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The Effects of Post-Encoding Stress and Glucocorticoids on Episodic Memory in Humans and Rodents

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Abstract

It is now well established that acute stress shortly after encoding (i.e., post-encoding stress) can benefit episodic memory. In the current paper, we briefly review the human literature examining the effects of post-encoding stress on episodic memory, and we relate that literature to studies of post-encoding manipulations of cortisol in humans, as well as studies of post-encoding stress and administration of corticosterone on analogous memory tasks in rodents. An examination of the literature reveals several important gaps in our understanding of stress and memory. For example, although the human literature shows that post-encoding stress generally improves memory, these effects are not observed if stress occurs in a different context from learning. Moreover, the rodent literature shows that post-encoding stress generally impairs memory instead of improving it, and these effects depend on whether the animal is habituated to the learning context prior to encoding. Although many aspects of the results support a cellular consolidation account of post-encoding stress, we present possible modifications, such as a network reset, to better account for the data. We also suggest that it is important to incorporate ideas of contextual binding in order to understanding the effects of post-encoding stress and glucocorticoids on memory.

Keywords

Stress; Memory; Cortisol; Corticosterone; Consolidation; Context

Introduction

The prevalence of stress in our lives has made its effects on episodic memory an area of priority for researchers, and a growing body of literature shows that both acute and chronic stress can have important effects on memory (for reviews see Conrad, 2010; Roozendaal, McEwen, & Chattarji, 2009; Sandi & Pinelo-Nava, 2007; Sauro, Jorgensen, & Teal Pedlow, 2003; Schwabe et al., 2012). Acute stress refers to stress that occurs over a relatively short period of time (e.g., giving a talk in front of a group of people), while chronic stress is

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measured over the lifetime and includes many repeated exposures to stress. Often the effects of stress on memory are deleterious, such as when subjects are stressed when they are attempting to retrieve information from memory (for a review see Gagnon & Wagner, 2016). However, one finding that has attracted considerable interest is that acute stress shortly after learning (i.e., *post-encoding stress*) can actually be beneficial for memory. For example, in a key study by Cahill, Gorski, and Le, (2003), subjects were presented with a series of slides, and this was followed either by a non-stressful control task (i.e., holding their arm in lukewarm water), or a stressful cold pressor task (i.e., holding an arm in ice water; CPT) which produced a significant increase in the endogenous stress hormone cortisol. When recall for the slides was tested one week later, subjects who were stressed after encoding remembered significantly more information about the studied slides than did the non-stressed subjects.

The beneficial effects of post-encoding stress on memory in humans have now been well established (e.g., Andreano & Cahill, 2006; Beckner et al., 2006; Cahill, Gorski, & Le, 2003; Smeets, Sijstermans, et al., 2008; Yonelinas et al., 2011), and this is consistent with the rodent literature that has shown that post-encoding administration of corticosterone improves memory (e.g., Lupien & McEwen, 1997; Oitzl & de Kloet, 1992; Sandi & Rose, 1994). These results are important in showing that acute stress can impact memory processes that occur after the initial event has already been encoded into memory, and together, they present a compelling argument for a cellular consolidation account of post-encoding stress, whereby glucocorticoids (such as cortisol) bind to glucocorticoid receptors in the amygdala, which then over a period of minutes to hours modulates consolidation in other brain regions such as the hippocampus (e.g., McGaugh, 2000; McGaugh & Roozendaal, 2002; Roozendaal et al., 2009; Schwabe et al., 2012). We note that this form of cellular consolidation is distinct from systems consolidation, which refers to the gradual transfer of episodic memories from the hippocampus to the cortex, which is thought to take years or decades (e.g., Kandel, Dudai, & Mayford, 2014; Dudai, 2004).

However, a growing literature has suggested that the effects of post-encoding stress on memory may be more complex, and that they may present important challenges to the standard cellular consolidation view. For example, post-encoding stress often impairs memory in rodents (e.g., Guercio et al., 2014; Kogan & Richter-Levin, 2010; Li et al., 2012; Maroun & Akirav, 2008)—a finding which seems inconsistent with the consolidation account. In addition, studies examining the effects of administering glucocorticoids during the post-encoding period in humans have yielded inconsistent results. That is, post-encoding glucocorticoid administration sometimes improves (e.g., Wilhelm, Wagner, & Born, 2011), but sometimes impairs memory (Plihal & Born, 1999; Wilhelm et al., 2011), which also complicates the standard cellular consolidation view of post-encoding stress effects. These challenges have led some to propose supplementary theoretical accounts of post-encoding stress effects (Shields et al., 2017); within this review, we expand on the *contextual binding* account, which posits that the stressor itself serves as a particularly memorable event that enhances memory for other events that share the same context. Given all of the above, we felt it would be useful to conduct a review of the human and rodent literature on post-encoding stress, as well as post-encoding administration of cortisol/corticosterone, in order to identify the factors that may be responsible for these apparent discrepancies.

One other challenging finding emerging from the human literature is that the effects of post-encoding stress appear to be dependent on the spatial context in which the stressor occurs, in the sense that post-encoding stress only benefits memory if it occurs in the same spatial context as the initial learning experience (for review see Shields et al., 2017). This has led to a contextual binding account of post-encoding stress whereby the stressor itself is thought to serve as a particularly memorable event that enhances memory for other events that share the same context (Shields et al., 2017; Sazma et al., under review). The notion is that episodic memory requires the binding of items with the experimental context, and that the post-encoding stress manipulation itself leads to the formation of a well encoded event, such that it facilitates the retrieval of other events that share the same experimental context. In this way, post-encoding stress can benefit memory when it occurs in the same spatial or mental context as the learning materials, but it can reduce memory it if occurs in a different context. This could explain why stress effects can sometimes reverse, and why the effects are context-specific. Whether the account is consistent with the rodent literature or the literature on the glucocorticoid administration has not yet been carefully considered, and is a question we will return to after reviewing that literature.

In the current paper, we will briefly review the human literature, first by examining the effects of post-encoding stress on episodic memory, then by surveying the effects of post-encoding administration of cortisol on episodic memory. Next, we consider the rodent studies, beginning again by reviewing the post-encoding stress literature, and then examining post-encoding corticosterone administration effects on memory. In order to isolate the effects of post-encoding manipulations on memory, we only included studies that actively manipulated stress or cortisol/corticosterone shortly after encoding. The stressor used must have been established as reliably inducing a cortisol/corticosterone response (or include biological measures demonstrating such). We excluded any studies that manipulated stress before encoding, as it is impossible to disentangle post-encoding stress effects from encoding stress effects in those cases (e.g., stress may enhance or disrupt attention during encoding). Additionally, to be included in the current review, retrieval must have occurred more than 90 minutes after the stress manipulation to reduce the likelihood of stress hormones exerting effects during retrieval. To assess episodic memory, we selected studies that included tests of recall and recognition in humans, and analogous tasks in rodents (i.e., maze learning tasks that requiring recall of learned locations and object recognition tasks). We did not include studies of Pavlovian conditioning because it is less clear how these paradigms relate to episodic memory, and as far as we are aware, no human studies of post-encoding stress have used these paradigms. Nevertheless, we do briefly consider the relevant conditioning results when interpreting the rodent literature.

After reviewing the current literature, we then highlight the areas of agreement and disagreement across these literatures in order to identify areas in which additional studies will be useful in furthering our understanding of the effects of post-encoding stress and glucocorticoids on memory. Finally, we consider the challenges that these results present for theories of stress and consolidation.

Human Studies of Post-Encoding Stress

The effects of post-encoding stress on human episodic memory have now been examined in a number of studies (for reviews see Schwabe et al., 2012; Wolf, 2009; and for a recent meta-analysis see Shields et al., 2017). To select studies for this review, we searched PubMed and Google Scholar using the following string ((memory) AND (emotion OR positive OR negative OR neutral OR emotional) AND (encoding OR retrieval OR consolidation OR pre-encoding OR post-encoding OR storage OR reconsolidation) AND (Recognition OR Recall) AND (Stress OR Stressful OR Stressor)), as well as examining citations and references. Table 1 lists those studies, along with a number of potentially important characteristics of each study. An examination of Table 1 indicates that post-encoding stress generally leads to an increase in episodic memory, and these effects are quite robust (i.e., stress led to an increase in memory in 15 out of 22 independent experiments). For example, beneficial effects of stress have been observed using a variety of different stressors such as skydiving (Yonelinas et al., 2011), the Trier Social Stress Test (Beckner et al., 2006; Preuss & Wolf, 2009), as well as the more commonly studied cold pressor task (e.g., Andreano & Cahill, 2006; Cahill et al., 2003; McCullough & Yonelinas, 2013; Smeets, Otgaar, et al., 2008). In addition, they have been observed for various different materials, including words (Smeets, Otgaar, et al., 2008; Zoladz et al., 2015), pictures (Bryant, McGrath, & Felmingham, 2013; Cahill et al., 2003; Felmingham, Fong, & Bryant, 2012; Felmingham, Tran, et al., 2012; McCullough & Yonelinas, 2013; Preuss & Wolf, 2009; Yonelinas et al., 2011), and stories (Andreano et al., 2012; Nielsen, Ahmed, & Cahill, 2014). Although some studies have suggested that the effects are larger for emotionally negative than neutral materials (Andreano et al., 2012; Bryant et al., 2013; Cahill et al., 2003; Felmingham, Tran, et al., 2012; Nielsen et al., 2014; Smeets, Otgaar, et al., 2008), other studies have either shown larger effects for neutral materials (McCullough & Yonelinas, 2013; Preuss & Wolf, 2009; Yonelinas et al., 2011) or similar effects for both types of materials (Andreano & Cahill, 2006; Beckner et al., 2006; Felmingham, Fong, et al., 2012; Larra et al., 2014; Zoladz et al., 2015). Additionally, stress related improvements in memory have been seen in tests of recall (Andreano & Cahill, 2006; Andreano et al., 2012; Bryant et al., 2013; Cahill et al., 2003; Felmingham, Fong, et al., 2012; Felmingham, Tran, et al., 2012; Nielsen et al., 2014; Smeets, Otgaar, et al., 2008; Zoladz et al., 2015) and recognition memory (Beckner et al., 2006; Larra et al., 2014; McCullough & Yonelinas, 2013; Smeets, Sijstermans, et al., 2008; Yonelinas et al., 2011). Moreover, within recognition, there is evidence that post encoding stress benefits familiarity-based responses (McCullough & Yonelinas, 2013; Yonelinas et al., 2011), as well as recollection of qualitative information as measured by source memory (Smeets, Sijstermans, et al., 2008) and subjective reports of remembering (McCullough et al., 2015; Sazma et al., submitted for review).

The beneficial effects of post-encoding stress, however, are critically dependent on a number of important factors. Most notably, the spatial context of the stressor is critical in determining whether the stress benefits are observed. As can be seen in Table 1, the majority of studies that found an enhancing effect of post-encoding stress on memory had stress occur in the same context (typically the same room) as learning. In contrast, the studies in which participants changed rooms before undergoing the stress task, post-encoding stress tended to impair memory (McCullough et al., 2015; Pardilla-Delgado et al., 2016; Trammell & Clore,

2014). Moreover, in a recent study, Sazma et al., (submitted for review) directly manipulated the stressor context by having subjects stay in the same room or move to another room for the stress/control manipulation, while keeping the timing constant between groups. They found that stress improved memory when it occurred in the same context as learning, but it tended to reduce memory when it occurred in a different context.

Another potentially relevant factor in studies of post-encoding stress is the sex of the participants. In our review of the literature, studies that included both males and females found significant post-encoding stress effects. Additionally, a meta-analysis found that participant sex was not a moderating factor across studies (Shields et al., 2017), although several studies have reported larger effects in males than females (Andreano & Cahill, 2006; McCullough & Yonelinas, 2013; Yonelinas et al., 2011). These effects are likely due to several factors. For example, cortisol responses were found to be reduced in women using hormonal contraceptives (Nielsen et al., 2013), and the normal post-encoding stress enhancement was not found in women using hormonal contraceptives (Nielsen et al., 2014). In addition, the effects of post-encoding stress on memory appear to depend on menstrual phase (Zoladz et al., 2015). These results suggest that similar stress effects can be observed in males and females, but that they may be more variable in females.

Another important factor to consider in studies of post-encoding stress is the extent to which cortisol plays a role, but the relationship between stress, cortisol, and memory is complex. Common stress manipulations like the cold pressor and social stress are reliably found to lead to increases in salivary cortisol, and more than half of the reported studies have found that stress-related increases in cortisol are correlated with memory (see Table 1). However, this is often for only a subset of the study sample (e.g., one study finds a correlation between cortisol change and memory for males only, another finds it for females and negative items only). Moreover, in reviewing the studies of post-encoding stress, Shields et al. (2017) found that there was no overall relationship between the magnitude of the stress related cortisol increase and the magnitude of the memory effects observed across studies. In addition, there is some evidence that there may be nonlinear effects of cortisol on memory. For example, Andreano and Cahill (2006) found that cortisol was related to memory in an inverted U-shape manner, such that subjects showing a moderate stress related increase in cortisol showed a benefit in recall, whereas those showing a large increase in cortisol performed more poorly. Similarly, McCullough et al. (2015) tested recognition memory and found that recollection-based responses also exhibited an inverted U-shaped relationship with cortisol change. In contrast, familiarity-based recognition responses were found to exhibit a shallow but continuously increasing linear relationship with cortisol. Although addition studies are needed, these results suggest that the relationship between cortisol and memory may depend critically on the magnitude of the cortisol increase, and the type of memory that is being assessed.

Additionally, time-of-day effects are another factor that has been hypothesized to be critical for stress effects. Cortisol levels are at their peak in the morning and then decline throughout the day. These differing baseline levels of cortisol may mean stress has different effects on memory in the morning compared to the afternoon. The recent meta-analysis by Shields et al., (2017) found significant post-encoding stress effects regardless of what times the studies

began, but they did find that studies that only began after noon showed larger post-encoding stress effects on memory than studies that ran participants at any time of day.

Finally, sleep is another factor that is thought to be important for consolidation. (e.g., Stickgold, 2005). The majority of studies on post-encoding stress include a delay of at least 24 hours that naturally includes sleep, however a couple studies have found similar effects even with a shorter delay that does not include sleep (Yonelinas et al., 2011; McCullough et al., 2013). This indicates that sleep is not necessary for the post-encoding stress effects to occur. None the less, the effects of stress may interact with sleep (e.g., Payne & Nadel, 2004; Wagner & Born, 2008), so future studies experimentally manipulating both stress and sleep will be informative.

In sum, acute stress immediately after encoding improves recognition and recall in humans - unless the stressor occurs in a different spatial context from learning. The effects are seen for both neutral and emotional materials, and they appear to be similar for both males and females, but they may be more variable in females due to variations in menstrual phase and hormonal contraceptive use. Finally, the exact relationship between changes in cortisol and memory remains elusive, but it may be nonlinear and may be related to the type of memory being tested.

Human Studies of Post-Encoding Cortisol

Given that stress leads to an increase in cortisol, several studies have examined the effects of administering cortisol immediately after encoding on human memory (see Table 2). We searched Google Scholar and PubMed with the following string (cortisol OR corticosterone OR “drug administration” OR administration) AND (memory) AND (post-learning OR post-encoding OR “after learning OR “after encoding” OR consolidation) AND human), as well as examining citations and references for additional relevant studies. Unfortunately, there are very few memory studies that administered cortisol after learning, and the results are somewhat mixed (i.e., cortisol led to a decrease in memory in 2 cases, an increase in 1 case, and no effect in 2 other cases), making it difficult to draw any strong conclusions. However, based on the existing studies it appears that the effects of post-encoding cortisol depend on whether the drug is administered during wake or sleep. For example, Wilhelm et al. (2011) contrasted the effects of post-encoding administration of cortisol in subjects that napped after encoding to those that were kept awake after encoding. In a subsequent memory test, they found that cortisol administration led to an increase in temporal order memory in the awake subjects, which is consistent with the stress effects described above. In contrast, in subjects who were allowed to sleep immediately after the cortisol/placebo administration, cortisol was found to decrease memory. Consistent with this, one other study examining cortisol during sleep found a negative effect of cortisol on memory (Plihal & Born, 1999), although another study found no effect (van Marle et al., 2013). In addition, another study examining cortisol during wake found no significant effect on memory (de Quervain et al., 2000).

In sum, although post-encoding cortisol can have effects on human memory, it is clear that more studies examining these effects are needed since there are only a small number of published studies of this type, and the existing results are mixed. Nonetheless, there is some

suggestion that post-encoding administration of cortisol may improve memory in awake participants, whereas it may disrupt memory during sleep.

Rodent Studies of Post-Encoding Stress

The effects of post-encoding stress on memory have also been examined in studies of rats and mice (see Table 3; for an earlier review see Cazakoff, Johnson, & Howland, 2010). We used the following string to search PubMed and Google Scholar: (restraint stress OR social defeat OR predator stress OR acute stress) AND (“consolidation” OR “post-encoding” OR “post-learning” OR “after learning” OR “after encoding”) AND (“object recognition” OR “morris water maze” OR “barnes maze” OR “spatial memory” OR “recognition memory” OR “odor recognition”), as well as examining citations and references. In contrast to human studies, these studies show that post-encoding stress leads to a decrement, rather than an improvement, in memory (i.e., stress led to a decrease in memory in 10 cases, an increase in memory in 1 case, and it had no effect in 5 cases). The detrimental effects of stress have been observed across rodent strains and species. Moreover, they have been observed in studies of object recognition (Guercio et al., 2014; Li et al., 2012; Maroun & Akirav, 2008; Segev, Ramot, & Akirav, 2012) and spatial water maze tasks (Kogan & Richter-Levin, 2010; Li et al., 2012; Vales, Fukuda, & Almeida, 2014). In addition, post-encoding stress impairments on memory were found across various stressors, including restraint (Guercio et al., 2014; Li et al., 2012; Vales et al., 2014), elevated platform (Maroun & Akirav, 2008; Segev et al., 2012), foot shock (Busquets-Garcia et al., 2016; Kogan & Richter-Levin, 2010), and tail suspension (Busquets-Garcia et al., 2016) stress paradigms. However, note that the only study to use predator odor as the stress manipulation did not find an effect of post-encoding stress on memory (Homiack et al., 2017). The effects were also reported across various durations of the stressor from 2.5min to 90min, and various delays between learning and retrieval testing ranging from 4 hours to 28 days.

One variable that appears to play an important role moderating the stress effects observed in rodents is whether the animals are habituated to the learning context prior to encoding. In a majority of the studies examining post-encoding stress, the rodents were habituated to the learning and testing context prior to the encoding phase of the study (typically they were familiarized with the context on several days prior to learning), and in most of these studies an impairing effect of stress was found. In contrast, when animals were not habituated to the learning context, in only 1 out of 4 cases did stress lead to a decrease in memory. In fact, two studies directly assessed the effects of habituation (Maroun & Akirav, 2008; Segev et al., 2012), and found that while stress led to a significant reduction in memory when the animals were habituated to the learning context, the effect was not observed when the animals were not habituated. One of these studies found a memory increase in the stress group when the animals were not habituated (Maroun & Akirav, 2008), while the other found no differences in memory when the animals were not habituated (Segev et al., 2012).

Based on the human studies suggesting that the stress effects may depend on sex and on the context of the stressor, we also included these two factors in Table 3. All of the studies examined used only male rodents, and all of them included a context change between study and stress (i.e., the rodents were removed from the learning apparatus in order to administer

the stressor), so it is unknown what role sex or context may have played in the observed post-encoding stress effects seen in rodents.

It should be noted that a number of studies have examined the effects of post-encoding stress on Pavlovian conditioning paradigms in rodents, but those results have been quite mixed, with some studies finding post-encoding stress enhances memory but others finding it impairs memory (e.g., Sardari, Rezayof, & Khodagholi, 2015; Yang et al., 2013; for a review, see Sandi & Pinelo-Nava, 2007). Why the conditioning studies are mixed is not clear, and as far as we know no human studies have examined the effects of post encoding stress on classical conditioning. Thus, future studies directly contrasting the effects of stress on episodic tests of memory to conditioning tasks would be fruitful.

In sum, post-encoding stress generally impairs recognition and spatial memory in rodents. However, there is evidence that the negative effects of post-encoding stress can be eliminated or reversed if the animals are not habituated to the learning context prior to encoding. All of the studies of post-encoding stress in rodents have administered the stressor in a different context than the memory materials and have studied only males, so it is unclear if these factors impact the stress effects.

Rodent Studies of Post-Encoding Corticosterone

Several studies have examined the effects of corticosterone administered shortly after learning on memory in rodents (see Table 4; for an earlier review see Roozendaal, 2002). For this review, we used the following string to search Google Scholar and PubMed: ((“hydrocortisone” OR “corticosterone” OR “dexamethasone” OR glucocorticoid) AND (“consolidation” OR “post-encoding” OR “post-learning” OR “after learning” OR “after encoding”) AND (“object recognition” OR “morris water maze” OR “barnes maze” OR “spatial memory” OR “recognition memory” OR “odor recognition”), as well as examining citations and references for additional relevant studies.

Generally, the literature indicates that post-encoding corticosterone administration enhances maze learning and recognition memory (i.e., corticosterone produced a significant increase in memory in 7 cases, a decrease in only 1 case, and no effect in 3 cases). Note that the findings are consistent with studies of Pavlovian conditioning such as fear conditioning and avoidance tasks which have also suggested that post-encoding administration of glucocorticoids improves conditioning (for reviews see McGaugh, 2000; McGaugh, 2015; Roozendaal, Okuda, De Quervain, et al., 2006; Roozendaal, 2002; Roozendaal, 2009).

In addition, there is some evidence that the post-encoding corticosterone enhancement may be eliminated if the rodents are habituated to the learning context prior to learning (i.e., in 6 of the 7 cases that showed positive effects of corticosterone on memory the animals were not habituated to the learning context). In addition, one study (Okuda, Roozendaal, & McGaugh, 2004) found that administration of corticosterone led to a significant increase in object recognition in rats that had not been habituated to the learning context prior to encoding, whereas it did not impact memory in rats that had been habituated to the learning context. This pattern of results was also found in a study by Roozendaal, Okuda, Van der Zee, et al., (2006). However, another study found that both habituated and non-habituated rodents

showed enhancements in memory when corticosterone was administered after learning (Roozendaal et al., 2010). This discrepant result may be the product of using different species; in particular, the non-habituated rodents that showed a memory benefit in Roozendaal et al.'s (2010) study were mice that needed to be habituated to the environment in order to show any memory for the task (Stefanko et al., 2009).

This habituation effect has been taken as evidence that arousal may be necessary for post-encoding corticosterone to exhibit effects (Roozendaal, Okuda, Van der Zee, et al., 2006). That is, rodents that are habituated to the learning context are expected to be less aroused than non-habituated animals, and so stress after learning may only facilitate memory when arousal is present during learning. In support of this possibility Roozendaal, Okuda, Van der Zee, et al., (2006) found that the stress effects could be induced in habituated rats if they were injected with Yohimbine, which is known to increase arousal. However, another study (Sandi, Loscertales, & Guaza, 1997) showed that while post-encoding corticosterone improved memory in a standard water maze task, when the water maze task was made more arousing and stressful by using cold water, corticosterone no longer had any effect, indicating that increasing arousal during encoding sometimes decreases the effects of post-encoding corticosterone. Another study found that unhabituated, food-deprived rats who received corticosterone after encoding showed a decrease in taste memory (Ruetti et al., 2014). Thus, it is not yet clear whether habituation moderates post-encoding stress effects by impacting arousal or via another process.

To our knowledge, only one rodent study has examined the effects of post-encoding corticosterone during sleep, but—consistent with the human studies—it found that corticosterone during sleep impaired memory in rodents, whereas corticosterone improved memory if administered while the rodent was awake (Kelemen et al., 2014). However, it is important to note that memory was tested within 90 minutes of corticosterone administration, so it is difficult to distinguish post-encoding effects from retrieval effects in this study.

In sum, post-encoding administration of corticosterone generally enhances memory in rodents. This effect is reduced if the animals are habituated to the learning context prior to encoding, which may be related to the amount of arousal the rodents experience at encoding.

Why Does Post-Encoding Stress Improve Memory in Humans and Reduce Memory in Rodents?

The empirical literature on stress and memory reveals a number of important regularities, but it also points to a number of open questions that will need to be addressed in future studies, and it reveals some apparent contradictions in the literature that will need to be reconciled. Perhaps the most glaring contradiction in the literature is the fact that in humans, post-encoding stress generally benefits episodic memory, whereas in rodents, post-encoding stress leads to a reduction in memory. One possible account of this discrepancy is that it may be due to the different types of memory tasks that have been examined in the different species. In humans, stress-induced benefits in memory have been observed in tests of free recall and recognition, as well as on both familiarity- and recollection-based judgments within recognition. In rodents, stress has been found to impair memory on maze learning

tasks as well as object and location recognition. Although we examined the literature in a way to make the memory tasks as comparable as possible between rodents and humans, it is impossible to rule out the impact of differences in the memory tasks entirely. However, we do not think that task differences in themselves account for the discrepancies. First, given that the positive effects of stress in humans generalizes across a variety of different tasks, and conversely the negative effects of stress in rodents also generalize across a variety of tasks, suggests that the patterns of results are not particularly sensitive to specific task demands. In addition, the task demands of the recognition memory tests in humans are quite similar to those of the recognition tests in rodents, so it would be surprising if stress manipulations would have different effects on those tasks in the different species. Finally, the existing literature on the human and rodent tests of memory have in general provided convergence with respect to the role that different medial temporal lobe structures play in supporting these tasks across these species (Eichenbaum, Yonelinas, & Ranganath, 2007; Poldrack & Packard, 2003; Squire, 1992) leading one to expect that these different tasks tap similar memory processes across species.

Another possible factor that may play a role in the differences in results across species is the use of different types of stressors. In humans, stress related memory increases have been produced using the cold pressor task, social stress tasks, and skydiving, whereas in rodents, stress related reductions in memory have been produced by restraint stress, elevated platform stress, and foot shock. The stressors used in human studies tend to be fairly moderate, last between 3–20 minutes and result in cortisol levels less than double baseline levels. Some rodent stress manipulations are very stressful (e.g., 90 minutes of restraint stress) and produce corticosterone levels many times baseline levels. However, other rodent stressors are fairly moderate and result in corticosterone levels less than double baseline (e.g., elevated platform). An examination of Table 3 shows that the negative effects of stress in rodents are not limited to the most stressful tasks, nor is there evidence that more positive effects of stress on memory in humans are seen in the less stressful tasks. Thus, differences in the stressor severity does not seem to provide a simple explanation for the species differences.

A related possibility, however, is that the stressors may have different long-lasting effects on memory retrieval in humans and rodents (we thank Brian Wiltgen for pointing this out). That is, it is possible that when rodents that were stressed after learning are reintroduced to the experimental environment for the memory test, they may experience a stress response again, and this increased stress may impair memory retrieval. In this way, any beneficial effect of post-encoding stress on memory may be masked by a greater negative effect of stress on retrieval. No post-encoding rodent stress studies measured corticosterone at retrieval to see if rodents have elevated stress levels at test. In contrast, human subjects that were stressed previously may not experience the same stress response at retrieval (due to differing expectations or experiences), and so the post-encoding stress enhancement may not be masked by a stress retrieval effect. Indeed, many human studies of post-encoding stress have tested cortisol before retrieval, and do not find elevated levels (e.g., McCullough et al., 2015). If the species differences are due to differences in stress responses during the final test phase, then the differences may be reduced if there is a longer delay before the final test phase. However, an examination of Tables 1 and 3 does not provide any evidence that the

direction of the stress effects were influenced by the test delay. Nonetheless, we think that this possibility warrants further consideration.

One other difference between the human and rodent studies is that all of the rodent studies to date have been limited to testing male animals. Although the human literature suggests that the stress effects are sometimes reduced in females compared to males, they are generally observed in both sexes. Whether the observed stress effects in rodents are observed in females as well as males is not known. Nevertheless, it does not seem like the discrepancy between the stress effects in rodents and humans can be attributed solely to differences in the sex makeup of these studies, since human males generally show stress related increases in memory, whereas rodent males show a decrease.

There is one other major difference between the human and rodent studies of post-encoding stress that may well have been responsible for the observed inconsistencies observed across species, and that has to do with the context in which the stress manipulation takes place. In all of the rodent studies of post-encoding stress, the stress manipulation occurred in a different context from the learning phase (e.g., the animals were removed from the learning context in order to complete the stress/control phase of the study). In contrast, most human studies present the stressor in the same context as the learning materials (i.e., typically the stress/control manipulation was conducted in the same room as the study phase). Moreover, the human studies that have conducted the stress/control manipulation in a different context from the study materials often show that stress either has no effect or it leads to an impairment in memory, suggesting that the stress context must be the same as the study context before the stress-related benefits in memory are observed. As far as we are aware, no rodent studies have directly manipulated the extent to which the learning and stress contexts are varied, so rodent studies that directly manipulate the similarity of the study and stress contexts will be important in testing the generality of these effects.

What is the Role of Habituation?

The existing rodent literature indicates that post-encoding stress generally leads to an impairment in recognition and spatial memory, but that this effect can be eliminated or even reversed if the animals are not habituated to the learning context prior to encoding. Moreover, directly manipulating post-encoding corticosterone in rodents generally leads to an increase in memory, unless the animals are habituated to the learning context. As far as we are aware, no human studies have yet examined the effects of habituation on post encoding stress effects, so further studies should be aimed at asking whether the human stress effects are impacted by habituation.

If the habituation effects can be verified in human studies, how could these effects be explained? As discussed earlier, the rodent results have been interpreted as indicating that post-encoding administration of glucocorticoids alone may not be sufficient to produce an increase in memory consolidation, but rather it may be necessary to increase arousal during initial learning as well, and so it is the interaction between the arousal and stress systems that is necessary to initiate consolidation (Roozendaal et al., 2004). In this way, because habituated animals are not expected to be as aroused during the learning phase, they do not show the stress-related increase in memory. However, another possible account—described

in detail below—is that habituation might alter the extent to which learning is linked to the experimental context.

What Are the Neural Processes Underlying the Effects of Post-Encoding Stress on Memory?

Although the effects of post-encoding stress on memory are becoming clearer, less is known about the neural processes that produce these effects. For example, although there is evidence that stress-related increases in cortisol are related to memory in humans, additional studies further clarifying the relation between stress, cortisol, and memory are needed. The existing human studies suggest that stress related increases in cortisol can be related to increases in memory, but there are conditions in which this relationship appears to be nonlinear, and may differ for different forms of episodic memory (e.g., recollection vs familiarity). Moreover, although there are rodent studies that have directly manipulated the amount of corticosterone to assess its effects on memory (for review see Baldi & Bucherelli, 2005), the human findings have been correlational, as no studies have directly manipulated either cortisol dose or stressfulness and directly related that to memory performance. Although there is strong evidence that post-encoding corticosterone in rodents can enhance memory, there are far too few analogous studies in humans. Moreover, whether the cortisol/corticosterone effects are dependent on sleep has not yet been well established.

Also important, will be studies that examine other hormones and immune system processes that may play a critical role in producing the stress effects on memory. For example, stress upregulates circulating sex hormones in humans (Lennartsson et al., 2012), and post-encoding administration of estradiol (Inagaki, Gautreaux, & Luine, 2010) and progesterone (Harburger et al., 2008) both enhance object recognition memory in rodents. Thus, it is possible that enhancing effects of post-encoding stress on memory in humans may be due to effects of stress on sex hormones, although research has yet to directly test this possibility. Similar to sex hormones, immune system proteins known as cytokines— which primarily function as messengers involved in the coordination and maintenance of inflammation—increase in response to stress (Segerstrom & Miller, 2004; Steptoe, Hamer, & Chida, 2007) and influence memory when administered post-encoding (for reviews see Donzis & Tronson, 2014; Rachal Pugh, Fleshner, Watkins, Maier, & Rudy, 2001).

In addition, in reviewing the human literature we found only three neuroimaging studies examined the neural correlates of the effects of post-encoding stress, and it seems that additional studies of this kind will be critical in advancing our understanding of the neutral circuitry underlying the stress effects on memory. For example, Ritchey et al., (2017) found that for participants showing large cortisol increases in response to stress, memories became more correlated with hippocampal and amygdala activity observed during encoding, thereby shifting the distribution of recollected events toward those that had elicited relatively high activation. The results suggest that stress does not uniformly enhance memory, but instead selectively preserves memories that are strongly encoded by the amygdala and hippocampus. In addition, de Voogd et al., (2017) looked at post-encoding resting state connectivity and found that greater hippocampal-amygdala connectivity was related to better memory, but connectivity was not enhanced when subjects were stressed compared to when they were

not. Finally, Van Marle et al., (2013) had participants study negative and neutral pictures and then administered hydrocortisone immediately afterwards, just before the participants slept. The next day they had participants perform a recognition memory test in the scanner, and they found that hydrocortisone administration led to an increase in memory for negative compared to neutral materials, but led to reduced activity in the amygdala and hippocampus for the negative items during the retrieval scan. These results were interpreted as suggesting that consolidation of emotional materials may have led to an attenuation of the intrinsic levels of arousal that was linked to the emotional memories. Overall, these neuroimaging studies suggest that the hippocampus and amygdala are involved in post-encoding stress effects, but additional studies of this type will be necessary to verify these results and to identify the specific functional roles that these regions play in producing the observed stress effects.

Explaining the Effects of Stress in Humans and Rodents

As discussed in the introduction, the initial human findings by Cahill et al. (2003) provided support for the rodent pharmacological work that suggested stress-related increases in corticosterone may facilitate the cellular consolidation of recently encoded memories (McGaugh, 2000; Roozendaal, 2002). As the current review shows, subsequent studies provide additional support for this notion in showing that these beneficial effects of stress are consistently observed across a wide variety of materials, test procedures, and various stress manipulations.

However, other findings appear to complicate the consolidation account considerably. First, the finding that stress leads to a reduction in memory when the stressor occurs in a different spatial context than learning is not predicted by a general consolidation process. The results indicate that stress-related increases in cortisol do not simply facilitate the consolidation of recently encoded memories, but instead stress selectively facilitates memory for events that occurred in the same context as the stressor. As an additional complication to the standard consolidation account, the rodent results indicate that post-encoding stress in rodents generally reduces memory, while it benefits memory in humans. It is not clear why post-encoding stress would facilitate consolidation in humans and disrupt it in rodents. One possibility is that these discrepancies may be due to differences in the timing of the stressor after the encoding event in the different studies, but the current review provided little support for this possibility. Finally, in humans, post-encoding cortisol administration appears to lead to a decrease in memory during sleep whereas it leads to an increase in memory during wakefulness. Sleep is generally thought to facilitate consolidation rather than inhibit it (e.g., Stickgold, 2005), so these findings do not seem consistent with the traditional consolidation account. However, it is possible the levels of cortisol that are optimal to promote consolidation are fundamentally different during wake compared to sleep. In our view, the results seem to present a number of puzzles for the cellular consolidation account of post-encoding stress, but we do not think that the results directly rule against the account. However, we do think the consolidation account does need to be modified considerably to address these issues. At present, there is not enough data to be certain of how the consolidation account of post-encoding stress should be modified, but we explore some possibilities here.

One possibility is that changing contexts induces a network reset (e.g., Bouret & Sara, 2005) that causes a shift away from the neuronal networks that were responsible for learning in the previous context. Once in the new context, any stress hormones released will strengthen the consolidation of events that occur in the new context, but not for events that occurred before the context shift and the resulting network reset. Indeed, both hippocampal (e.g., Smith & Mizumori, 2006) and noradrenergic (Bouret & Sara, 2005) activity have been shown to be modulated by context, and it is possible that coordinated activity in these systems is necessary for glucocorticoids to exert their beneficial effects on consolidation. Switching contexts then disrupts the ongoing activity of these systems and subsequent glucocorticoid release can no longer benefit consolidation. This theoretical account is an extension of existing cellular consolidation theories of post-encoding stress that can account for the data reviewed here.

Another possibility is that stress may not be sufficient to promote cellular consolidation unless memories have been tagged as particularly relevant (e.g., Frey & Morris, 1997; Mather et al., 2016). Although tagging is generally thought to be related to arousal, perhaps ongoing context serves as a type of tag that guides molecular mechanisms involved in cellular consolidation. Although some early studies reported that stress benefits were only observed for emotional materials, and this was taken as support for the notion that consolidation may act preferentially preserve arousing memories, subsequent work indicated that similar effects could be obtained for both emotional and neutral materials. Thus, context —perhaps more than arousal—may be involved in this memory tagging.

We have also proposed a contextual binding account whereby the stressor itself serves as a memorable event that enhances memory for other events that share the same context (Shields et al., 2017; Sazma et al., under review). By this account we assume that that episodic memory requires the binding of items with the experimental context, and that the post-encoding stress manipulation itself leads to the formation of a well encoded episode. In this way, one can explain why stress benefits memory when it occurs in the same spatial or mental context as the learning materials, but it can reduce memory it if occurs in a different context. Moreover, it can explain why the stress effects can be observed for both emotional and neutral materials. In addition, contextual binding may also help explain why rodents do not show stress enhancements when they are habituated to the learning context. By this account, stress benefits should be most pronounced when the encoding leads to strong binding between the items and the experimental context. If the learning context is highly habituated prior to encoding, it should become a less salient aspect of the study event, and thus less well bound to the study items, and so the beneficial effects of stress should be reduced. Similarly, if drugs like Yohimbine lead to an increase in general arousal, this may lead to better binding of the items and the context, which would also lead to an increase in the observed stress effects. Finally, from the context binding perspective, the different effects of cortisol seen during wake and sleep may be explained as reflecting the fact that sleeping leads to a change of mental context. Thus, post-encoding administration of cortisol during wake may benefit memory because it occurs in a similar context as the learning materials, whereas in the sleep conditions, the mental context is quite different from the awake state, and so the administration of cortisol is no longer occurring in the same context as the learning materials. Finally, we suggest that the contextual binding account may also help

explain effects of pre-encoding stress. Although not the focus of the current study, pre-encoding stress tends to enhance memory if it occurs immediately before encoding, but not when it occurs longer before encoding (for review see Shields et al., 2017), as one might expect if stress produces a memorable memory that facilitates memory for items that share the same context. Future studies that more directly manipulate the context of the stressor in pre- and post-encoding studies of stress will be important in testing this approach further.

This contextual binding account helps explain a number of results that seem problematic for the initial consolidation account, however other results are less well explained. For example, the fact that post-encoding stress effects are modulated by sex-related factors like hormonal contraceptives or menstrual phase is difficult to explain as reflecting differences in contextual binding. The evidence that context is important for post-encoding stress effects is mounting, and the contextual binding framework is just one possibility that we are putting forth to help explain the literature. Modified cellular consolidation accounts of post-encoding stress also can also explain the current data equally well, so future studies aimed at differentiating these different accounts will be important.

In conclusion, the finding that post-encoding stress can benefit human episodic memory is well established, and the conditions necessary to observe these effects are becoming clearer. In rodents, post-encoding stress has been established as impairing memory, but there appear to be plausible reasons for these opposing results. Although the human findings were initially assumed to reflect the operation of a general stress-facilitated consolidation process, growing evidence points to the importance of context in producing these effects. Future studies designed to further assess these accounts promise to advance our understanding of stress and episodic memory.

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Highlights:

- Post-encoding stress benefits memory in humans, but is context dependent
- Post-encoding stress impairs memory in rodents, but is dependent on habituation
- Post-encoding cortisol in humans improves or impairs memory dependent on sleep
- Post-encoding corticosterone benefits memory in rodents, dependent on habituation

Table 1.

Human Studies of Post-Encoding Stress Effects on Memory

Studies are arranged by the direction of the primary effects observed, with post-encoding stress studies that showed a benefit on subsequent memory coming first. A visual examination of the table shows that the majority of the studies that did not introduce a context change between encoding and stress found a positive effect of stress, while the majority of studies that had a context change found a negative effect. These findings appear consistent across various types of stressors, delays, and stimuli.

Authors	Stressor	Stress Delay after Encoding	% Male	Stimuli	Were Stimuli Emotional?	Retrieval Test	Test Delay	Context Change?	Cortisol Correlation	Effect	Notes
Larra et al., (2014)	CPT	0	49%	Faces	Yes	Recognition	24 hours	No		+	Effects only for those with large heart rate increase during CPT
Smeets, Otgaar, et al., (2008)	CPT	5 min	2%	DRM	Yes	Recall	24 hours	No	/	+	Effects only for emotional items, cortisol correlation was for both neutral and emotional items
Felmingham, Tran, et al., (2012)	CPT	0	51%	Pictures	Yes	Recall	48 hours	No	/	+	Effects only in females for emotional items. Cortisol correlated for emotional items in females, and neutral items in males
Felmingham, Fong, & Bryant (2012)	CPT	0	0%	Pictures	Yes	Recall	48 hours	No	/	+	Effects only in females with high progesterone levels. Cortisol correlated only with emotional items.
Andreano et al., (2012)	CPT	0	0%	Story	Yes	Recall	1 week	No	/	+	Effects only for emotional items (both memory and cortisol correlation)
Bryant, McGrath,	CPT	0	47%	Pictures	Yes	Recall	48 hours	No	/	+	Effects only for emotional items in

Authors	Stressor	Stress Delay after Encoding	% Male	Stimuli	Were Stimuli Emotional?	Retrieval Test	Test Delay	Context Change?	Cortisol Correlation	Effect	Notes
Felmingham (2013)											females. Cortisol correlated only for neutral items in males.
Beckner et al., (2006)	TSST	10 min	36%	Film	No	Recognition	48 hours	?*	/	+	Cortisol correlated for verbal information, and trended (p=.07) for overall recognition
Preuss & Wolf (2009)	TSST	10 min	100%	Pictures	Yes	Recall & Recognition	24 hours	Yes	/	+	Effects only for neutral items on recall test. Cortisol correlated only for neutral items in recall (with a trend for emotional items)
Andreano & Cahill (2006)	CPT	0	44%	Story	No	Recall	1 week	No	∩	+	Effects only in males (both memory and cortisol correlation)
Cahill, Gorski, & Le (2003)	CPT	0	29%	Pictures	Yes	Recall	1 week	No	o	+	Effects only for emotional items
McCullough & Yonelinas (2013)	CPT	10 min	50%	Pictures	Yes	Recall & Recognition	2 hours	No	o	+	Effects only in males. Memory also tested at 3 months and showed same effects
Smeets, Sijstermans, et al., (2008)	CPT	0	40%	Motor Actions	No	Recognition & Source	24 hours	No	o	+	
Nielsen, Ahmed, & Cahill (2014)	CPT	0	0%	Story	Yes	Recall	1 week	No	o	+	Effects only for emotional items in normally cycling women.
Yonelinas et al., (2011)	Skydiving	0–45 min	50%	Pictures	Yes	Recall & Recognition	2 hours	Yes	o	+	Effects only for familiarity for neutral items in

Authors	Stressor	Stress Delay after Encoding	% Male	Stimuli	Were Stimuli Emotional?	Retrieval Test	Test Delay	Context Change?	Cortisol Correlation	Effect	Notes
											recognition for males.
Zoladz et al. (2015)	CPT	5 min	52%	Words	Yes	Recall & Recognition	24 hours	No		+	Effects only in free recall
Andreano, Arjomandi, & Cahill (2008)	CPT	0	0%	Story	Yes	Recall	1 week	No	/	O	Cortisol correlated only for females in mid-luteal phase
Nielsen et al., (2013)	CPT	0	0%	Pictures	Yes	Recall	1 week	No	o	O	Half of the subjects were using hormonal contraceptives
Pardilla-Delgado et al. (2016)	TSST	0	39%	DRM	No	Recall & Recognition	24 hours	Yes	\	−	Effects only significant in recognition, but similar pattern in recall. Cortisol correlated with false memory
McCullough et al., 2015	CPT	20 min	100%	Pictures	Yes	Recognition	24 hours	Yes	∩	−	Effects only for recollection. Cortisol correlated in an inverted U shape for recollection, and linearly for familiarity.
Trammell & Clore (2013) Expt 1	CPT	0	39%	Words	Yes	Recall	48 hours	Yes	o	−	
Trammell & Clore (2013) Expt 2	CPT	0	47%	Pictures	Yes	Recall	48 hours	Yes	o	−	
Trammell & Clore (2013) Expt 3	CPT	0	46%	Pictures	Yes	Recall	48 hours	Yes	o	−	

Note: / represents a positive linear correlation, ∩ is a non-linear correlation, \ is a negative linear correlation, o means it was examined and there no correlations, and a blank cell means the authors did not mention doing any correlation tests. + represents an enhancing effect of stress on memory, o represents a null effect, and - represents an impairing effect.

*Participants were shown a new room, but prepared speeches in room where encoding took place

Table 2.

Human Studies of Post-Encoding Cortisol Effects on Memory

Studies are arranged by the direction of the primary effects observed, with post-encoding cortisol administration studies that showed a benefit on subsequent memory coming first. A visual examination of the table reveals that sleep may be an important factor in the direction of results, with the majority of studies that administered cortisol during wake finding a positive effect, while the majority of studies that administered cortisol during sleep finding a negative effect.

Authors	Drug Administration	Drug Delay	% Male	Stimuli	Were Stimuli Emotional?	Retrieval Test	Test Delay	Sleep?	Effect	Notes
Wilhelm et al., 2011	IV Cort (13 mg)	15 min	100%	Story	Yes	Recall, Recognition, Temporal Order	6 hours	No	+	Effects for temporal order only, no effect on item memory
De Quervain et al., 2000	Oral Cort (25mg)	0	50%	Words	No	Recall & Recognition	0 & 24 hours	No	o	
Van Marle et al., 2013	Oral Cort (20mg)	15 min	100%	Pictures	Yes	Recognition	24 hours	Yes	o	
Wilhelm et al., 2011	IV Cort (13 mg)	15 min	100%	Story	Yes	Recall, Recognition, Temporal Order	6 hours	Yes	−	Effects for temporal order only, no effect on item memory
Plihal & Born, 1999	IV Cort (13 mg)	15 min	100%	Word Pairs	No	Recall	3 hours	Yes	−	

Note: + represents an enhancing effect of cortisol on memory, o represents a null effect, and - represents an impairing negative effect.

Table 3.

Rodent Studies of Post-Encoding Stress Effects on Memory

Studies are arranged by the direction of the primary effects observed, with post-encoding stress studies that showed a benefit on subsequent memory coming first. A visual examination of the table reveals that habituation may be an important factor in the direction of results, with the majority of studies that habituated rodents to the learning environment finding a positive effect of post-encoding stress on memory. All studies used exclusively male animals, and all studies introduced a context change between learning and stress.

Authors	Stressor	Stress Delay after Encoding	% Male	Strain/species	Stress Duration	Retrieval Test	Test Delay	Context Change?	Habituated?	Effect	Notes
Maroun & Akirav (2008), Exp. 2	Elevated platform stress	0min	100	Wistar rats	30min	Object recognition	24 hours	Yes	No	+	
Segev et al. (2012), Exp. 2	Elevated platform stress	After microinjectiAon	100	Sprague-Dawley rats	30min	Object recognition	24 hours	Yes	No	o	
Kogan & Richter-Levin (2010), Exp. 2	Foot shock	60min	100	Wistar Hanover rats	5min	Morris water maze	48 hours	Yes	No	o	Warm water (i.e., less stressful)
Homiack et al. (2017)	Predator odor	30min	100	Wistar rats	30min	Four-arm water plus-maze	24 hours	Yes	Yes	o	Warm water, but plus maze
Vales et al. (2014)	Restraint stress	0min	100	Wistar rats	60min	Modified Morris water maze	672 hours	Yes	Yes	o	Warm water (i.e., less stressful)
Li et al. (2012), Exp. 1	Restraint stress	0min	100	Swiss albino mice	60min	Object and location	4 hours	Yes	Yes	o	
Busquets-Garcia et al. (2016), Exp. 1	Tail suspension	20min	100	Swiss albino mice	5min	Object recognition	24 hours	Yes	Yes	−	Mediated by cannabinoid system
Busquets-Garcia et al. (2016), Exp. 2	Foot shock	20, 60, 120, 180, 240 mins	100	Swiss albino mice	2.5min	Object recognition	24 hours	Yes	Yes	−	Mediated by cannabinoid system
Guercio et al. (2014), Exp. 1	Restraint stress	0min	100	C57BL/6 mice	90min	Object recognition	24 hours	Yes	Yes	−	
Guercio et al. (2014), Exp. 2	Restraint stress	0min	100	C57BL/6 mice	90min	Object recognition	24 hours	Yes	Yes	−	
Guercio et al. (2014), Exp. 3	Restraint stress	0min	100	C57BL/6 mice	90min	Object recognition	24 hours	Yes	Yes	−	
Guercio et al. (2014), Exp. 4	Restraint stress	0min	100	C57BL/6 mice	90min	Object recognition	24 hours	Yes	Yes	−	
Li et al. (2012), Exp. 2	Restraint stress	0min	100	Swiss albino mice	60min	Object and location	24 hours	Yes	Yes	−	Impairment present in both tasks
Maroun & Akirav (2008), Exp. 1	Elevated platform stress	0min	100	Wistar rats	30min	Object recognition	24 hours	Yes	Yes	−	
Segev et al. (2012), Exp. 1	Elevated Platform stress	After microinjection	100	Sprague-Dawley rats	30min	Object recognition	24 hours	Yes	Yes	−	

Authors	Stressor	Stress Delay after Encoding	% Male	Strain/species	Stress Duration	Retrieval Test	Test Delay	Context Change?	Habituated?	Effect	Notes
Kogan & Richter-Levin (2010), Exp. 1	Foot shock	60min	100	Wistar Hanover rats	5min	Morris water maze	48 hours	Yes	No	−	Cold water (i.e., more stressful)

Note: + represents an enhancing effect of stress on memory, o represents a null effect, and - represents an impairing effect.

Table 4.

Rodent Studies of Post-Encoding Corticosterone Effects on Memory

Studies are arranged by the direction of the primary effects observed, with post-encoding corticosterone administration studies that showed a benefit on subsequent memory coming first. A visual examination of the table shows that for the majority of studies where the animals were not habituated to the learning environment, there was a positive effect of post-encoding administration of corticosterone.

Authors	Drug Administration	Drug Delay	% Male	Strain/species	Retrieval Test	Test Delay	Habituated?	Effect	Notes
Okuda et al. (2004)	IV Cort. 0.3, 1.0, or 3.0 mg/kg	0min	100	Sprague-Dawley rats	Object recognition	24 hours	No	+	Benefit only for 1 mg/kg dose
Roozendaal et al. (2006), Exp. 1	IV Cort. 0.3, 1.0, or 3.0 mg/kg	0min	100	Sprague-Dawley rats	Object recognition	24 hours	No	+	Benefit for 1 & 3 mg/kg dose. Propranolol in BLA blocked the effect
Roozendaal et al. (2006), Exp. 3	IV Cort. 0.3, 1.0, or 3.0 mg/kg	0min	100	Sprague-Dawley rats	Object recognition	24 hours	No	+	Benefit for 1 & 3 mg/kg dose. Propranolol in BLA blocked the effect
Roozendaal et al. (2006), Exp. 4	IV Cort. 0.3, 1.0, or 3.0 mg/kg	0min	100	Sprague-Dawley rats	Object recognition	24 hours	No	+	Benefit for all doses. Propranolol in HC did not block the effect
Roozendaal et al. (2010)	IV Cort. 1.0 mg/kg	0min	100	Sprague-Dawley rats	Object and location	24 hours	No	+	
Roozendaal et al. (2010)	IV Cort. 1.0 mg/kg	0min	100	C57BL/6J mice	Object and location	24 hours	Yes	+	Strain of mice needs to be habituated to do task
Sandi et al. (1997), Exp. 1	IV Cort. 5.0 mg/kg	0min	100	Wistar rats	Water maze (warm)	24 hours	No	+	Cort given after each training session (3 days)
Okuda et al. (2004)	IV Cort. 0.3, 1.0, or 3.0 mg/kg	0min	100	Sprague-Dawley rats	Object recognition	24 hours	Yes	o	
Roozendaal et al. (2006), Exp. 2	IV Cort. 0.3, 1.0, or 3.0 mg/kg	0min	100	Sprague-Dawley rats	Object recognition	24 hours	Yes	o	Yohimbine in BLA enhanced memory only for 1 mg/kg dose
Sandi et al. (1997), Exp. 2	IV Cort. 5.0 mg/kg	0min	100	Wistar rats	Water maze (cold)	24 hours	No	o	Cort given after each training session (3 days)
Ruetti et al. (2014)	IV Cort. 1.0, 3.0, or 5.0 mg/kg	0min	100	Wistar rats	Taste recognition	24 hours	No	-	Impairment only for 5 mg/kg dose.

Note: + represents an enhancing effect of corticosterone on memory, o represents a null effect, and - represents an impairing effect.