates these cells from the cells in the hippocampus that did not exhibit a similar response for a second new scene with the same rewarded target location.

The third category of learning-related activity described in the SEF and FEF was termed "learning-static" (Fig. 4C; ~24.5% of learning-related cells in the SEF). Like the learning-dependent cells, these cells also changed their activity in response to novel conditions and the activity was maintained for as long as the session lasted. In contrast to the learning-dependent cells, when the learning-static cells reached stable performance levels, there was a significant difference between the level of activity in response to the novel condition and the reference condition with the same rewarded target location. In this way, learning-static cells resemble the sustained changing cells observed in the hippocampus (Cahusac et al., 1993; Wirth et al., 2003). Similar to hippocampal changing cells, learning dependent, learning selective as well as learning static cells were observed during both the visual stimulus presentation and delay intervals in the SEF and FEF. However, unlike hippocampal cells, a relatively large proportion of SEF and FEF cells also signaled learning during the pre and postsaccadic periods of the task, consistent with their important roles in eye movement responses. Thus, while both hippocampal as well as frontal eye movement regions signal change during stimulus and delay periods, the SEF and FEF appear to play a more prominent role in signaling learning during the motor response periods of the task.

An analysis of the relative timing of neural and behavioral change in SEF and FEF suggested that the learning-selective population changed an average of 0.51 ± 2.35 trials after learning with a range of four trials before learning to eight trials after learning. The learning-dependent population changed an average of 0.86 + 1.88 trials after learning with a range of three trials before learning to six trials after learning. For both the learning-dependent and learning-selective cells, the largest percentage of cells changed either after learning (42% for learning-selective and 49% for learning-dependent) or at the same time as learning (37% for both learning-selective and learning-dependent). The smallest percentage of cells changed before learning (21% of the learning-selective and 14% of the learning-selective). Thus, while many cells in these regions have activity that is correlated with learning, most cells signal learning either in parallel with behavioral learning or slightly after behavioral learning. While a direct comparison of the timing of these learning-related signals is difficult to do because of differences in the analysis methods applied to these studies, in general, the learning signals appear to be slightly earlier in the hippocampus compared to the motor-related areas of the frontal lobe (Suzuki and Brown, 2005).

ASSOCIATIVE LEARNING IN THE PREFRONTAL CORTEX

Asaad et al. (1998) described the activity of cells in the prefrontal cortex during a conditional visual motor task with reversals. In this task, monkeys saw two novel visual stimuli each day and learned to associate those stimuli with either a left or right eye movement response. Once this initial set of two associations was learned, the object-response contingency was reversed. Many of the prefrontal cells described in this study signaled the impending direction of movement assessed with a direction selectivity index (absolute value of the difference in activity to the two saccade directions divided by their sum and then converting this value to a percent difference). However the appearance of directional selectivity alone did not reflect the learned associations since prefrontal cells continued to reflect the impending movement direction irrespective of whether the response was correct or incorrect. Instead, learning appeared to be most strongly correlated with the decreasing latency of appearance within the trial of direction selectivity (Table 1). Early in learning, the direction selectivity was observed late in the trial near the time when the response was executed (Fig. 5). With learning, this direction selective signal shifted earlier in the trial towards the stimulus presentation period. These results suggest that the earlier appearance of directional selectivity within prefrontal neurons was related to behavioral learning. However a quantitative analysis of the precise temporal relationship between the shifts in directional selectivity and behavioral learning was not presented. Like cells in the SEF and FEF, cells in the prefrontal cortex signaled learning during the stimulus, delay as well as during presaccadic portions of the task.

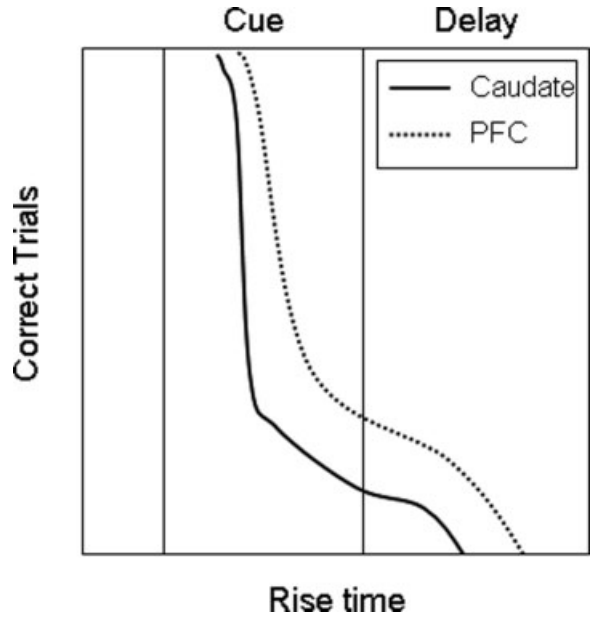

FIGURE 5. Schematic representation of the decreasing latency of the development of direction selective activity seen in the caudate and prefrontal cortex during learning and reversals of a conditional motor task. In this graph, the rise time denotes the timing within the trial that direction selectivity first developed. Note that the direction selective response develops both more quickly as well as eventually starts earlier in the trial compared to the direction selective activity in the prefrontal cortex. Adapted from Pasupathy and Miller, 2005.

ASSOCIATIVE LEARNING IN THE STRIATUM

Pasupathy and Miller (2005) compared the pattern of learning-related activity in the caudate and prefrontal cortex using the same conditional motor association task with reversals described in their earlier study of prefrontal learning-related activity (Asaad et al., 1998). They report that for neurons in the caudate and in the prefrontal cortex, learning was reflected in the earlier appearance within the trial of direction selectivity as learning progressed (Fig. 5; Table 1). Early in learning the direction selectivity was observed late in the trial near the time when the response was executed. With learning, this direction selective signal shifted earlier in the trial towards the stimulus-presentation period. The most striking finding reported was that not only was the same shift in direction selectivity seen in caudate neurons, but the speed of the temporal shift with learning was substantially more robust in the caudate cells compared to the prefrontal cells. Indeed the shift in latency appeared to occur before the relatively slow learning exhibited by the animals, though no direct comparisons were done to determine the precise relationship between the shifts in neural response latency and behavioral learning. The authors argue that their results support the hypothesis that rewarded associations are first identified by the basal ganglia and the output of this structure may serve to train neurons in the prefrontal cortex. However, an analysis of the error trials showed that caudate neurons did not differentiate between correct and error trials at any time point during the trial (See Supplementary Fig. 3 of Pasupathy and Miller, 2005). Thus, it remains unclear if these early direction directional signals in the caudate serve as a "teacher" for other brain areas or simply reflect early preparation or anticipation of the motor output.

Other studies describe learning-related signals in the striatum that resemble more the learning-related signals described in the SEF, FEF and hippocampus. Brasted and Wise (2004), for example, compared the learning-related activity in the caudate and putamen to activity in the premotor cortex using a conditional motor association task with an arm movement responses. They reported that both premotor cells as well as cells in the caudate and putamen exhibit clear learning related changes in activity similar to their previous reports in the SEF and FEF (Chen and Wise, 1995a,b). Similar findings were also reported by Hadj-Bouziane and Boussaoud (2003) Tremblay et al. (1998) and Inase (Inase et al., 2001). Similar to the SEF and FEF, Brasted and Wise (2004) also showed that the largest proportions of premotor and caudate cells change their activity either at the time of learning or after learning and few examples

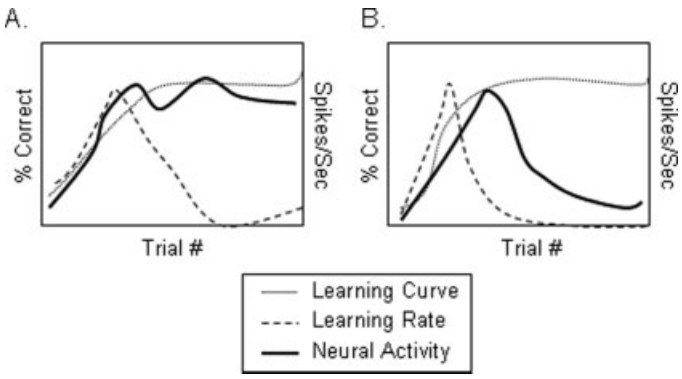

FIGURE 6. Schematic representation of the sustained (A) and transient (B) learning signals observed in the striatum during conditional motor learning as described by Williams and Eskandar (2006).

of cells that change before learning (Fig. 10 of Brasted and Wise, 2004).

Williams and Eskandar (2006) also recorded in both the caudate and putamen during a conditional motor association task very similar to the one used by Brasted and Wise (2004). While learning-related signals were seen during the entire trial period, this group found the most prominent striatal learning-related signals during the feedback period of the task. Two major patterns of striatal learning related activity were described (Table 1). Many caudate cells would either show increases or decreases in firing rate that was strongly correlated with the rate of learning, defined as the slope of the learning curve (Fig. 6B). Learning rate was maximal during the steepest part of the learning curve and minimal when performance is not changing. Thus, these learning-related cells in the caudate resemble the transient cells reported in the hippocampus by Cahusac et al. (1993) and the learning selective cells described by Wise and coworkers in the SEF, FEF, and caudate (Chen and Wise, 1995a,b; Brasted and Wise, 2004). In contrast to the learning-related signals in the caudate, most cells with learning-related activity in the putamen either increased or decreased their level of activity correlated with the learning curve but not the learning rate (Fig. 6A), similar to the sustained changing cells described in the hippocampus (Cahusac et al., 1993; Wirth et al., 2003) and the learning static cells described in the SEF, FEFE, and caudate (Chen and Wise, 1995a,b; Brasted and Wise, 2004). Furthermore, this group showed that electrical stimulation of the caudate during correct trials but not during error trials could significantly increase the rate of learning suggesting that this neural activity in the caudate was causally involved in the learning process. Specifically, they suggest that the caudate is responsible of adjusting the associative weights between sensory cues and motor responses during learning.

DISCUSSION

To examine how widespread brain areas participate in new associative learning, we have reviewed the patterns of learning-related neural signals seen across multiple brain areas during performance of conditional motor association learning tasks. This review shows that prominent associative learning signals are seen throughout the hippocampus, motor-related areas of the frontal lobe, prefrontal cortex as well as the striatum. Both commonalities as well as clear differences in the learning-related activity are seen across these areas. For example, cells in the hippocampus, SEF, FEF premotor cortex and striatum all signal learning by either increases or decreases in neural activity that are correlated with the animal's behavioral learning curve. While common themes are seen across brain areas, the differences in the learning-related signals across these brain areas provide insight into the unique functions of these different brain areas. One of the major differences is the relative prominence of direction-based/motor-based learning signals. For example, in the hippocampus, there is strong evidence that neither the sustained, baseline sustained, or transient signals signal learning specific for a particular response direction (Cahusac et al., 1993; Wirth et al., 2003). There is also some evidence that the learning-related hippocampal signals are not specific for particular visual stimuli (Miyashita et al., 1989; Cahusac et al., 1993). The neurophysiological evidence reviewed above is consistent with the idea that the primate hippocampus is involved in signaling the salient associations between objects/scenes or between objects/scenes and responses. These signals are neither response-based nor purely object/scene-based, but instead appear selective for the particular associations being learned. This interpretation is consistent with the relational theory of hippocampal function that stresses the importance of this structure in forming flexible new associations between different stimuli irrespective of modality (Eichenbaum et al., 1999; Eichenbaum, 2000; Buckmaster et al., 2004).

In contrast to hippocampal cells, cells in the SEF, FEF, premotor cortex, prefrontal cortex and striatum can signal learning in a direction-based or motor-based frame of reference. Cells in these areas signal new learning for a particular target location with either increases (learning-dependent) or decreases (learning-selective) in activity. While some cells are selective for only new learning in a particular direction (learning-selective), other cells signal both new learning and previously established associations specific for a particular direction (learning-dependent). These findings are consistent with the idea that these areas are involved in the ability to form arbitrary mappings between objects and particular actions (Murray et al., 2000). The changes in latency of the appearance of direction selective responses in the striatum and prefrontal cortex described by Miller and colleagues (Asaad et al., 1998; Pasupathy and Miller, 2005) are also consistent with a role in motor-based learning signals.

Also consistent with this idea is the observation that while neurons in the SEF, FEF premotor cortex and striatum all exhibit learning signals in the stimulus and delay portions of the task a relatively large proportion of cells that signal learning in and around the motor response period of the task. In contrast, fewer cells in the hippocampus signal learning during the motor portions of the task and relatively larger proportions signal learning during the scene and delay periods of the task.

These findings suggest a temporal differentiation between these regions where the hippocampus may be particularly (but not exclusively) involved in signaling learning during the sensory and delay periods of the task and other motor-related areas become more prominent later in the trial during the motor response periods of the task.

Thus, while all these brain areas participate in new condition-motor associative learning, different structures appear to participate in unique aspects of the associative learning process. The hippocampus participates in this task by signaling new associations between scenes and targets or responses. In contrast, motor related areas have stronger motor-based learning strategies (learning about particular motor responses) and in general provide stronger learning-related signals in the motor related portions of the task at the end of the trial. Another critical question involves the timing of these differential learning-related signals relative to behavior and whether different structures signal learning in parallel or interact during the learning process. While preliminary evidence suggests that the hippocampal cells may signal learning earlier than SEF and FEF cells (Suzuki and Brown, 2005) the detailed temporal relationship between changes in neural activity and learning remains to be fully characterized in the striatum and prefrontal cortex. Previous studies have suggested that prefrontal cortex plays an important role in top-down control of activity in the medial temporal lobe during performance of working memory tasks (Miller et al., 1996), however, in new associative learning that does not involve new rule learning, the specific relationship between hippocampal prefrontal learning-related activity remains to be specified. Studies in the hippocampus and caudate have suggested that these areas may compete for control of behavior during spatial working memory tasks with the hippocampus controlling more flexible spatial learning strategies and the caudate controlling more rigid habit like learning strategies (Packard et al., 1989; Packard and McGaugh, 1996). It will be of interest to determine if the caudate and hippocampus also competes for control of associative learning. However, another possibility is that they work together to coordinate their activity during conditional motor learning. Future studies that record simultaneously in both structures will be useful to address this question.

In conclusion, conditional motor learning paradigms offer a unique opportunity to compare and contrast learning-related neural activity across widespread brain areas. While neurophysiologists tend to focus on the activity of single brain areas for performance of the task, this review makes the point that widespread brain areas participate in conditional motor learning. While the hippocampus appears to signal the associative side of new learning, the various motor related areas exhibit learning in a motor-based frame of references, though all areas also share some overlapping learning signals. These results are consistent with findings from lesions studies that damage of one area rarely produces complete impairment since other brain areas can take over. Finally, while this review has provided preliminary insight into the strong and parallel associative learning signals that exist across widespread brain areas, it will be important to record in parallel across these areas in the same animal to determine exactly how these areas work in parallel, interact or possibly compete during new conditional motor learning.

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