Stress and the trade-off between hippocampal and striatal memory

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Abstract

Stress can strongly influence memory, in part by modulating the relative engagement of multiple memory systems. Over the last fifteen years, researchers have demonstrated that stress leads striatal, rather than hippocampal, memory to be dominant in both humans and non-human animals. This shift has been proposed to explain the etiology and maintenance of symptoms of stress-related psychopathology. However, it remains unclear how hippocampal and striatal memory are affected individually in order to facilitate this trade-off. Recent studies provide empirical support for (at least) three different pathways by which stress could modulate these memory systems. Evidence for these diverse effects of stress, and circumstances under which each might occur, are discussed.

Stress can profoundly influence what we learn and remember. As we have multiple memory systems with distinct neural networks for encoding, storing, and retrieving different types of information [1,2], one important way that stress can impact memory is by modulating the relative involvement of these memory systems. A remarkably consistent finding is that stress—acute and chronic—leads to the preferential engagement of striatal over hippocampal memory in tasks where either system could be used. The hippocampus encodes flexible associative memories, whereas the striatum encodes rigid stimulus-response memories [3,4]. The stress-induced trade-off between these memory systems has been proposed to play a role in psychopathologies such as posttraumatic stress disorder and addiction [5,6]. Despite the clinical relevance of this shift, the ways in which stress modulates hippocampal and striatal memory are not well understood.

In part, the effects of stress remain elusive because of how the relative engagement of hippocampal and striatal memory is generally assessed. Most studies use *dual-solution* tasks, in which only one memory system drives performance. Because only one memory is expressed, it is not clear how stress influences each system individually. This is especially complex as hippocampal and striatal memory can function independently [7,8], compete [9-13], compensate [14], and each drive behavior [15]. Thus, there are at least three pathways by which stress could cause a shift in memory systems (Figure 1). Stress could impair hippocampal and enhance striatal memory, impair both forms of memory, or have no effect on hippocampal but enhance striatal memory. As we will demonstrate, there is empirical support for each of these pathways.

In this review, we briefly discuss the evidence from dual-solution tasks for stress causing a shift from hippocampal to striatal memory. To understand why this shift occurs, we then consider data showing how each memory system is affected individually, finding distinct patterns of effects. We demonstrate that factors like stressor timing, previously shown to change the strength and even the direction of stress effects on memory [16-18], can change the pathway by which the trade-off between memory systems occurs. We conclude by highlighting directions for future research to more clearly understand how stress modulates the relative engagement of hippocampal and striatal memory.

Stress and the relative use of hippocampal and striatal memory

The classic example of a dual-solution task that discriminates hippocampal and striatal memory in rodents is the plus maze. In this task, rodents learn to approach a “goal arm” in a plus-shaped maze for a reward. They could achieve this by learning the spatial context (e.g., location of the goal arm relative to other arms), engaging the hippocampus, or using a stimulus-response association (e.g., when placed in this maze, turn right), engaging the striatum [7]. To test which memory was formed, researchers conduct a “probe test” in which rodents start at a new point in the maze. If the rodents navigate to the same location in which the reward appeared previously, this reflects hippocampal memory; if they repeat the “turn to the right” response, this indicates striatal memory.

Using this task and others like it, researchers have shown that if rodents were chronically stressed [19-21], or acutely stressed before learning [5,22-25], they shifted toward expressing striatal memory during the probe test. Even when they learned normally, if

they were acutely stressed prior to the probe test they also tended to use striatal memory [26,27] (Figure 2). However, stress did not cause observable differences in learning before the probe test (e.g., trials to criterion [22,23,28] but see [24]), making it difficult to determine whether the process of learning hippocampal or striatal-dependent associations was affected by stress.

In humans, the tasks used to assess the relative engagement of hippocampal and striatal memory are varied. Some also use a probe test, in which only one memory system drives performance [20,29-31], while others use computational modeling to determine whether a hippocampal or striatal strategy was used [32,33]. We recently developed a task in which we could assess implicit memory for context (hippocampal) and stimulus-response (striatal) associations by measuring their influence on visual search [34] and then test which memory was dominant in a dual-solution task where both associations were cued (Goldfarb et al., under review).

As in the rodent literature, chronic stress [20], acute stress before learning ([29,32,33], but see [30]), prenatal stress [31], and greater lifetime stress exposure (Goldfarb et al., under review) have each been shown to cause more people to use striatal memory (Figure 2).

What causes this shift?

Below we present evidence supporting three mechanisms by which stress could cause preferential engagement of striatal memory in a dual-solution task. This is not meant to be comprehensive, but rather to highlight different ways in which stress has been shown to modulate the use of these memory systems.

1. Impaired hippocampal and enhanced striatal memory

Two rodent studies make a compelling case that impaired hippocampal and enhanced striatal memory underlies the stress-induced trade-off between memory systems. Using separate tasks to measure hippocampal and striatal memory, Wingard and Packard [35] administered the same stressor (anxiogenic drug) immediately after learning each task. Rats stressed after learning the hippocampal task showed impaired memory, while those stressed after the striatal task showed enhanced memory. Another study used a (putatively hippocampal) spatial radial arm water maze [28]. Some rats that were stressed (predator odor) prior to training showed impaired memory; however, other stressed rats were not impaired. The researchers found that, while all stressed rats showed less *c-fos* expression (indicating decreased activity) in the hippocampus, those that showed better memory also had greater *c-fos* expression in the dorsolateral striatum [28]. These results suggest that enhanced striatal function after stress could compensate for impaired hippocampal function and rescue performance.

The evidence above suggests that dominant striatal memory in a dual-solution task arises from stress impairing hippocampal and enhancing striatal memory. These effects are often observed when stress is administered before learning. As mentioned before, pre-learning stress led to dominant striatal memory in rodents [5,22-25] and humans [29,32,33]. Pre-learning stress has also been shown to both impair hippocampal memory

in rodents [36,37] and humans [38-40], and enhance stimulus-response memory in rodents [24] and humans [41]. In humans, physiological stressors led to greater dorsal striatal BOLD responses [42]. This pattern of effects is also supported by research on chronic stress, which also facilitates dominant striatal memory [19-21]. Chronic stress is known to impair hippocampal function [43,44] and has also been shown to enhance dendritic branching in the dorsal striatum [19,45].

II. Impaired hippocampal and impaired striatal memory

Another possibility is that both memory systems are impaired by stress, but to varying degrees, such that striatal memory would still be dominant in a probe test. In rodents, glucocorticoid administration has been shown to impair hippocampal memory [46], and was recently also shown to impair striatal memory [47] (although the dosages differed). In humans, acute stress (socially evaluated cold pressor) can impair both recognition [48] and stimulus-response [49] memory.

This pathway—both memory systems are impaired by stress, but striatal memory is still dominant—has been observed when stressors were administered prior to a memory test. Like pre-learning stress, pre-retrieval stress led animals to shift from using hippocampal to striatal memory in a dual-solution task [26,27]. Acute stress administered pre-retrieval can impair hippocampal memory in rodents [36,37,46] and humans ([50-54], but see [55]). Very little research has examined pre-retrieval stress and striatal memory, but, as described above, recent studies showed that pre-retrieval stress also impaired the expression of this form of memory in rats [47] and humans [49]. This may be due to an adaptive stress-induced shift into a “memory formation” mode, in which memory for information occurring in the same temporal context as the stressor is enhanced but processes like retrieval are impaired [56]. More research is needed to determine circumstances under which striatal memory is impaired by stress, and whether a trade-off from hippocampal to striatal memory would continue to occur.

III. Unimpaired/enhanced hippocampal and enhanced striatal memory

A key assumption in the preceding two scenarios is that stress causes a shift from hippocampal to striatal memory by way of impairing hippocampal memory. As McDonald and colleagues noted, “Any event that leads to a dampening of hippocampal function could result in increased dominance of other memory/behavioral systems” [57]. However, stress can also enhance hippocampal memory [16,58-60]. Could stress still cause striatal memory to be preferentially engaged, even if it does not impair hippocampal memory?

Recent results from our laboratory suggest that this may be the case (Goldfarb et al., under review). As mentioned earlier, we showed that individuals with lower levels of lifetime stress exposure were more likely to use hippocampal (context) memory, while those with moderate levels were more likely to use striatal (stimulus-response) cues in a dual-solution task. Because we measured acquisition of these associations separately, we could test whether differences in learning predicted which memory would be expressed. The groups did not differ in learning context associations, but low stress participants were significantly impaired at forming stimulus-response associations. Thus, differences in

stimulus-response learning alone were sufficient for the groups to differ in dominant stimulus-response memory in the dual-solution task.

This study raises the possibility that stress could lead to dominant striatal memory without impairing hippocampal memory. Although more studies are needed to test whether this pathway generalizes to other stress situations, it broadens the range of mechanisms by which stress could modulate multiple memory systems.

One pathway that has not yet been considered is how stress would modulate the relative engagement of hippocampal and striatal memory if stress enhanced both memory systems. For instance, post-encoding stress is known to enhance hippocampal memory in rodents ([61], but see [35]) and humans [59,60], and also to enhance striatal memory in rodents [62,63]. However, the effects of post-encoding stress on dual-solution task performance are not known.

Conclusion

In this review, we described research examining the effects of stress on hippocampal and striatal memory. We raised the question of how stress influences these memory systems individually such that, in a competition where only one form of memory could be expressed, stress would consistently elicit a shift toward striatal memory. This question is clinically relevant for memory symptoms in stress-related psychopathology [5,6] as well as the consequences of treating these conditions with stress hormones [64]. As we have shown, there are several mechanisms by which this trade-off could occur. The stress-induced shift from hippocampal to striatal memory has been associated with 1) impaired hippocampal and enhanced striatal memory; 2) impaired hippocampal and impaired striatal memory; and 3) unchanged hippocampal and enhanced striatal memory. Stress-related factors such as timing (pre-learning vs. pre-retrieval) and intensity (acute vs. cumulative lifetime exposure) changed the effects of stress on each system individually, but still resulted in dominant striatal memory in a dual-solution context.

Considering how stress leads to dominant striatal memory opens new avenues for future research. First, to understand why one form of memory is dominant under stress, memory systems should be assessed separately as well as in competition. These assays should be comparable, so that the relative magnitude of the effects can be determined. This approach also clarifies whether stress influences memory systems directly or indirectly. In a dual-solution context, stress may act on the prefrontal circuitry [65] involved in choosing to implement hippocampal or striatal strategies [66]; using separate tasks enables measurement of the direct impact of stress on memory regions.

Second, studies examining memory systems separately should use the same stress conditions (e.g., both pre-encoding). Previous research has identified conditions that help resolve seemingly contradictory effects of acute stress on hippocampal memory [16,18]. For example, when memoranda share a context with the stressor, memory is enhanced, while memory for information outside that context is impaired [16,56,67]. It is not yet known whether such conditions apply to striatal memory. By systematically probing how the same stress conditions influence each type of memory, this question—and whether

such stress manipulations consistently cause preferential expression of striatal memory—could be addressed.

By manipulating a range of stress-related factors, and measuring hippocampal and striatal memory separately as well as in competition, the field will gain insight into how the stress-induced shift from hippocampal to striatal memory occurs. As we have shown, factors like stressor timing can change the way that stress modulates multiple memory systems, although this only becomes clear when these memory systems are measured separately. Delineating which stress-related factors are relevant will enable researchers to both predict when stress will cause a shift between memory systems, as well as design interventions to prevent this shift.

Acknowledgements

Funding: This work was supported by the National Institutes of Health (1R01MH097085, EAP) and the National Science Foundation (GRFP, EVG).

Figure Legends

Figure 1. Pathways by which stress can modulate hippocampal and striatal memory.

Stress research consistently shows that when only one memory system can be used striatal memory (purple) is expressed and hippocampal memory (green) is not. There are distinct pathways by which this trade-off can occur. Here we illustrate that striatal memory could be enhanced and hippocampal memory impaired, both memory systems could be impaired (to varying degrees), and striatal memory could be enhanced and hippocampal memory unchanged.

Figure 2. Effects of stress on the relative engagement of hippocampal and striatal memory. Data from rodent (top) and human (bottom) studies examining the effects of stress on performance on a dual-solution task are shown. Under conditions of no (or low) stress (NS), the majority of participants in most studies expressed hippocampal (green) and not striatal (purple) memory. However, with stress (S) this shifted, so that the majority of stressed participants used striatal and not hippocampal memory. This pattern is largely consistent for studies examining chronic stress as well as acute stress administered before encoding or before retrieval. Numbers shown above each set of graphs correspond to different papers. In the rodent studies, N = 10-15 per group; in the human studies, N = 17-44.

References: ¹Kim et al., 2001; ²Packard & Wingard, 2004; ³Schwabe et al., 2010; ⁴Leong & Packard, 2014; ⁵Elliott & Packard, 2008; ⁶Taylor et al., 2014; ^{7,13}Schwabe et al., 2008; ⁸Ferragud et al., 2010; ⁹Schwabe et al., 2007; ¹⁰Schwabe et al., 2009, ¹¹Schwabe et al., 2012; ¹²Goldfarb et al., under review; ¹⁴Schwabe et al., 2012

Note: Only studies that provided details about the number of participants in each group using each memory system are included. From ref 8, only data from subordinate stress subjects are shown. In ref 11, the remaining participants (27% NS, 28% S) could not be classified as using either memory system.

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The authors provide an in-depth review of the effects of stress, focusing on the cascade of hormonal events following acute stress exposure and their influence on hippocampal memory. By highlighting different facets of the stress response that lead to distinct memory effects, this review raises questions for future studies regarding how these would influence the relative engagement of hippocampal and striatal memory.

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This study examined striatal morphology and performance on a dual-solution plus maze task in rats exposed to two weeks of chronic variable stress. They found enhanced dendritic complexity in the dorsolateral striatum of stressed rats, and while the majority of non-stressed rats used hippocampal strategies in the plus maze, the majority of stressed rats used striatal strategies. This study provides an important link between stress, structural changes in the striatum, and functional differences in memory performance.

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In this study, pre-training exposure to predator odor led rats to use striatal memory in a dual-solution plus maze task, but this was blocked by post-training injections of bupivacaine (providing temporary inactivation) into the basolateral amygdala. Pre-training predator odor was also shown to enhance performance on a single-solution (striatal) task. This study demonstrates that an ecologically valid stressor could modulate hippocampal and striatal memory, and provides further support for the role of the amygdala in the effects of stress on these memory systems.

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This study demonstrated that both hippocampal and striatal memory could separately, and implicitly, facilitate attention in a visual search task. The task described provides a useful tool to concurrently and comparably measure hippocampal and striatal memory in humans, while controlling for several cognitive processes that could be influenced by stress.

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Human participants were given hydrocortisone or placebo before learning stimulus-response and spatial tasks. Twenty-four hours later, the participants who received hydrocortisone showed better spatial and stimulus-response memory. This is one of the first studies using the same stressor to assess its impact on both spatial and stimulus-response memory formation in humans.

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In this study, rats were trained on a radial arm maze that required use of stimulus-response memory. Twenty-four hours later, those that received a systemic injection of corticosterone prior to a memory test showed significantly worse memory, while those treated with metyrapone (reduces cortisol production) did not show an impairment. This study was one of the first to show that pre-retrieval

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This study showed that post-training injections of corticosterone enhanced memory on a cued (stimulus-response dependent) water maze, but that these effects were blocked by injections of propranolol. This creates important parallels with hippocampal memory, in which both adrenergic and glucocorticoid components of the stress response are necessary for post-training enhancement (e.g., Roozendaal et al., 2006).

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