COMMENTARY

Homeostatic Regulation of Memory Systems and Adaptive Decisions
Sheri J.Y. Mizumori,* and Yong Sang Jo

ABSTRACT: While it is clear that many brain areas process mnemonic information, understanding how their interactions result in continuously adaptive behaviors has been a challenge. A homeostatic-regulated prediction model of memory is presented that considers the existence of a single memory system that is based on a multilevel coordinated and integrated network (from cells to neural systems) that determines the extent to which events and outcomes occur as predicted. The “multiple memory systems of the brain” have in common output that signals errors in the prediction of events and/or their outcomes, although these signals differ in terms of what the error signal represents (e.g., hippocampus: context prediction errors vs. midbrain/striatum: reward prediction errors). The prefrontal cortex likely plays a pivotal role in the coordination of prediction analysis within and across prediction brain areas. By virtue of its widespread control and influence, and intrinsic working memory mechanisms, thus, the prefrontal cortex supports the flexible processing needed to generate adaptive behaviors and predict future outcomes. It is proposed that prefrontal cortex continually and automatically produces adaptive responses according to homeostatic regulatory principles: prefrontal cortex may serve as a controller that is intrinsically driven to maintain in prediction areas an experience-dependent firing rate set point that ensures adaptive temporally and spatially resolved neural responses to future prediction errors. This same drive by prefrontal cortex may also restore set point firing rates after deviations (i.e., prediction errors) are detected. In this way, prefrontal cortex contributes to reducing uncertainty in prediction systems. An emergent outcome of this homeostatic view may be the flexible and adaptive control that prefrontal cortex is known to implement (i.e., working memory) in the most challenging of situations. Compromise to any of the prediction circuits should result in rigid and suboptimal decision making and memory as seen in addiction and neurological disease. © 2013 The Authors. Hippocampus Published by Wiley Periodicals, Inc.

KEY WORDS: hippocampus; striatum; prefrontal cortex; predictions; error correction

INTRODUCTION

Different motivational systems can be simultaneously active, and as such, they must compete for control over decision processing and behavioral responses. For example, a hungry animal may explore a territory for food while “keeping an eye out” for potential mates and predators. In this case, a single behavioral sequence is engage but it may be driven from moment to moment by whichever motivation is the strongest. The current and strongest motivation should determine which cues draw one’s attention, the appropriate behavioral responses, and one’s expectations for particular outcomes of choices and actions. As such, motivation state likely influences the organization of currently active neural representations in memory-related brain structures. Indeed, it has been shown that different hippocampal place field “maps” (which presumably reflect different memories) are recalled depending on whether rats are searching the same space for food or water after being made hungry or thirsty, respectively, in a single environment (Kennedy and Shapiro, 2004).

The ability to efficiently switch between different mnemonic influences on choices and actions is undoubtedly essential for the continuous execution of adaptive behaviors. A current challenge for the field of memory research is to understand the mechanisms by which different memory systems are dynamically and continuously coordinated according to one’s current goal. There are numerous excellent reviews of literatures that define the functionality of individual memory systems of the brains (e.g., Eichenbaum and Cohen, 2001; Tulving, 2002; Boyden et al., 2004; Colombo, 2006; Yin and Knowlton, 2006; Fuster, 2009; Kesner, 2009). To address the issue of how these memory systems work together to provide what appear to be unitary control over behaviors, the following first presents an organizational scheme for memory processing in the brain that includes decision neural circuitry (Schultz and Dickinson, 2000; Hikosaka et al., 2008). Then we discuss how the different mnemonic brain regions may be dynamically regulated via a homeostatic-like mechanism that insures the continuous generation of adaptive decisions.

MULTIPLE PROCESSORS OF MNEMONIC INFORMATION

From the early reports of memory problems of brain damaged amnesic patients came the view that different brain areas are responsible for distinct types of memories.

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Decades of experimental research supported this view since targeted lesions in animals produced memory dissociations that were comparable to those observed clinically. For example, hippocampal damage produced episodic (including event or spatial) memory deficits that were not shown by animals with striatal lesions; the latter instead showed habit learning deficits. The accumulation of similar anatomically defined distinctions led to the commonly held view that hippocampus mediates episodic or event-related memory and the striatum mediates habit or procedural memories (Sherry and Schachter, 1987; Packard et al., 1989; Knowlton et al., 1996; Squire and Zola, 1996; White and McDonald, 2002). Additional research identified roles for other brain structures in specialized memory functions: the amygdala is considered important for learning and remembering emotionally relevant information (Kim and Jung, 2006; Johansen et al., 2011), the prefrontal cortex preferentially mediates working memory (e.g. Jacobsen, 1936; Fuster, 2006, 2009), and sensory and motor memories are thought to involve parietal cortex, medial temporal cortex, and cerebellum (e.g. Duhamel et al., 1992; Bisley et al., 2004, Taylor and Ivry, 2012; Ito, 2013; Rochefort et al., 2013). Figure 1A provides a schematic of these memory systems, illustrating the parsimonious view that each separately contributes to a single decision or action selection process. It is often suggested that the differential strengths and efficiencies of the memory processing centers of the brain control behaviors according to task demands (Packard and McGaugh, 1996; Mizumori et al., 2004; Fig. 1B). In fact numerous physiological and theoretical models describe mechanisms, from broad neural systems to cellular perspectives, by which these brain structures enable efficient and accurate mnemonic functions. By comparison, little is known about how these multiple processors of mnemonic information work interactively to result in continuously adaptive, experience-dependent behaviors and choices in a complex natural world.

By definition, all memory systems have a common purpose, and that is to remember information. However, all memory systems do not play equal roles in determining the impact of experience on particular decisions or actions. What accounts for this difference? Abundant evidence from primate and rodent studies show that (internal and external) sensory, behavioral, task rule and reward information are often represented experientially in brain areas thought to mediate different forms of memory (e.g., Wiener et al., 1993; Lavoie and Mizumori, 1994; Wiener, 1996; Pratt and Mizumori, 2001; Yeshenko et al., 2004, Barnes et al., 2005; Smith and Mizumori, 2006; Puryear et al., 2010). Thus, the nature of the represented information per se cannot explain the unique mnemonic contributions of different brain areas. Rather their unique mnemonic contributions are likely to be more strongly determined by brain area-specific computational network architectures, and their afferent and efferent connections.

**HIPPOCAMPUS AND CONTEXT ANALYSIS**

There is substantial evidence to support the view that hippocampus is essential for the processing of context information (Hirsh, 1974; Myers and Gluck, 1994; Anagnostaras et al., 2001; Maren, 2001; Fanselow and Poulos, 2005; Bouton et al., 2006). For example conditioned fear responses to contextual stimuli are eliminated with hippocampal lesions even though responses to discrete conditional stimuli remain intact (Kim and Fanselow, 1992; Phillips and LeDoux, 1992).

![Figure 1](image-url)
In these earlier experiments, the term “context” was used to refer to only the external sensory environment. However, more recently, it has become evident that the type of context processing carried out by hippocampus is more complex, and that it includes sensory (external and internal), behavioral, and motivational information that characterizes and defines a specific situation or event (Nadel and Wilner, 1980; Mizumori et al., 1999; Nadel and Payne, 2002; Jeffery et al., 2004; Smith and Mizumori, 2006; Mizumori, 2008a; Penner and Mizumori, 2012a,b). The firing patterns of individual hippocampal neurons change when any aspect of a familiar situation changes, including internal and external sensory information, the behavior and cognitive requirements to achieve a desired goal, one’s motivational state, and one’s expectations for a particular reward value (e.g., Markus et al. 1994; Wood et al., 2000; Jeffery et al., 2004; Yeshenko et al., 2004; Ferbinteneau and Shapiro, 2006; Smith and Mizumori, 2006; Leutgeb et al., 2007). These place field changes have been described as being of one of two types: “global remapping” in which the location of the field is altered, and “rate remapping” in which the in-field firing rates is altered but not the absolute field location (e.g., Leutgeb et al., 2004). The former is thought to reflect switches between episodic memories or maps, while the latter is considered to reflect changes in a familiar memory, or map. In both cases place fields are thought to represent sensory, behavioral or cognitive features of a context, as well as the learned value (i.e., economic utility; Penner and Mizumori, 2012a,b), or salience, of each context defining feature. An example is the learned probability of obtaining a reward when a particular choice is made in a particular location. Evidence is indeed beginning to emerge to support this view as place fields have been observed to change according to the probability of expected reward values (Hollup et al., 2001; Lenck-Santini et al., 2001, 2002; Lee et al., 2012; Penner et al., 2012). Also, recent neuroimaging studies with humans show that HPC becomes selectively active during value-based decision making (Wimmer and Shohamy, 2012), perhaps to generate prediction error signals during learning (Kumaran and Maguire, 2007; Kuhl et al., 2010; Chen et al., 2011; Dickerson et al., 2011; Foerde and Shohamy, 2011; Duncan et al., 2012a,b).

In freely-navigating animals, hippocampal context information is represented within a spatial framework (Nadel and Wilner, 1980; Mizumori et al., 1999, 2000; Nadel and Payne, 2002; Mizumori et al., 2007; Mizumori, 2008a,b). A spatial bias to hippocampal neural representations has been described as location- and/or directionally selective firing in mice, rats, bats, birds, and monkeys (O’Keefe, 1976; Rolls et al., 1989; Nakazawa et al., 2002; Hough and Bingman, 2004; Yartsev and Ulanovsky, 2013). Human hippocampal neurons also show spatially organized representations as subjects solve virtual spatial navigation tasks (e.g. Maguire et al., 1998; Burgess and O’Keefe, 2003; Etchamendy et al., 2012). It is possible, then, that the imposition of a spatial organization on context information is a fundamental process that facilitates hippocampal mnemonic operations, and as such, it is prominent and commonly found across species. In this case, hippocampus can be thought of as representing the value of sensory, behavioral, and cognitive information relative to one’s motivation and spatial experiences in a given environment.

The multifaceted neural code that is associated with unique contexts provides hippocampus with appropriately detailed information to strategically guide future decisions, behaviors, and memories based on event-specific information. Events are distinguished not only by their sensory and behavioral significance, but also the variation of the significance across time. Thus an important function of hippocampus may be to identify when one significant event ends and the next begins (Smith and Mizumori, 2006). One way to make such identifications is to signal when expectations are, or are not, met. Of interest in this regard, there is growing evidence that an important hippocampal algorithm is to identify times when actual experiences vary from those expected based on past experiences. It is worth noting that the same basic algorithm can be applied in novel situations and when familiar conditions change (Fig. 2). Many laboratories have shown that hippocampal place fields change characteristics (i.e. remap) during initial exposures to novel situations (e.g. Frank et al., 2006; Roth et al., 2012) but that with continued exposure the same place fields stabilize (i.e. they do not continue to remap). The degree of stability is related to the amount of direct experience that an animal has with a particular environment (Rowland et al., 2011). In novel situations, any “expectation” would probably not match actual experiences since by definition there is no prior knowledge from which to form accurate expectations. Thus, all input should initially generate a mismatch signal, and these should subside with experience. After familiarity is established, hippocampal neural activity shows sensitivity to changes in familiar environments, or contexts: significant alterations in hippocampal neural representations are observed when subjects are exposed to unexpected (i.e. mismatch) conditions (e.g. Mizumori et al., 1999; 2000; Kumaran and Maguire, 2007; Mizumori, 2008a,b; Chen et al., 2011; Duncan et al., 2012b; Penner and Mizumori, 2012a).

A general function of the hippocampus, then, may be to detect mismatches between the expected and actual contextual features of a task so that “context prediction error” (CPE, Fig. 2) signals can be forwarded to efferent systems for subsequent evaluation of the significance of the change. In this way CPEs can ultimately be used to define contexts associated with specific outcomes or intentions. This ability to discriminate contexts has been proposed to reflect a fundamental computation that defines and predicts events, or meaningful episodes (O’Keefe and Nadel, 1978; Cohen and Eichenbaum, 1993; Dusek and Eichenbaum, 1998; Redish, 1999; Smith and Mizumori, 2006; Lisman and Redish, 2009; Gill et al., 2011; Penner and Mizumori, 2012a), a function that makes hippocampus essential for normal episodic memory.

Hippocampus
Analogous to hippocampus, the midbrain dopaminergic system may also generate prediction error signals but in this case the focus is on whether the outcome of goal-directed behaviors occurs as predicted based on past experience (Hollerman and Schultz, 1998; Hollerman et al., 1998; Bayer and Glimcher, 2005; Mizumori et al., 2009; Stalnaker et al., 2012). In particular, it is thought that dopamine neurons transmit information about the subjective value of rewards in terms of reward prediction error signals (RPEs; Fig. 2). RPEs are thought to initiate three distinct and parallel loops of information processing between striatum and neocortex as new associations become learned sufficiently to habitually drive behaviors (e.g., Alexander et al., 1986; Alexander and Crutcher, 1990; Haber, 2003). Penner and Mizumori (2012b) recently summarized this vast literature starting with the limbic loop through which information flows between ventromedial prefrontal cortex with the ventral striatum (Alexander and Crutcher, 1990; Graybiel et al., 1994; Voorn et al., 2004; Yin and Knowlton, 2006; Graybiel, 2008; Pennartz et al., 2009) to mediate learning about the significance of previously neutral stimuli (i.e. as occurs in Pavlovian learning). The associative loop involves the medial prefrontal cortex and the dorsomedial striatum to support action-outcome learning. The sensorimotor loop involves transmission between somatosensory and motor cortical areas with the dorsolateral striatum. The latter loop is suited for incremental sensory-motor learning as happens when new procedural memories are formed. It is hypothesized that the transformation of newly learned behaviors to habits occurs as a result of multiple iterations of information flow through these three information loops starting with the limbic loop, the associative loop, and then finally the sensorimotor loop. Importantly, information flow through these systems is thought to be continually informed about the expected values of goals via dopamine signaling from the ventral tegmental area (VTA) and/or the substantia nigra (SN; Horvitz, 2002; Nicola et al., 2004; Schultz, 2010). Thus, when performing learned habits, the striatum is particularly suitable to rapidly control behavior or to provide feedback about behaviors that led to prediction errors (Stalnaker et al., 2012) because of its rather unique pattern of reciprocal connections with sensory and motor cortical regions (Alexander and Crutcher, 1990; Groenewegen et al., 1999; Haber, 2003), and because striatum can receive immediate feedback when goal outcomes are not what was expected. In this way, midbrain signals of errors in predicting rewards may initiate adjustments to future planned behaviors (Penner and Mizumori, 2012b).

Sensory and motor predictions: In addition to hippocampus and striatum, various sensory and motor cortical and cerebellar areas have been reported to generate prediction errors when expected sensory or motor-related input does not match expectations (e.g. Tanaka et al., 2009; Scheidt et al., 2012). This sort of feedback permits temporally and spatially precise behavior adjustments based on past outcomes. Also, information about expected sensory and motor events can be used to plan future sensory expectations and specific anticipatory movements (e.g. Duhamel et al., 1992). Such prediction error mechanisms are thought to fine tune actions to optimize the chances of securing a desired goal.
FIGURE 3. Building on the model shown in Figure 2, here it is shown that if hippocampal context prediction analysis concludes that there were NO changes in the context (i.e. a “match”), then the currently active memory network becomes strengthened to increase the likelihood that it will be activated the next time that animals are in the same context. If, on the other hand, the hippocampus concludes YES there was a context change (i.e. a “mismatch”), then the prediction error signal that is transmitted to the midbrain-striatal system begins an evaluation of the significance of the change. The midbrain-striatal system should then determine whether the value of the outcome occurred as expected originally. If the answer is NO, then the memory network that generated the initial expectation should be strengthened since it still produced the desired goal. If, on the other hand, it was determined that YES, the outcome is different from what was expected, then the memory network should be updated accordingly. At other times, there may be an unexpected change in reward outcome, and this should initiate a prediction error signal at the level of the midbrain-striatum. This YES conclusion should lead to a memory update that the expected context did not result in rewards as predicted, and this in turn would be reflected in the future expectation information provided to the hippocampus. From this point, a similar context comparison will be carried out as described above. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Individual neurons face a continual barrage of excitatory inputs relative to their perceived utility or value, and thus ultimately determine future decisions and behavior (e.g. Schultz and Dickinson, 2000; Doll et al., 2012; Walsh and Anderson, 2012). In fact it has been suggested that the ability to predict behavioral outcomes has essentially driven the evolution of the entire brain (Llinas and Roy, 2009). If this is the case, the underlying organization and detailed neural mechanisms of predictions are likely foundational for complex cognitive functions like decision making, learning and memory, and thus likely to be highly conserved across species (Watson and Platt, 2008; Adams et al., 2012).

At a cellular level, prediction error signals may elevate the level of excitability of efferent neurons such that they become more responsive to outcome signals. This greater neural responsiveness may enhance the temporal and spatial resolution of future neural responses, and this in turn should ultimately result in improved accuracy of future predictions. For example, if hippocampus detects a mismatch between expected and actual contextual features, it may generate an error signal that “alerts” striatal efferent structures so that they become more responsive to future rewards (Schultz and Dickinson, 2000; Mizumori et al., 2000, 2004; Lisman and Grace, 2005; Mizumori, 2009, Penner and Mizumori, 2012a,b; Fig. 3). Midbrain-generated reward prediction error signals may destabilize cortical neural (memory) networks so that they become more readily updated with new information (Mizumori, 2008a; Penner and Mizumori, 2012b). The updated memory information can then be passed on to hippocampus in the form of the most up-to-date context expectations (Fig 3). This view of how error signals can inform future processing in other prediction regions of the brain suggests a high level of interdependence across mnemonic structures regardless of the task (as suggested by Yeshenko et al., 2004; Mizumori et al., 2004).

Individual neurons face a continual barrage of excitatory inputs across tens of thousands of synaptic connections. Yet, neurons cannot maintain high levels of excitability and remain viable in the long term. Fortunately, individual neurons appear to be able to naturally and automatically engage mechanisms that control their level of excitability. This may occur by sensing and controlling the flow of various ions across cell membranes (e.g., Turritigiano, et al., 1998; Burrone et al., 2002; Turritigiano, 2008; see more detailed description below). Optimal levels of neuronal activity can be maintained also by achieving a relatively constant balance of excitatory and inhibitory synaptic input (e.g. Burrone et al., 2002). Together these factors define the baseline level of tonic activity against which phasic error signals are imposed. Interestingly, the tonic level of cell excitability can be set according to the motivational state of an animal (Fig. 4; Pecina et al., 2003; Cagniard et al., 2006; Puryear et al., 2010). In this way, one's motivational state may play a significant role in determining the threshold for phasic neural and behavioral responding.

Motivational state information (e.g. signals of hunger or thirst) may arrive in prediction error structures such as the hippocampus or striatum via hypothalamic afferent systems. For example, lateral hypothalamus signals of hunger that reach brain areas that evaluate predictions may increase subsequent reward-responsiveness of efferent target neurons. Elevated responses to reward could presumably reflect higher subjective values of the reward, and this interpretation is consistent with the biological needs of an animal. The amygdala, on the other hand, is thought to mediate a different motivational variable, and that is the emotional state of animals (Johansen et al., 2011). A message reflecting the current emotional state may emerge from the amygdala's role in associating cues with their aversive consequences (e.g. Chau and Galvez, 2012; Paz and Pare, 2013). One scenario is that the amygdala may alter its neural activity in response to fear (Ciocchi et al., 2010; Hauben et al., 2010; Li et al., 2013). Since the amygdala has direct excitatory effects on substantia nigra or VTA neurons (Lee et al., 2005; Zmam et al., 2011), fear-induced amygdala activation may increase the likelihood that dopamine neurons
transition to a more excitable “up-state” (Wilson, 1993; Wilson and Kawaguchi, 1996) when hippocampal messages arrive (Fig. 4). In this way, in urgent situations, animals can more readily assess the value of a changed context since transitioning to an “up-state” could make the dopamine cells respond more quickly to an input. This could be adaptive since responses can be implemented more quickly.

In addition to generally biasing the levels of neural excitability (which may translate to biasing the threshold for prediction error signaling), the amygdala may modulate prediction error-based learning efficiency on a trial by trial basis. For example, it is known that there is increased attention to cues or rewards that are unexpected or surprising based on past experiences (Rescorla and Wagner, 1972; Pearce and Hall, 1980). The
errors, or MPE). There are others as well (area X prediction error, or SPE), and the motor cortex (motor prediction error, or SPE), sensory cortex (sensory prediction error, or SPE), and the motor cortex (motor prediction errors, or MPE). There are others as well (area X prediction error, or XPE). These prediction error areas connect with each other, and they have reciprocal connections to the prefrontal cortex. Messages from the prediction brain areas relay activity state information to the prefrontal cortex. It is proposed that in a familiar situation (i.e., when there are no prediction errors) the prefrontal cortex is continually driven to maintain afferent neural activity to a set point via a complex pattern of excitatory (+) and inhibitory (-) efferent connections to the brain areas that sent state information to the prefrontal cortex previously. In this way, the prediction neuronal networks will be prepared to generate temporally and spatially accurate error signals when needed. After prediction errors are detected, error messages are sent to other prediction centers and to prefrontal cortex. The latter may coordinate the efficiencies of the different prediction centers based on recent outcomes of behaviors. This heightened coordinated activity could result in transient co-modulation across brain structures, and it could effectively extend working memory operations beyond the prefrontal cortex. Motivation may tune the efficiency of the prediction analysis system by raising or lowering prediction thresholds across multiple brain areas. Motivational influences likely arrive from structures such as the amygdala and hypothalamus. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

dopamine system clearly plays a role in surprise-induced enhancement of learning (e.g., Schultz et al., 1997; Schultz and Dickinson, 2000), and this may relate to an influence of the amygdala on dopamine neurons since this prediction error-based learning effect is abolished in rats with amygdala disruption (Holland and Gallagher, 2006) with no effects on the subsequent expression of surprise-induced enhanced learning (Lee et al., 2008). The amygdala and hypothalamus, then, may orchestrate information processing circuits/systems by ultimately setting the threshold for future error detection via direct connections to prediction error structures such as the hippocampus, striatum, sensory and motor cortex, and the cerebellum.

The prefrontal cortex can also be thought of as playing a modulatory role in the processing of prediction errors but for reasons that are different than the amygdala. The prefrontal cortex is commonly thought to be important for holding information online in a working memory buffer (e.g., Fuster, 2008; Arnsten et al., 2012). This function is considered essential to be able to select appropriate responses and/or for switching behavioral strategies (Ragozzino et al., 1999a, b; Young and Shapiro, 2009), and this interpretation is consistent with findings that transient functional connections exist between the prefrontal cortex and the hippocampus or striatum especially when working memory is helpful for optimal behaviors. For example hippocampal and prefrontal theta become co-modulated at times when animals make choices (e.g., Hyman et al., 2005; Shirvalkar et al., 2010) but not at other times during task performance. Co-activation of striatal and prefrontal activity has also been observed when working memory is required for accurate response selection (Levy et al., 1997; Scimeca and Badre, 2012). Thus, the functional connections between striatum and prefrontal cortex, or between hippocampus and prefrontal cortex, can vary in strength and impact depending on the current task demands (Fig. 4). Presumably this variation reflects the phasic task-dependent coordination of patterns of excitation and inhibition between prefrontal cortex and its efferent targets. Since the prefrontal cortex is thought to play a role in prediction analysis (e.g., Hollyroyd et al., 2002), we suggest the possibility that the coordination across prediction areas is at least in part regulated by prefrontal cortex via regulation of its inhibitory and excitatory projections to multiple types of neurons (i.e., both interneurons and projection neurons) in efferent prediction brain areas (as reviewed in Khan and Muly, 2011; Arnsten et al., 2011, 2012), neurons that then return information back to prefrontal cortex. Neocortex has indeed been shown to regulate the excitability states of subcortical neurons (e.g., Plenz and Arnsten, 1996; Plenz and Kitai, 1998; Calhoun and O’Donnell, 2013). Prefrontal cortex in particular may likely continually receive information about the current level of neural activity in target regions, and then use these afferent data to determine the extent and type of excitatory and inhibitory control needed to achieve optimal tonic activity within each of the multiple.
A PREDICTION MODEL OF MEMORY ORGANIZATION

The brain contains a dynamic and interactive architecture by which memories of past experiences can continually and adaptively guide choices and behaviors. The fundamental elements of such an adaptive memory system necessarily include a) mechanisms for detecting errors in predictions about sensory, motor, decision and event outcomes (e.g. Yiv and Schoenbaum, 2008), b) the computational architecture to then coordinate different sorts of mismatches or errors between memory-based predictions and actual events with the goal of selecting adaptive decisions or actions, c) mechanisms for selecting and predicting the future outcomes of the chosen decision or action, and d) the ability to quickly and strategically restore baseline activity levels in such a way that the outcomes of future predictions can be rapidly and optimally assessed. This sort of adaptive memory system is made possible by natural neural regulatory systems that are driven to resolve uncertainties that result from failed predictions (Fig. 6; e.g. Dayan, 2012). Indeed, brain mechanisms have been identified that respond to outcomes only (or primarily) under uncertain conditions (Fiorillo et al., 2003, 2008). An inability to accurately resolve uncertainties will preclude the ability to correctly predict the outcomes of responses or significant events, and this in turn will result in maladaptive decisions and actions.

Hippocampus

![Diagram](image)

**FIGURE 6.** A: A homeostatic model of memory processing suggests that the primary goal of prefrontal cortex interactions with prediction centers of the brain (e.g., hippocampus and the midbrain-striatal area) is to maintain the baseline (tonic) firing rate of neurons within these centers at a set point level that is optimal for detecting future prediction errors. Modulating factors such as one's motivation or emotional state can elevate or reduce the baseline firing rates. According to Figure 5, the prefrontal cortex continually receives information from the prediction areas regarding the current population firing rates. If the baseline rates become elevated (e.g., due to stress) the prefrontal cortex is equipped to anatomically and physiologically restore firing rates (red straight arrows) to their optimal (baseline) levels. If the rates become too low (e.g., in depression), the prefrontal cortex should engage mechanisms to elevate firing to optimal levels over time. When a prediction error signal arrives in, or is generated by, a given prediction structure, firing rates can increase (in cases when prediction errors are positive) or decrease (when prediction errors are negative). The degree of rate increases or decreases scales to the degree of mismatch that is detected, and the slope of the increase or decrease in firing may vary between individuals and/or as a function of experience (blue arrow). B. The prefrontal cortex is responsible for restoring the firing rates back to optimal levels and this reduces the uncertainty that was generated by the prediction error signals. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Be most adaptive if the prefrontal cortex lowered the level of excitability of its target cells so that optimal responsivity can be restored in the target region.

Recurrent neurocircuitry within the prefrontal cortex is thought to contribute to its working memory capacity (e.g. Arnsten et al., 2012), and as such this circuit is a clear candidate system to not only integrate error signals arriving from the different prediction error brain regions, but to also bias the thresholds and strengths of subsequent error-related signals from the brain regions that originally produced the error signal. The particular constellation of excitatory and inhibitory biases presumably will result in the most desired behavioral outcome.

In summary, at specific times when working memory is needed, the intrinsic recurrent neural circuits of the prefrontal cortex (Arnsten et al., 2012) may selectively and strategically exploit (differentially or in concert) its rich array of excitatory and inhibitory efferent connections to regulate firing rates in different prediction areas of the brain. In this way, the prefrontal cortex may regulate the relative responsiveness of different prediction brain regions in task-dependent ways. When prediction errors are detected and firing rates change, the prefrontal cortex may not only integrate the signal within its recurrent (working memory) intrinsic circuitry, but it may have a key restorative function in efferent structures such that the firing rates return to a baseline tonic level that optimizes subsequent responsiveness to input. Thus, the prefrontal cortex may bias efferent neurons' ability to engage in, or efficiently use, prediction error analysis and hence their ability to adaptively guide future behaviors.
The fundamental elements of the proposed prediction model of memory include the following:

**DETECTING ERRORS IN PREDICTIONS ABOUT SENSORY, MOTOR, DECISION, AND EVENT OUTCOMES**

It was emphasized above that most of the brain areas that traditionally have been ascribed to have specific memory functions (e.g. hippocampus, striatum, amygdala, sensory and motor cortex, cerebellum) engage in match-mismatch operations for the purpose of detecting prediction errors. The specific types of information that are evaluated vary across brain areas as this is determined by their different constellation of inputs. We suggest that these error detection systems have in common output that effectively alerts other prediction error systems (either directly or via prefrontal cortex regulation, Fig. 5) so that memories can be updated (and behaviors implemented) as quickly and accurately as possible.

**COORDINATING DIFFERENT SORTS OF MISMATCHES OR ERRORS IN PREDICTION**

By virtue of its unique and sophisticated pattern of connections with prediction areas of the brain, as well as its capacity to retain information within an internal recurrent collateral system, the prefrontal cortex is strategically situated to receive and integrate prediction error messages simultaneously from the various memory regions of the brain via both inhibitory and excitatory mechanisms. It is proposed that much of the coordination is driven by natural and automatic tendencies to maintain neural networks in stable states. This also just happens to be the state where the neural sensitivity to prediction errors is maximal. That the brain is driven to resolve uncertainties that arise with prediction errors (Fiorillo et al., 2003; Knill and Pouget, 2004; Doya, 2008; Schultz et al., 2011; Bach and Dolan, 2012; Dayan, 2012) should ensure adaptive and predictable outcomes. Given the role for neighboring orbital frontal cortex in risky or probabilistic decision making (e.g. O’Neill and Schultz, 2010; Roitman and Roitman, 2010; Schultz et al., 2011), it is likely that the orbital frontal and prefrontal cortex normally work together to result in the most accurate decisions that reduce uncertainty (Rushworth and Behrens, 2008; O’Neill and Schultz, 2010). Future work aimed at understanding in more detail the relationship between the orbital and prefrontal cortices should shed new light on the mechanisms of the frontal cortical response to uncertainty and prediction errors. Also, since one’s past experiences can bias one’s interpretation of prediction errors and outcome values, prefrontal cortex coordination of prediction-based brain areas should also be impacted by expectancy information provided by existing long-term memories.

When no prediction errors are present (i.e., when working memory is not needed for successful performance of a task), the prefrontal cortex may continue to automatically monitor (and then maintain) a level of neural activity that is optimal for detecting future errors of prediction. This ability to constantly check for possible errors in prediction seems necessary to optimally execute adaptive behaviors.

If prefrontal cortex has an active role in coordinating activity within and across prediction centers of the brain, organisms would be endowed with a high degree of behavioral flexibility at precisely the times when multiple factors need to be considered simultaneously to make a choice or decision. This type of processing is consistent with a common definition of (prefrontal-mediated) working memory in which a working memory “buffer” allows information to be manipulated. However, analogous to an alternative view of prefrontal function proposed by Fuster (2006, 2009), it is suggested here that managing the network activity between the prefrontal cortex and connected prediction areas of the brain is what produces working memory capacity. If this is the case, the critical role of the prefrontal cortex in adaptive behaviors should be most obvious when multiple prediction errors need to be processed simultaneously. Indeed, combinations of prefrontal cortex and connected prediction areas appear co-activated during “working memory” function (e.g. Levy et al., 1997). Prefrontal coordination of prediction centers may be continuous even in situations that do not require working memory, thereby enabling organisms able to rapidly change behaviors as needed by changing environmental conditions. With prefrontal cortex damage, then, one may not observe behavioral deficits unless conditions change and prediction errors need to be detected in order to make accurate choices. The continuous and automatic functioning of memory regions of the brain has been postulated by a number of investigators (e.g. Mizumori et al., 2004; Tse et al., 2007). Prefrontal cortex damaged that results in inefficient behaviors could be due to an impaired ability of error detection systems to guide adaptive behaviors and/or relatively ineffective compensatory mechanisms that were engaged (Ragazzino et al., 1999a).

In summary, working memory may be possible because it is involved in (or in this case controls) organized exchanges across widely distributed networks across the brain (Fuster, 2006, 2009). An important implication is that prefrontal cortex does not by itself make executive decisions but rather it has the highly influential role of biasing the impact of one or a combination of prediction error analyses depending on the successes and failures of recent predicted outcomes. In this way, prefrontal cortex ultimately determines which behavior should next be implemented.

**SELECTING FUTURE BEHAVIORS AND PLANNED OUTCOMES**

The circuit described thus far accounts for animals’ ability to correct behaviors based on past outcomes. What happens when there is more than one option for a decision or action? In order to make that decision, one needs to look ahead in time...
to determine the expected outcomes one, two, or more choices down the road, then select the option that will eventually lead to the most desired outcome. If one can determine that the ultimate goal can be achieved by going down path A but not B, greater certainty could be associated with choice A. While it is not known how such prospective analysis takes place in the brain, recent data reveal that neurons in at least the hippocampus have the capacity to prospectively and retrospectively code spatial context information (e.g., Wilson and McNaughton, 1994; Buzsaki, 1989; Frank et al., 2000; Ferbinteau and Shapiro, 2003; Gupta et al., 2012). It is possible, then, that when animals are faced with choice points, the hippocampus guides the prefrontal cortex analysis into the future by providing it with a sequence of information that does not reflect the current location of the animals, but rather the expected locations and their significance. When prefrontal cortex receives “expected” location information, it may naturally retrieve the relevant information from long term memory about the associated expected outcomes. Indeed patients with hippocampal damage lose the ability to plan for the future (Hassabis et al., 2007; Schacter and Addis, 2007), a finding consistent with evidence that rodent hippocampus can construct experienced and never-before-experienced paths (Gupta et al., 2010).

**RESTORING BASELINE ACTIVITY LEVELS**

As elaborated above, the prefrontal cortex is thought to continually monitor the tonic activity levels of connected prediction areas of the brain to ensure an optimal threshold for detection of prediction errors. This is the case regardless of whether prediction errors are detected or not. In this way prediction-relevant neural networks are driven to reduce uncertainty so that future predictions are accurate and so that desired goals are achieved in the most efficient way.

**IMPLICATIONS FOR THEORIES ON THE ORGANIZATION OF MEMORY IN THE BRAIN**

The proposed prediction model of memory asserts that different brain areas to mediate different forms of memory because they support different type of prediction analysis. The hippocampus evaluates the extent to which contextual features have changed, while the midbrain-striatum evaluates whether responses resulted in the expected goal outcomes. Sensory regions of brain determine whether expected sensory events occurred as predicted, and motor cortex and cerebellum signal whether a specific behavioral act resulted in a specific outcome. These different prediction analyzers interact to inform each other if prediction errors occur, and this may have the effect of altering future prediction thresholds across the brain. As an example, errors of one type (e.g. episodic memory) may increase the bias to use other (e.g. response) strategies to solve a task by lowering the threshold for detecting a prediction error.

A coordinated and goal-directed set of responses to prediction errors is needed when multiple error messages are generated. The prefrontal cortex is suggested to coordinate the thresholds for prediction detection across many brain areas in order for the animal to produce the most adaptive responses to unexpected events. Similar to the suggestion by Fuster (2009), working memory reflects not just processing internal to prefrontal cortex, but this function emerges from the diverse and simultaneous interactions of the prefrontal cortex with prediction centers. In this case, prefrontal cortex’s control may be defined by the nature of its feedback messages in response to changes in the activity level in the connected prediction areas. The prefrontal cortex may seek to maintain optimal (stable) activity levels in the prediction centers so that they are maximally prepared for meaningful responses when needed. Prefrontal cortex, then, could be thought of as effectively regulating the balance between stable and flexible neural processing in connected brain areas. By this logic, the prediction model of memory views the vertebrate brain as having a single memory system that is continuously integrating different sorts of prediction analyses. The pattern of differential biases of controlled neural activity by the prefrontal cortex determines the selection of a particular adaptive behavior or choice. Decisions, then, reflect the relative weighting of signals across brain areas that generate prediction error signals. The clear benefit of this type of system is that when one type of prediction analysis fails, others may ramp up their influence over future decisions and actions without having to “learn from scratch”.

The effectiveness of the regulation of prediction centers by prefrontal cortex likely reflects modulating influences from motivation and/or emotion processing areas such as the amygdala. Such modulation reflects the current (or expected) emotional or motivational state, and this regulation is manifested by changing baseline firing rates in prediction brain areas (Fig. 6). If the baseline remains too high (e.g., in states of high arousal) or low (e.g., in states of depression), prefrontal cortex should receive feedback about these changes in firing rates and then implement mechanisms to restore neural activity to normal levels via its bidirectional-regulatory system. If prefrontal cortex is damaged, then neural activity levels may remain exceptionally high or low, resulting in poor choices, decisions, and behavioral adaptation. If one of the prediction centers is damaged (and this results in abnormal activity levels) then it would be expected that prefrontal cortex will not be able to restore optimal activity levels. If baseline activity in an intact brain is restored after the onset of an arousing incident, one should become able to analyze a situation by coordinating the normal prediction-error based analysis that leads to adaptive decisions and behavior selections. Supporting this view are reports that altered emotional states (e.g., depression) are correlated with changes in prefrontal cortex function (Baxter et al., 1989; Mayberg et al., 1999). The connection between the prefrontal cortex and the amygdala provides reciprocal functional regulation since targeted disruption of prefrontal cortex results
in clear changes in affective states (e.g., Covington et al., 2010; Hamani et al., 2010).

**SCENARIO 1**

As an example of the interactive nature of the different prediction error regions of the brain, let’s consider the case when an error signal is initially generated from the midbrain system (e.g., when an expected reward does not occur), then transmitted to the prefrontal cortex (to activate working memory processes) or directly to other prediction areas of the brain. The error signal is transmitted to the prefrontal cortex (to activate working memory processes) or directly to other prediction areas of the brain. The error signal is transmitted to the prefrontal cortex (to activate working memory processes) or directly to other prediction areas of the brain. The error signal is transmitted to the prefrontal cortex (to activate working memory processes) or directly to other prediction areas of the brain. The error signal is transmitted to the prefrontal cortex (to activate working memory processes) or directly to other prediction areas of the brain.

**FIGURE 7.** Schematic illustration of the activation patterns of amongst context prediction error (CPE) and reward prediction error (RPE) systems, and their coordination permitted by working memory (WM). Activated systems are circled in red, and thicker lines reflect increase information transfer. A: When there are no prediction errors, neural systems are stable and there is little or no uncertainty in terms of outcome expectations. Arrows reflect the baseline levels of reciprocal information exchange between RPE, CPE and WM systems. B: (1) An error signal is initially generated from the midbrain system (e.g., when an expected reward does not occur), then transmitted to the prefrontal cortex (to activate working memory processes) or directly to other prediction areas of the brain. (2) Using its working memory circuitry, the prefrontal cortex then informs hippocampus about the reward prediction error. C: Hippocampus becomes activated so that it is better prepared to detect context prediction errors. If a context prediction error is generated, this will be signaled to striatum where continued memory processes) or directly to other prediction areas of the brain. (Fig. 7B1; so that they become more responsive to subsequent incoming information). The prefrontal cortex in turn informs hippocampus about the reward prediction error (Fig. 7B2). Hippocampus may show elevated firing (Fig. 7B3), indicating that it is receptive to processing new information that will eventually reduce the uncertainty that arose after the striatal prediction error message. If a context prediction error is generated, this will be signaled to ventral striatum and the midbrain dopamine regions (Fig. 7B3) where continued reward prediction analysis should be encouraged (Fig. 7B4). 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reduced uncertainty) reflects the fact that long terms memories have been updated, i.e. expectancies now match one’s experiences.

Initially, after the first prediction error signal from the striatum, the currently active memory network will be made more labile so that new information can eventually be incorporated into the memory network (Fig. 3). According to theoretical models of cortical memory systems (e.g. McClelland et al., 1995), this updating process should occur slowly to avoid catastrophic effects on existing memories. As long term memories become updated, information about one’s expectations for a given situation or context should also be update, and this information will be fed forward to hippocampus to be used in subsequent prediction analyses. As an example of the above process, let’s say that on the next trial, an expected reward again does not occur. As long term memories become updated with this information, expectations for a reward will decline, and this will result in an eventual “match” signal by hippocampus. This will reduce signals to striatum to be responsive to rewards. Indeed, this pattern of reduced responses to reward has been observed empirically after learning is complete (Fig. 7C; Schultz et al., 1997; Puryear et al., 2010).

**SCENARIO 2**

A different example of interactions amongst prediction error and general modulatory centers of the brain considers the case when the first prediction error signal is generated by hippocampus, e.g. after an unexpected change in a familiar context (Fig. 7D1). A context prediction error signal will be sent to both striatum and prefrontal cortex to facilitate subsequent reward valuation of the context change (striatum) and to inform other prediction error brain regions (e.g. via prefrontal cortex). The signal to the reward and response system of the striatum may facilitate transition to an “up” state from a “down” state (Fig. 7D2; Wilson, 1993; Wilson and Kawaguchi, 1996) for striatal and dopamine neurons so that they are better prepared to respond to outcome information. Subsequently, prefrontal cortex may enhance the responsiveness of multiple prediction monitoring brain systems to facilitate the rapid analysis of changed conditions so that future behaviors and decisions are flexible (Fig. 7D3). Since the ventral striatal system will receive input from both the hippocampus and prefrontal cortex it may be particularly sensitive to response and reward value outcome information. If the value of the reward is deemed to have changed significantly (either higher or lower than expected), then long term memories should begin to be updated according to terms of the actual context in which the response that generated the changed reward value was made (Fig. 4). Again, the memory updating process may be incremental, and thus appear slow. If the changed reward value continues to be experienced in the new context, eventually hippocampus will no longer generate error signals since the memory that defines the expected context features will be updated to match the actual context. As more context match signals are generated by hippocampus, prefrontal cortex may down-regulate the excitatory drive that it was imposing on striatum when the mismatch signals first occurred (Fig. 7D4).

**COMPETITION OR COOPERATION BETWEEN PREDICTION CENTERS**

Many have described interactions amongst memory systems as reflecting a type of competition and/or cooperation for the control of behavior (Poldrack et al., 2001; Colombo, 2004; Gold, 2004; Mizumori et al., 2004, Lee et al., 2008; Gruber and McDonald, 2012). What are the mechanisms of this competition or cooperation? Our prediction model of memory systems offers some new insights.

Evidence for competition or cooperation amongst memory systems comes primarily from the result of studies of the effects of reducing the functional capacity of one brain area (e.g. by lesions or hormone treatment, McDonald and White, 1993; McElroy and Korol, 2005; Gruber and McDonald, 2012) while observing subjects’ performance on tasks that require normal function of other intact memory areas. With this paradigm, it was shown that hippocampal lesioned rats showed faster learning of response or cue tasks that are usually considered to be mediated by the striatum (McElroy and Korol, 2005). It was reasonably concluded that there is a natural competition between striatum and hippocampus that disappeared after the lesion, and this enabled striatum to function more effectively. A prediction model of memory provides additional insight. According to this view, both striatal and hippocampal prediction systems should be operational simultaneously during baseline states regardless of the task at hand. In this way, striatum can continually evaluate whether actions result in the expected rewards and hippocampus continually assesses the extent to which the context-defining features of current situation match those expected based on past experience. Indeed, both the striatum and hippocampus contain spatial, reward, and behavioral representations that respond to different types of errors in prediction regardless of whether the task is spatially or response based (e.g., Yeshenko et al., 2004; Eschenko et al., 2007; Mizumori et al., 2004).

If the hippocampus become dysfunction (e.g., after a lesion) it should still be possible to learn according to prediction errors generated by the remaining systems. For example, striatum should still be able to generate prediction error signals that underlie response or cue learning, and thus rats will tend to switch to a response strategy after a hippocampal lesion (e.g. Packard and McGaugh, 1996). The prediction model of memory interprets this finding as a demonstration that hippocampal prediction error messages that normally arrive in striatum increase the analysis load on striatal prediction analysis networks. When the hippocampal input is removed, the processing load is lessened and striatum is now able to more effectively evaluate whether reward outcomes occurred as
predicted by a specific behavioral sequence of the animal. According to this explanation, striatum and hippocampus do not directly compete for control of a behavior per se but rather they effectively compete for access to the outcome valuation process. Another implication is that habit learning may not by itself be incremental and slow as is commonly thought. Rather, in intact animals, habit learning may appear slow because of a prioritization for valuation of hippocampal context prediction error signals relative to reward prediction error signals. Indeed rats seem to have a predisposition to learn tasks using context cues rather than response information when the solution to a problem is ambiguous (Packard and McGaugh, 1996). This prioritization may reflect a natural and innate hierarchy of processing priorities for decisions making systems based on the adaptive value of one strategy or algorithm or another. Context processing may confer greater adaptive flexibility than learning only by habits. One prediction, then, is that striatal-dependent learning may be found to be rapid if learning explicitly did not involve context processing (e.g., aversive conditioning).

In the event that striatum is impaired, hippocampal-based behaviors should remain at least initially intact since the reward prediction neural circuitry includes key structures afferent to the striatum (i.e., within the network that includes the habenula-ventral tegmental (dopamine) circuit, Hikosaka et al., 2008). Thus it is possible that reward prediction error signals can continue to influence hippocampus prediction analyses, albeit perhaps less efficiently. However, an important part of especially navigation-based learning is to understand the relationship between sequences of actions and a desired outcome. Therefore, it is predicted that if striatal-lesioned subjects are challenged with complex spatial navigation problems, or complex econometric analysis, deficits will emerge because rats will have difficulty learning the expected consequences of multiple, flexible behavioral trajectories. Such a result would imply that optimal continued performance on a complex navigation-based task requires the maximum types of behavioral flexibility that is normally supported by the collection of prediction error mnemonic processors.

The intrinsic regulation attributed to the components of a prediction model of memory is remarkably analogous to the homeostatic regulatory system that has been shown to operate at the synaptic level (Turrigiano, 1999; Marder and Goaillard, 2006; Turrigiano, 2011). In what follows we explore the possibility that principles that guide homeostatic neural plasticity at the synaptic level also apply at the neural systems level to account for the self-regulatory and interactive capacity of the many memory processors of the brain. First, we briefly describe a model for the self-regulation of synaptic efficiency (Marder and Goaillard, 2006; Turrigiano, 2011). This neuroregulatory perspective is then compared to the interactive prediction model of memory in an attempt to not only account for the remarkable and precise coordination of memory processing in the brain but to also further illustrate how memory and decision making brain circuitry are so intimately tied together that one cannot function without the other.

Since the early 1930s scientists have described the remarkable ability of the body to maintain optimal function despite perturbations of the surrounding environment (e.g., Cannon, 1932). This adaptive process, termed homeostasis, includes sensors that detect deviations in physiological states relative to a previously defined optimal state (or set point). Errors or deviations detected by the sensors inform a controller to up or down regulate mechanisms that can bring the current physiological state closer in line with the set point. Principles of homeostasis can account for self-regulatory synaptic mechanisms (e.g., Turrigiano, 1999; Marder and Prinz, 2003; Turrigiano and Nelson, 2004; Turrigiano, 2008, 2011) and this has led to the view that neural circuits are also subject to homeostatic regulation (Turrigiano, 1999; Marder and Goaillard, 2006; Turrigiano, 2011). Thus, homeostatic regulation could be a key mechanism that maintains the balance between stability and flexibility that neural networks needed to support dynamic and adaptive responses.

At the synaptic level, homeostatic regulation is possible because a form of calcium-mediated plasticity allows neurons or neural networks to maintain a key physiological parameter (firing rate), within an optimal range, or set point, despite new excitatory and/or inhibitory inputs. Such homeostatic plasticity helps to ensure that cells do not, for example, suffer catastrophic effects of overexcitation when constant and strong excitatory inputs arrive (as in the case of LTP). Upon arrival of strong excitatory input, self-regulation of firing rates is evident by the fact that the synaptic strengths of all synapses of the stimulated cell are reduced while maintaining the relative distribution of synaptic weights across the cell. This “scaling” process makes it possible to retain new information while still allowing for future plastic changes (Turrigiano, 1999; Turrigiano et al., 1998).

Marder and Goaillard (2006) suggested that homeostatic plasticity may be nested: calcium sensors may monitor neural firing rates, then up or down regulate the availability of glutamate receptors to ramp up or down firing rates. Groups of neurons or neural networks may sense changes in firing collectively to regulate population activity levels and patterns of activation. In this way homeostatic plasticity enables groups of neural circuits to find a balance between flexible and stable processing as needed to learn from experiences, and to be responsive to future changed inputs. The specific details of how neural networks engage in homeostatic regulation remain to be discovered. Nevertheless, it is worth noting that homeostatic regulation at the neural systems level clearly occurs as evidenced by studies of brain development, as well as from studies of reactive or compensatory neuroplasticity mechanisms that occur in response to experience (e.g. sensorimotor learning; Froemke et al., 2007) or brain injury (e.g. brain trauma or addiction; Robinson and Kolb, 2004; Nudo, 2011). While homeostatic neural plasticity mechanisms have not been used...
Hippocampus could impact prediction error processing in other brain areas as deviations from the firing rate set point, and this error message errors, then prefrontal cortex may engage mechanisms to the optimal state needed for detecting future prediction brain may be “sensed” by the prefrontal cortex via directafferents. Key neural variable may be the optimal level of excitability of neurons in prediction areas of the brain. In this case, changes in calcium flux may be an important part of the sensing system as it reflects the current level of neural activity. When firing rates become higher or lower than the optimal level, this could be taken as an indicator of a mismatch between optimal and actual rates, and a controller mechanism should be engaged to bring the firing rates back to the optimal levels so that cells are prepared to respond to subsequent input. However, merely up or down regulating firing rates is a short term response to altered firing induced by uncertain or unexpected situations. Long term adjustments necessarily include the regulation of decisions and behaviors that resolve uncertainty or errors in prediction. Given that prediction error brain areas are highly interconnected with the prefrontal cortex, a likely candidate structure that serves as the main controller for prediction error-based memory systems is prefrontal cortex. In this case, firing rates of cells within the prediction error processing areas of brain may be “sensed” by the prefrontal cortex via direct afferent fibers. If the baseline rates are too high or too low relative to the optimal state needed for detecting future prediction errors, then prefrontal cortex may engage mechanisms to restore the firing rate to a predetermined “set point”. According to the model in Figures 5 and 6, the detection of a prediction error, or mismatch, should produce significant deviations from the firing rate set point, and this error message could impact prediction error processing in other brain areas as well as the controller function of the prefrontal cortex. Prefrontal cortex, in turn, should orchestrate the information flow to and from all prediction error brain areas according to homeostatic principles. With the goal of ultimately restoring the set point of neural activity in prediction error brain regions (i.e., reduce error signals to restore a stable neural state that reflects greater certainty about outcomes of decisions and actions), prefrontal cortex should continually and automatically receive feedback about the current excitatory state, and then strategically up or down regulate the excitability of different processing systems depending on the past outcomes of behaviors (Fig. 6). Part of this process is to incorporate information (presumably from the striatum) about the successes of recent behaviors so that the same or different behaviors can be next selected. The intrinsic recurrent circuitry of the prefrontal cortex may serve this function well (Arnsen et al., 2012).

With regard to the impact of homeostatic regulation of prediction centers on established memories, it would be expected that the outcome of the prediction analysis (which includes error detection and controller functions) should guide the updating of memories with information about the success (or failures) of responses as an animal attempts to achieve a desired goal. In this way, the next time a particular memory is retrieved, the most recent and accurate information can be used to generate the next set of expectations. A memory of an event, then, should include not only the defining cues and outcomes, but also the emotional tone (since the amygdala is postulated to contribute to the threshold for detecting prediction errors), the context-specific behavioral actions that led to decisions, and the strategy associated with the reconciliation of error messages. It should be noted that while the prefrontal cortex may be a major controller of the impact of prediction error signaling in the brain, other sources of varying degrees of control may arise from the any of the brain regions that analyze prediction outcomes given that they are interconnected. For example, a prediction error from the hippocampus could be transmitted to midbrain-striatal neurons along pathways that do not initially include the prefrontal cortex. Indirect support for this idea comes from observations that conditions that produce error messages in the hippocampus change reward responses of dopamine neurons (Puryear et al., 2010; Jo et al., 2013), and phasic theta modulation is observed between hippocampus and striatum (DeCouteau et al., 2007) during decision tasks. In sum, homeostatic regulatory processes may account for the automatic and continuous self-regulatory nature of prediction error analysis, decision making, learning and memory. Such a natural and adaptive mechanism optimizes the contribution of different types of prediction error signals to future decisions and actions according to the pattern of recent successes and failures in prediction. This more dynamic view of the interactions between adaptive memory and decision making circuitry has important implications for the development of more efficient and long lasting cognitive and behavioral intervention methods for not only amnesic patients but also for disorders characterized by suboptimal decision processing such as addiction, autism, and schizophrenia. Therefore, the remainder of this article evaluates the extent to which the current...
literature validates key premises of a homeostatic view of memory and decision systems interactions. This discussion also highlights future directions for research that test the prediction model of memory.

**PREMISE 1**

There is a fundamental and common currency of information representation across prediction centers of the brain. A common currency should facilitate information exchange and regulation across brain regions. Also, if identified, one would be able to use the same neurometric to directly compare regional differences in aspects of decision and/or memory processing. A search for a common currency of representation has not been systematically carried out since a multitude of different behavioral or cognitive tasks are used in studies of neural representations. There is initial evidence, however, that support Premise-1 since strikingly similar types of neural representation are found across many memory processing regions of brain when rats perform appetitive tasks on open elevated mazes such as the plus maze or radial arm maze. The common currency includes representations of rewards, the spatial features or requirements of a task, task phase, and egocentric movement. Of these neural correlates, egocentric movement (in particular velocity or acceleration of translational movement across the maze) has been the most common and robust (as described in Penner and Mizumori, 2012b). In the future, these correlates of connected brain areas should be recorded simultaneously so that their temporal relations can be identified. Although not systematically assessed to date, one would expect to find common codes for econometric information regarding the salience of the common currency units.

**PREMISE 2**

The content of stored memories (as reflected in representations of expected information) should include not only the unique sensory and behavioral aspects of events, or contexts, but also information about the value of the sensory and behavioral information. Specifically, it should be possible to identify neural representations of learned information that dynamically vary according to its subjective value. While prediction error coding has been described in sensory, motor, striatal, midbrain, and hippocampal areas, a systematic and explicit econometric analysis of expectancy (i.e. memory) information remains to be conducted. As an example, it is common to record hippocampal place fields that seem to be driven by a particular constellation of external (usually visual) cues (Mizumori, 2008a), and prediction error coding is observed when rewards are unexpectedly omitted. However, the extent to which place fields incorporate the subjective value of the cues has only begun to be explored. Initial evidence suggests that econometric information is indeed part of the hippocampal neural (i.e. memory) code: Lee et al. (2012) and Penner et al. (2012) recently described place field remapping that depended on the expected probability of rewards of large or small magnitude.

**PREMISE 3**

Mismatch, or prediction error, messages in one brain area should induce system-wide responses. Based on known patterns of connectivity between brain regions, and in the interest of efficient system function, a prediction-based model of memory hypothesizes that the different prediction processing areas are interdependent in the sense that generation of error signals in one system should quickly influence the future firing patterns of neurons in other prediction areas. Although more direct evidence is needed, it is worth noting that neural responses from two or more brain areas show that each area generates prediction signals during the performance of the same behavioral task (e.g. Yeshenko et al., 2004). In these tasks, encounters with unexpected rewards presumably generated a reward prediction error signaled by greater dopamine and striatal responding (e.g. Fig. 7). This in turn should lead to reorganization of the distribution of place fields (i.e. the generation of a new “map” or memory). Following a context manipulation, one would expect to see alterations or remapping of place fields, followed by altered reward value signaling by the dopamine neurons. Several studies (e.g. Yeshenko et al., 2004; Smith and Mizumori, 2006; Puryear et al., 2010; Martig and Mizumori, 2011; Smith et al., 2012; Penner et al., 2012) now show that both hippocampal and striatal neural correlates are significantly affected by changes in context and reward processing during the performance of a maze-based task regardless of the optimal strategy needed to solve the task (e.g., place vs. response strategies).

Recordings in hippocampus and striatum have not always been simultaneous, however, and thus it is not possible to state with certainty that changes in one area preceded changes in the other. At this point we can only logically deduce this sequence of events based on past studies of dopamine and hippocampal responses to unexpected events, and findings that hippocampal place fields are severely disrupted when the dopamine system is not functional (Martig et al., 2011). The future application of new technologies and approaches (e.g. optogenetics, DREADD, targeted use of viral vectors, etc.) to studies of the functional connectivity of prediction circuitry in the brain should reveal important new information about the spatial and temporal causes of the changes in firing in one prediction error brain region relative to changes in firing in connected areas, and then to behavior.

**PREMISE 4**

Neural codes should become stronger (i.e. more predictive) when their type of prediction comes to dominate the control
of actions and decisions. Since a desired outcome of an adaptive decision making system is the accurate prediction of future consequences, one would expect that as learning progresses, the certainty and predictability with which desired outcomes occur will improve. Underlying this change, neural signals should become more predictive of cues or behaviors that lead to the desired outcome. Furthermore, neural codes might be expected to become more information-selective and reliable as these features come to reliably predict outcomes. Evidence in support of Premise-4 is that hippocampal place fields become more spatially-selective and reliable as hippocampal-dependent spatial learning progresses, and as animals acquire greater familiarity with a given environment (Muller and Kubie, 1987; Wilson and McNaughton, 1993; Markus et al., 1995; O’Keefe and Burgess, 1996; Hetherington and Shapiro, 1997; Mizumori and Kalyani, 1997; Lenck-Santini et al., 2001, 2002; Fenton et al., 2010), but see Jeffrey et al. (2003) and Cooper and Mizumori (2001). Also place cells generate different patterns of place fields when rats need to learn to distinguish the significance of different contexts (Smith and Mizumori, 2006). Striatal neural representations of egocentric directional movement (e.g. turns in a maze) become more prominent as rats learn a T-Maze task (Barnes et al., 2005). Further, with continued training and conditioning, dopamine burst firing and release become associated with cues that predict a reward (Schultz et al., 1997; Flagel et al., 2011).

**PREMISE 5**

The generation of more selective and reliable neural codes during learning should coincide with the evolution of more precise spatial and temporal coordination of neural activity within and across the relevant brain structures. When faced with uncertainty, e.g. usually after the detection of a prediction error, the working memory function of the prefrontal cortex should be engaged to simultaneously (although perhaps differentially) elevate the sensitivity of all prediction error brain structures in an attempt to facilitate the most rapid identification of all errors, as well as the determination of their significance.

While direct evidence that the prefrontal cortex simultaneously activates multiple prediction-related structures in a single task remains to be determined, the prefrontal cortex is considered to be strategically located to impact multiple memory systems as well as decision neural circuitry (e.g., see review in Euston et al. 2012; Hyman et al., 2012). Supporting this view, lesions or inactivations of the prefrontal cortex disrupts goal-related neural codes in hippocampus (Kyd and Bilkey, 2003; Hok et al., 2013) and the VTA (Jo et al., 2013) while rats perform a spatial maze task. Also prefrontal cortex damage impairs a wide range of learning and memory abilities (Fuster, 2008, 2009) presumably because of its widespread control over the balance of excitation and inhibition in the many prediction structures of the brain. There is initial evidence that after initial learning, there is greater coherence and synchrony of low frequency potentials (LFPs) between hippocampus and striatum (DeCouteau et al., 2007), and between prefrontal cortex and hippocampus (Hyman et al., 2005; Jones and Wilson, 2005a, 2005b; Siapas et al., 2005; Shirvalkar et al., 2010) when decisions are made. A challenge for future research is to understand the mechanisms and significance of integration across multiple frequencies of brain rhythms, and between LFPs and single cell activity, during decision making and different prediction error states (e.g. Hyman et al., 2010; Buzsaki and Wang, 2012; Lisman and Jensen, 2013).

**PREMISE 6**

Choice outcomes may be more related to neural representational patterns on subsequent trials than the current trial. As described earlier, the outcomes of choices should bias the efficiency with which prediction error regions of the brain function in the future, presumably by giving feedback to prefrontal cortex, which in turn incorporates the new information in its subsequent regulation of the excitability state of prediction memory circuitry. Most single unit studies correlate the specificity and reliability of characteristics of neural representations with performance on the trial in which the neural data were collected. This is indeed a reasonable comparison to make. However, our prediction-based model of memory makes the explicit suggestion that the neural correlates should be even more striking if related to choices made on recent trials, and perhaps even to specific prior choices of the same trial.

Indirect support of Premise 6 can be found in studies that show that neural firing is related to past events and choices. This sort of retrospective coding was illustrated when hippocampal place fields were shown to correlate to past behavioral trajectories of the rat being recorded (Frank et al., 2000; Wood et al., 2000; Ferbinteanu and Shapiro, 2003; Mizumori et al., 2004; Lee et al., 2006). Also many laboratories have demonstrated that neural codes during sleep reflect a temporal organization of neural firing that was recently experienced (e.g. Wilson and McNaughton, 1994; Shapiro and Ferbinteanu, 2006; Bender and Wilson, 2012). More direct evidence in support of Premise 6 was recently reported. Motor cortical and parietal cortex neurons showed firing rates that vary depending on the specific outcomes of prior choices (e.g. Marcos et al., 2013), and it has been shown that rats adjust choices based on the delay imposed on prior trials (Mazur, 1988; Cardinal et al., 2002). There is also evidence of prospective coding in that neural firing correlates with intended behaviors or expected goal outcomes (e.g. Buzsaki, 1989; Wilson and McNaughton, 1994; Frank et al., 2000; Wood et al., 2000; Louie and Wilson, 2001; Lee and Wilson, 2002; Pennartz et al., 2002; Ferbinteanu and Shapiro, 2003; Yeshenko et al., 2004; Foster and Wilson, 2006; Gupta et al., 2012). However, the prediction
error model suggests that the behavioral correlate of cells with prospective codes should be found to be even more selective if correlated with performance on the prior trial. Finally, Gupta et al. (2012) have shown striking forward sweeping of sequential activation of place fields but the sweep began from a prior location of the animal. That is, the apparent predictive nature of prospective codes was based on the results of prior choices.

PREMISE 7

The plasticity of the brain’s memory circuitry is homeostatically and intrinsically regulated to result in the self-regulated and dynamic coordination of plasticity mechanisms at multiple levels, from ion channels, synapses, single unit, to local and extended neural networks. Adaptive interactions between the modulatory and prediction error components of the brain’s memory circuitry require coordination across all levels of function and integration. In this way, not only can a healthy balance between neural stability and flexibility be achieved, but an optimal level of stable behavior should maximally prepare animals to detect the need to engage in behavioral change. Demonstrating this sort of multilevel coordination remains a grand challenge for it requires technology that monitors multiple levels simultaneously in behaving animals. Although still in its infancy, Fujisawa and Buzsaki (2011) have demonstrated the feasibility of this general approach as they recorded simultaneously single unit activity and LFP (local field potentials) across multiple regions of the brain. New forms of neural coordination were described, as well as new neural phenomenon (a 4 Hz synchronizing rhythm) that could be used to explain how prefrontal cortex might coordinate neural signals from multiple brain areas (Penner and Mizumori, 2012b). Additional details about the functional significance of prefrontal cortex control over prediction areas is expected to emerge as new technologies (e.g. optogenetics combined with electrophysiology, Warden et al., 2012) are applied to the problem of understanding the organization of memory processing in the brain.

CONCLUSIONS

A homeostatic model of memory posits the existence of a single, self-regulated (Buzsaki, 2013) memory system that reflects multilevel (from cells to neural system) integration across different prediction processing areas of the brain. These different prediction processors have been more commonly referred to as different memory systems such as the hippocampus (episodic memory) and striatum (response or habit memory). Significant evidence suggests that these memory systems have in common output that signals errors in prediction of events and/or their outcomes, but they differ in terms of the nature of the prediction generated (e.g. context prediction errors vs reward/response prediction errors). It is suggested that the prefrontal cortex plays a critical role in coordinating the multiple levels (from genes to cells to circuits) of prediction analysis across multiple prediction centers. From the widespread control and influence of the prefrontal cortex emerges an essential capacity for the flexible use of information to generate adaptive behaviors and to predict future outcomes. A homeostatic function of the prefrontal cortex is suggested to maintain optimal baseline (tonic) firing rates that ensure appropriate sensitivity for the future detection of prediction errors. That is, analogous to the suggestion by many computational models, predictive memory systems are driven by mechanisms that reduce uncertainty, and the prefrontal cortex is ideally situated to serve as a controller that seeks to resolve uncertainty. We hypothesize that prefrontal cortex accomplishes this task by continually engaging corrective mechanisms that restore optimal baseline firing rates after prediction error signals are generated. Emergent outcomes of this process are flexible and adaptive behaviors even in the most challenging of situations. Accordingly, compromise to any of the prediction circuits should result in less flexible and adaptive behaviors. This reduction of flexibility and adaptability could result in rigid and suboptimal decision making, learning, and memory as is seen in cases of addiction (e.g., Monterosso et al., 2012), and neurological diseases such as Alzheimer’s and Parkinson’s disease. The symptoms presented in such extreme cases of maladaptive behaviors reflect not only that a particular prediction processing system has gone awry but also the brain’s attempt to compensate for the lost function.

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