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Minireview

Significant life events and the shape of memories to come: A hypothesis

Tracey J. Shors *

Department of Psychology, Center for Collaborative Neuroscience, Rutgers University, USA

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Abstract

Much has been said about how significant life events modulate our response to stimuli that are integral to those events. However, we know less about the more general consequences of these events, that is, how they affect subsequent learning abilities that are seemingly irrelevant to the initial event. Here, it is proposed that significant life events, most often stressful in nature, alter future learned responses by inducing nonspecific and persistent changes in neuroanatomical structures. These changes are induced in the presence of sex and stress hormones, which are released either in response to the event itself or as a consequence of stages of life. To illustrate, the effects of acute stressful experience on learning processes and their regulation by the release of hormones are reviewed. I discuss how these events and their hormonal consequences alter anatomical substrates such as those involved in neurogenesis and synaptogenesis. It is proposed that these modulatory processes allow past experiences to change the shape of memories to come. In this way, memorable life events become less about the past and more about the future.

Keywords: Learning; Memory; Stress; Hormones; Sex differences; Neurogenesis; Synaptogenesis; Hippocampus; Trauma; Glucocorticoids; Estrogen; Dendritic spines

1. Introduction

Intense life experiences are not only memorable in and of themselves, but they also can change the way we experience events in the future. In thinking about this issue, I recalled a report some years ago about two patients, known as K and F (Cohen, 1996; Treadway, Mccloskey, Gordon, & Cohen, 1992). They both experienced a profound retrograde amnesia upon neurological insults. At the age of 53, K was found holding an electrical device from an oven, and all indications were that he suffered severe electrical shock. Nearly 40, F suffered an aneurysm from a large hematoma in her temporal lobe. In both cases, these people suffered a temporally distinct loss of memory and even personal identity. For K, he could remember next to nothing between the time of 1946 and 1980, a nearly 40 year gap. For F, she remembered little between 1960 and 1979. These deficits were not limited to autobiographical information but rather extended into memories for world events and even skills acquired during those time periods. In some instances, they acted as if they were still the person from before their respective traumas. Despite being an older adult, K often behaved like a teenager, skipping, giggling, and blushing about girls. Interestingly enough, the beginnings of these "gaps" in memory were bound by stressful life events. In the case of K, his loss of memory went back to the end of World War II, when his grandmother to whom he was very close had died, and his family's house had burned down, leaving them quite destitute. In the case of F, her memory loss began at a time in her life when she became involved in an illicit affair with a married man and was pregnant with his baby. They had also experienced some stressful events just prior to their brain trauma, but the most telling are those that occurred decades before. It's as if their lives had

* Fax: +1 732 445 2263.
E-mail address: shors@rci.rutgers.edu.

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been recorded in all their complexity on some kind of tape and the tape was erased from the time of one stressful event to another.

These are two very unusual cases and ones that would be impossible to examine in a systematic or experimental way. But minimally, they do suggest that we have a number of parallel systems involving emotions, memories, skill learning, and contextual information that are seemingly organized across our individual time lines. How can this be? How does an experience in one situation and phase of life alter completely different experiences in the future? In this review, I will address a related question: how do significant life events interact with and alter our ability to learn about new events in the future? I will try to take the question a step further and ask how this system is orchestrated by the brain.

2. Stressful life events and learning thereafter

We all have experienced stressful events in our lives and most of us ruminate to some extent about them. Is there a purpose—some adaptive reason that we remember so vividly the traumatic and salient times in our lives? Of course, some people repress these types of memories, do not ruminate, and respond in a maladaptive way. However, they are apparently the exception rather than the rule. In fact, it has been shown that humans recover quite remarkably from stressful life events (Bonanno, 2004; McNally, 2003). Apparently, if you ask people how they think they will respond after some hypothetical stressor, many predict that they will be deeply affected and become dysfunctional. In reality, most people are resilient and do recover, even from horribly traumatic experiences (Gladwell, 2004; Rind, Tromovitch, & Bauserman, 1998). Irrespective, the memories for those events become forever impregnated in their minds and alter many of their responses to future life events, even in those situations not obviously related to those of the stressful event. How does this happen? On the face of it, these effects of memorable life events seem permanent. But, how do these stimulus events induce persistent and in many cases permanent effects on subsequent behaviors? To address this issue, I will discuss results from experiments in rats, and first just in male rats. In these studies, animals were exposed to one significant "life" event. The event is stressful but acute, lasting 30 min or less. Typically, the stressor consists of brief intermittent tailshocks (30 over 30 min) or 20 min of inescapable swim stress. In response to either one of these events, which are qualitatively quite different, male rats tend to learn faster (Fig. 1) (Shors, 2004a; Shors, Weiss, & Thompson, 1992).

For most of the studies, we have used an associative learning task known as classical eyeblink conditioning. This task was chosen for a number of reasons, primarily because it has been extensively studied in a variety of species, including man and because much of its anatomical circuitry has been described (Thompson, 2005). In this task, the animal is presented with a conditioned stimulus (CS) of noise

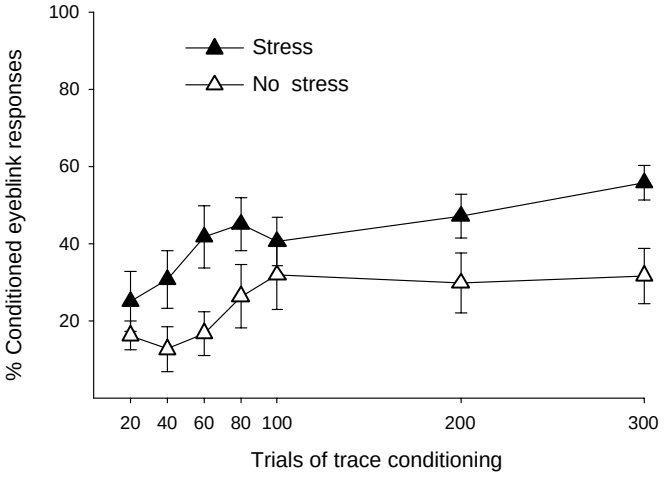

Fig. 1. Stressful experience enhances classical conditioning in males. Adult male rats were exposed to an acute stressor of brief, intermittent tail shocks (30, 1 s, 1/min) over 30 min and trained the next day on a trace task with an eyeblink as the unconditioned response. Rats exposed to the acute stressor emitted a greater percentage of CRs (eyelid responses during the trace interval) to the CS than animals that were not exposed to the stressful event (Hodes & Shors, 2005).

lasting a few hundred milliseconds. It is followed by an aversive stimulation to the eyelid which causes the animal to blink. This unconditioned response (UR) becomes conditioned as the animal learns that the CS predicts the occurrence of the eyelid stimulation, the unconditioned stimulus (US). After exposure to an acute stressful event, animals learn to associate the noise stimulus with the eyelid stimulation and blink in response to the CS sooner and more than do animals that are not exposed to the stressor (Shors et al., 1992). For most studies, their asymptotic performance is also elevated. One of the more interesting features of this phenomenon is its persistent time course and it is the reason it is relevant to the question posed in this review. The enhancement in conditioning is evident immediately after the stressor, which is perhaps not that surprising, since the animals are still quite aroused. However, the effect of stress on subsequent learning is also quite persistent. If, after the stressful event, the animal is placed back in its home cage for 24, even 48 h, and then trained anew, the enhanced responding still occurs (Shors & Servatius, 1997). It is important to note that exposure to the stressor affects new learning but does not alter conditioned responding that is already in progress; i.e., if the animal is stressed after the animals have acquired the learned response, the number of responses does not increase (Shors, 2001). Thus, exposure to the stressful event affects new learning of this response and is not simply increasing nonspecific responses to the conditioned stimulus. Also, the enhancement of learning transfers from one context to another; in most studies, animals are stressed in one context but trained a day or two later in a different context. This is not to say that context is not important because reexposure to the context in which the stressor took place does prolong the effect. To be specific, exposure to the acute stressful event in one context

enhances subsequent conditioning in another context and this effect persists for about 2 days but dissipates within 3 or 4 days. However, if animals are exposed to the stressor in one context and 3 days later placed back in the same context and trained, they condition faster than animals that are stressed and trained 3 days later in a novel context (Shors & Servatius, 1997). Thus, reexposure to cues related to the stressful event can enhance the effect but even in their absence, the effect of stress on subsequent learning is relatively persistent.

What is it about the stressful event that is able to induce such a long-lasting effect on subsequent behavior? One could propose that it is simply the aversive physical nature of the stimulus, i.e., exposure to the shocks. Recently, we addressed this hypothesis by manipulating controllability, a procedure with a long history in psychology, famously exploited in the "learned helplessness" studies of the 1960s. In these studies, animals were placed in a situation where they could learn to escape a footshock by shuttling over a barrier to the other side of the training environment. Another animal was yoked to the animal that could learn to escape. Thus, one animal established "control" over the stressor whereas the other did not but was exposed to the same number and duration of footshocks (Overmier & Seligman, 1967; Seligman & Maier, 1967). As a consequence of this manipulation, there were profound differences in the animals' subsequent behavior. The most recognized was that on subsequent escape learning. The animals that had learned to escape the shock by moving to the other side of the box readily learned a new escape task in which movement was critical. In contrast, animals that learned that movement did not alter the amount of shock that it received, did not learn the new task in which movement was critical. Using similar procedures, we examined the contribution of "controllability" to the stress-induced effects on eyeblink conditioning (Fig. 2). Animals were placed in a shuttle box apparatus and trained to escape a brief shock to the foot by running to the other side. They rapidly learn to escape. Yoked animals were exposed to the same amount of shock but could not escape. After a week of this training regime, rats were trained on the classically conditioned eyeblink response. Surprisingly, only the animals that could not escape the shock showed any effects on conditioning (Leuner, Mendolia-Loffredo, & Shors, 2004c). One might have expected that learning one task might somehow facilitate learning of a second task. The important point is that only those animals that could not establish control over the stressor showed enhanced responding whereas those that did establish control were unaffected. These results suggest that the absence of control induces a long-lasting effect on the animal's ability to form simple associations between stimulus events in its future.

At this point, I wish to offer a disclaimer about these findings, in particular whether they relate to other types of types of learning or whether they are limited to classical eyeblink conditioning. For the most part, other tasks have not been evaluated although in some cases, they have been

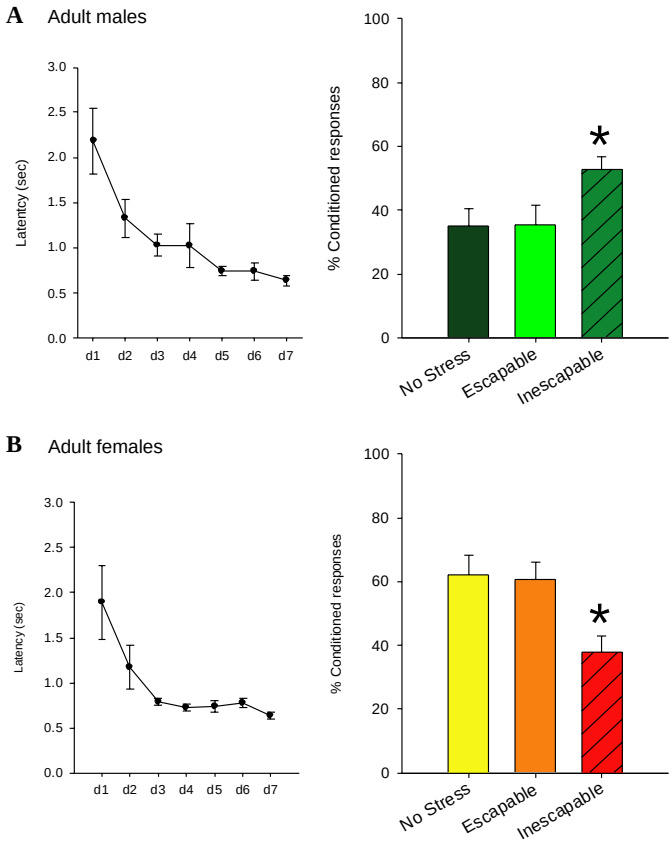

Fig. 2. Controllable versus uncontrollable stress affects subsequent trace conditioning differently in males versus females. (A) Adult male rats were trained for 7 days (d1–d7) on an operant conditioning task in which they could learn to escape from a mild footshock. The graph to the left shows response times (mean latency in seconds +SEM) for rats that could escape. These rats were yoked to animals that could not escape but were nonetheless exposed to the same amounts of shocks. One day after this manipulation, all animals were trained on the classical eyeblink conditioning task using a trace memory paradigm. The graph to the right shows the percentage of conditioned responses in all groups, including a group of animals that were not exposed to the escape training. As shown, only the animals exposed to the uncontrollable stress responded differently; males responded with a greater percentage of CRs. (B) Adult females were exposed to the same procedures. As shown in the figure to the right, females responded preferentially to the uncontrollable but not the controllable stress. However, they responded in the opposite direction of the males: females that were exposed to the uncontrollable stress emitted fewer CRs during trace eyeblink conditioning (Leuner et al., 2004c).

and the results are different (Shors, 2004a). I do not know if this is because of differences in performance effects or whether these effects of stress on learning are indeed specific to this type of training procedure. Given these qualifications, I would propose that these effects be viewed simply as that—effects that can be demonstrated in laboratory animals under relatively limited conditions. However, they are observable and robust and therefore may provide some insight into how systems related to stressful life events and those related to learning interact. This point is particularly salient as I present the next set of studies which involve females. It goes without saying that males are different from females but the extent of their differences at the neurobiological (and psychological) level has only recently become

realized. Many of the differences were not recognized because they were not observed and those that were observed usually presented themselves as differences in degree; for example, it is generally accepted that males perform better on spatial-learning tasks whereas females perform better on verbal tasks (Kimura, 1999). But there are a few examples in which males and females respond in opposite directions and I will focus on these here. To be explicit, when female rats are exposed to an acute stressful event such as those involving inescapable tailshocks or swimming, their ability to acquire the classically conditioned eyeblink response is reduced (Wood & Shors, 1998). Therefore, if females are exposed to the same stressor that enhances conditioning in males, they instead show a reduction in their ability to associate the white noise CS with the eyelid stimulation US. This effect, like that in males, is relatively long-lasting, occurring and persisting 1–2 days after the stressor. It is also sensitive to the context since the effect can be prolonged if animals are trained in the same context in which they experienced the stressor (Wood, Beylin, & Shors, 2001). Whether the stressful experience affects learning itself or asymptotic performance is unclear. In the 10 or more experiments that we have reported upon, stressed females have not attained the same level of performance as unstressed females.

3. Organizing the response to significant life events

Clearly, males and females CAN respond very differently to similar events, but in addition, animals (including humans) often respond to similar events differently at different times in their lives. Beginning with birth, most mammals transition through a number of stages from prepubescence to puberty and adulthood. The life of a female is further marked by stages of pregnancy, child birth, child care, and the eventual cessation of reproductive potential with aging (Fig. 3). The question then arises: how do stressful life events alter subsequent learning abilities in different phases of life, and are they different between males and females? The most studied systems involve the organization of adult sexual behavior. In the now classic studies of the1950s and 1960s, it was shown that exposure to sex hormones in utero or soon after birth dramatically alters the type of sexual activities that are expressed in adulthood (Arnold & Gorski, 1984; Feder & Whalen, 1965; Pfaff, Frohlich, & Morgan, 2002; Phoenix, Goy, Gerall, & Young, 1959). Males that are prevented from experiencing testosterone in utero become demasculinized and therefore as adults, do not express a normal copulatory (mating) response to a receptive female. If females, on the other hand, are exposed to testosterone shortly after birth, they can behave like males and try to copulate with females as adults. It is noted that these females do not develop a normal estrous cycle, are infertile and thus do not express normal maternal behavior as adults. But what about other behaviors not necessarily related to reproduction? In a series of experiments, we tested whether the effects of stress on subsequent learning abilities could be altered or even reversed by manipulating the presence of testosterone in utero or shortly after birth (Shors & Miesegeas, 2002). In males, castration at birth was ineffective, i.e., adult males that had been castrated at birth still emitted more conditioned responses after the stressful event as did males that were not castrated at birth. However, males that were not exposed to testosterone in utero did not respond to the stressor as adults; they were essentially demasculinized. In females, the story is perhaps more interesting since their behaviors reversed to resemble those of the opposite sex. Females were injected with one dose of testosterone on the day of their birth. As adults, they showed enhanced conditioning in response to the stressful event. Therefore, they were able to associate the conditioning stimuli more rapidly than females not exposed to the stressor and thus, they behaved like the intact males. Together, these studies indicate that changes in hormonal milieu during very early development alter the way that animals then respond to significant life events in their future.

These responses to manipulations at birth are not limited to those related to stress. We have also found that sex differences in learning itself are altered by these same manipulations. In adulthood, females tend to condition more efficiently than do males (Wood & Shors, 1998). They begin eyeblink conditioning by showing more conditioned responses and in some cases reach a higher level of asymptotic performance compared to that in males. However, the issue of asymptotic performance is difficult to address in females since their conditioning varies across stages of estrus, which cycle every 4–5 days. The estrous cycle is most often associated with ovulation, which is expressed hormonally by high levels of estrogen and behaviorally as receptivity to males. This stage is followed by estrus and diestrus, both of which are marked by lower levels of estro-

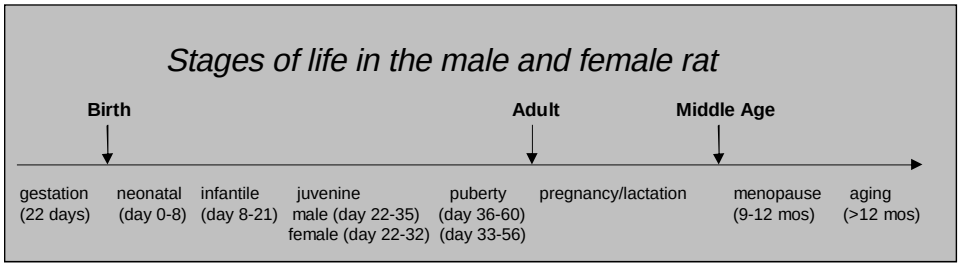

Fig. 3. Stages of life in the rat. A time line indicates the approximate ages of male and female rats as they transition from gestation through aging.

gen and not associated with ovulation. If female rats are first trained in proestrus, when estrogen levels are high, they tend to condition more than females first trained in other stages (Shors, Lewczyk, Paczynski, Mathew, & Pickett, 1998). Of course, this is a critical stage for the female since she must find, then attract a male to become impregnated. Thus, it is not surprising that there would be behavioral changes in responses to environmental events, even those not obviously related to reproduction.

4. Puberty and beyond

Puberty is marked by significant changes in overt behaviors, especially those related to sexual reproduction. It is also during this time that many sex differences in behavior emerge, as well as the expression of some mental illnesses. Recently, we examined the effects of acute stressful experience on conditioning in rats that were about to enter puberty and those that were experiencing puberty (Hodes & Shors, 2005). Before puberty, there was no observable effect of an acute stressor on classical conditioning. This was the case for both males and females. However, during puberty, both males and females emitted many more learned responses after exposure to an acute stressful event. Thus, males and females responded similarly and did so by showing an increase in learning. It is unclear what these responses indicate about puberty. Minimally, they indicate a distinctive response to stress in females during puberty, not to mention a dynamic one across the lifespan. Their response changed from none before puberty, to enhanced conditioning during puberty to a reduction in adulthood. Clearly, the female response to stress is dynamic and changes both in degree and direction simply as a matter of stage of life.

5. Motherhood: From pregnancy to postpartum

The experience of motherhood—pregnancy, birth and postpartum—are some of if not the most significant events in a woman's life. They are characterized by significant changes in behavior and lifestyle. Many women experience changes in emotionality during these times, most often those associated with anxiety. For the most part, these changes are regulated by reproductive hormones. Given these widespread changes in physiology and emotionality, we considered the possibility that pregnant females would respond differently to a stressful event than females that were still ovulating. However, we found no differences; both pregnant and cycling females emitted fewer conditioned responses after exposure to an acute stressful event (Leuner & Shors, 2005). Thus, despite widespread changes in hormonal milieu, the response to stress that is established in adulthood is maintained during pregnancy.

We next considered differences in how females respond to significant life events after giving birth. Certainly, females express many new behaviors upon birth of their young and these behaviors continue until the offspring are weaned. To account for such changes in behavior, it seems only logical that the brain is also experiencing reorganization. Even in rats, females respond very differently to stressful events if they are lactating and caring for their young. Specifically, lactating females do not express a behavioral response to an acute stressor, at least in terms of their responses during eyeblink conditioning (Leuner & Shors, 2005). Thus, in contrast to virgin females, which emit fewer learned responses after stress, they maintain similar rates and degrees of conditioning. The resistance to stress persists throughout the postpartum period, from days to weeks after birth. Thus, the resistance to stress is maintained even as the offspring begin to explore new and potentially dangerous environments, at least under naturalistic conditions. Its persistence seems to depend on the presence of the young since mothers that are separated from their young are once again affected by the stressor and show a deficit in conditioning. Whatever the adaptive significance of this response might be, it is evident that females experience or at least express the impact of a stressful life event very differently when they are caring for new offspring compared to when they are not.

It should be noted that these differences were not entirely unexpected. There are a number of studies showing that females, including women show very different responses to stress during the postpartum period. Most species are less anxious but will become more aggressive when faced with an intruder (Neumann, 2001). They also show a "blunted" hormonal response to stressful stimuli (Carter, Altemus, & Chrousos, 2001). Overall, hormonal and behavioral responses to stressful experience are suppressed during lactation, including those related to stress effects on learning. Again, these findings highlight the dynamic nature of the female response to stress as she enters different stages of life.

6. Under the influence

Up to this point, I have focused on endogenous changes that occur across the lifespan. However, humans also alter their "state of being" with drugs and medication. Probably the most common are the antidepressants, particularly serotonergic ones. Just consider the number of mental illnesses that they are used to treat and the ease with which one can be treated. Interestingly enough, these agents apparently are useful in treating many types of abnormal behaviors and yet they do not incite major changes in sensory/motor performance or general learning abilities. Given this, one might ask whether these pharmaceutical agents alter the response to significant life events and if so, whether they do so differently in males versus females? This seems like a particularly important question because males and females can respond so differently to stressful experience and because women are so much more susceptible to stress-related illnesses such as posttraumatic stress disorder and major depression.

It is of course very difficult to answer this question with humans, but it can be addressed in animals using models of depression and stress-related illness. In one such study,

male and female rats were treated daily for several weeks with the common antidepressant, fluoxetine, commonly known as Prozac. They were then exposed to an acute stressor of brief tailshocks or not (Leuner et al., 2004c). One day after the stressful experience, they were trained on the trace conditioning task. Interestingly, there was no observable effect of Prozac on overall responding during conditioning; in other words, antidepressant treatment did not alter the ability to acquire this particular response (Fig. 4). This observation is consistent with the clinical data in humans. However, females that were treated and then exposed to the acute stressful event behaved as if the event had not occurred (Fig. 4B). Like postpartum females, they were immune to the stressor, at least in terms of their conditioning. Oddly enough, males that were treated with the antidepressant still responded to the stressful event and showed their typical response—that of enhanced conditioning (Fig. 4A). These different responses to Prozac in males and females could be attributable to at least one of two things, either the treatment preferentially immunizes females to the consequences of stressful experiences or the treatment preferentially prevents negative responses to stress, i.e., reductions in learning. In either case, these findings show that the behavioral response to a stressful life event depends not only on the sex of the animal but also on the presence of psychotropic medications. Moreover, it seems likely that their presence not only alters the response to events in the present but also how those responses alter the response to events in the future.

7. Neuroanatomies of experience

Up to this point, I have discussed a number of ways that animals can respond to stressful life events, differences that arise as a matter of sex and even as a function of psychotropic medication. There must be neuronal responses that account for these response profiles. It has been known for decades now that there are anatomical differences between male and female brains, although the extent and nature of those differences remains controversial even today (Cahill, 2005). These differences begin early in development and extend through puberty and adulthood (Gogtay et al., 2004; Paus et al., 1999). And of course, there are the well-known changes in brain structure during aging, most often observed as a loss in volume (Fotenos, Snyder, Girton, Morris, & Buckner, 2005). Thus, anatomical changes within the brain are one way that the memory for a significant life event could be sustained and thereby alter the response to new experience. I will focus on two anatomical substrates here: One is synaptogenesis, i.e., the production of new synapses that occurs between neurons; the second is neurogenesis, i.e., the production of new neurons that occurs throughout life.

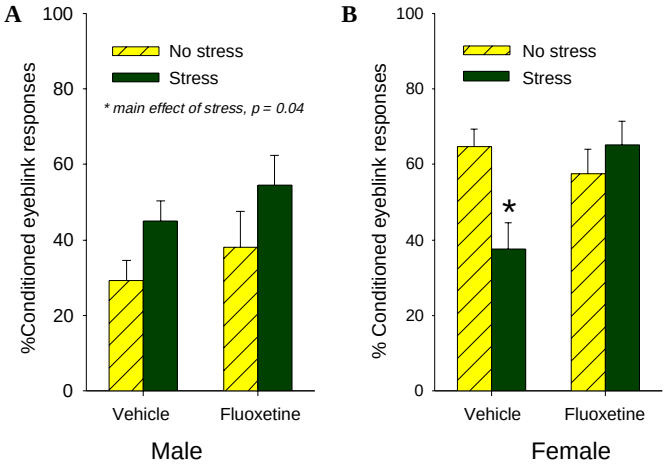

Fig. 4. Prozac prevents the detrimental effect of stress but not the more positive effects on learning. (A) The figure shows the percentage of conditioned responses emitted by males and (B) females that were either chronically treated with Prozac or provided the vehicle alone. Groups were either stressed or not and then trained 24 h later with trace conditioning. Treatment with Prozac prevented the effects of stress on conditioning in females but had no consequence on responding in males (Leuner et al., 2004c).

8. Synaptogenesis and memorable life events

It is often assumed that new learning depends on the formation of new synapses (Hebb, 1949). However, and somewhat surprisingly, there are few pieces of evidence to support this idea. This is in part because it is very difficult to visualize synapses forming while an animal is learning. Most techniques rely on brains that have been preserved in some static state long after the learning experience has occurred. Nonetheless, there have been a number of demonstrations that new experience can change the anatomical connections between neurons after the experience has occurred (Leuner & Shors, 2003). Most studies have focused on the presence of dendritic spines, which are tiny protrusions on dendrites and potential sites of synapse formation. Although, most excitatory neurons possess spines, most studies have concentrated on those in the hippocampal formation (Fig. 5A), and specifically on those located on CA1 pyramidal cells. These cells have been studied extensively, in part because they are responsive to learning manipulations and also because they are relatively easy to visualize. Interestingly enough, the first (or at least the most robust) demonstration of changes in spine density had little to do with learning. Rather, it was shown that exposure to estrogen in ovariectomized rats increases spine density (Gould, Woolley, Frankfurt, & McEwen, 1990). This response not only occurs under exogenous treatment but also as females enter different stages of the estrous cycle (Woolley, Gould, Frankfurt, & McEwen, 1990). Females in proestrus possess about 30% more dendritic spines than females in other stages. This finding is underscored by the fact that they came and went every 4 or 5 days as females entered different stages of their cycle. These findings presented us with a new and challenging view of these anatomical structures—that they are not only plastic and dynamic, respond to environmental manipulations, but are also extremely sensitive to changes in the hormonal status.

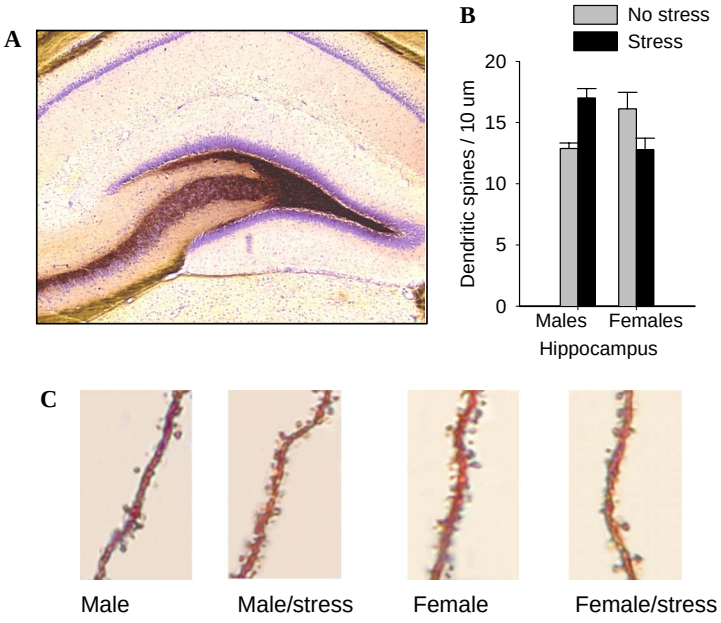

Fig. 5. The hippocampus and dendritic spines are sensitive to sex differences and stressful experience. (A) The hippocampus and its cell layers are shown. (B) Using Golgi staining techniques, it was determined that females in proestrus have a greater density of dendritic spines than males. However, in response to an acute stressful event, males produced more spines and females produce fewer. These responses to stress are represented as the mean number of spines along 10 μm of a dendrite in area CA1 of the hippocampus and (C) in representative examples (Shors et al., 2001; Shors et al., 2004).

One of the first questions to be asked is whether the effects of estrogen on spine density are behaviorally relevant. A number of findings suggest that they are, and probably the most convincing were reported by Sandstrom and Williams (Sandstrom & Williams, 2001). In their studies, animals exposed to the same amount of estrogen that enhances spine density also showed enhanced spatial memories. With respect to changes across the estrus cycle, there have been fewer examples. As discussed, females acquire the classical conditioned eyeblink response faster in proestrus than in other stages (Shors et al., 1998). They also acquired the response faster and performed better than did adult males. Thus, females in proestrus and in the presence of elevated levels of estrogen outperform females in other stages of estrus. Do such changes in learning relate to the presence of dendritic spines? It seems so, at least to the extent that learning abilities correlated with the presence of dendritic spines in the hippocampus. Thus, females in proestrus possess more spines and tend to perform better than males. They also possess more spines than females in other stages of estrus and outperform them as well (Shors, Chua, & Falduto, 2001). As a consequence of these data, we have proposed that the presence of spines is useful for acquiring new information and if those spines are already present at the time of training, they can be engaged rapidly for new learning, more rapidly than in animals that do not possess these extra structures (Leuner & Shors, 2003). It is important to note that most of the sex differences in learning and the response across the estrous cycle are not limited to learning tasks that are dependent on the hippocampus. Rather, animals with more spines emit more conditioned responses during both hippocampal-dependent and -independent learning tasks than those with fewer spines. Also, these effects of estrous cycle and sex differences are not synapse specific, rather it is likely that hundreds of thousands of spines are being affected. It seems that the response to the changes in the cycle is preparing the brain for new and as yet to be determined experiences. This is a means whereby experience during different stages of life can alter the response to stimuli that are seemingly irrelevant to the initial event.

Recall that males and females also respond to stressful experience differently: males show enhanced eyeblink conditioning and females show a reduction. If indeed the presence of spines somehow predicts learning abilities, then spine density should change after stressful experience and should do so differently in males versus females. This is indeed what occurs (Figs. 5B and C). Males exposed to the stressful event that enhances their later ability to learn also possess a greater density of spines at the time when training would occur (Shors et al., 2001). In contrast, females exposed to the same stressful event that impairs their later ability to learn possess fewer spines in the hippocampus, again at the time when the training would occur. Thus, on a relatively crude level, the density of spines in the hippocampus changes and predicts how well these animals will learn to associate events in their future.

These data suggest that traumatic experiences alter anatomy in the central nervous system and thereby change the animal's ability to respond to a future experience. Such a scenario would be more convincing if the actual structures affected by the trauma were also affected by learning. To examine this, animals were trained on various learning tasks, one requiring the hippocampus and the other not.

Other groups were exposed to unpaired stimuli or left in their home cage. One day after learning the conditioned response, the density of spines in the hippocampus was evaluated. There was an increase in animals that learned the conditioned response—those animals that were exposed to the paired stimuli possessed a greater density of spines (Leuner, Falduto, & Shors, 2003). Importantly, the increase occurred regardless of whether the animals were trained with the hippocampal-dependent or the hippocampal-independent type of learning task. However, the more salient point is that exposure to a learning experience increased the presence of spines, in ways similar to those observed after stress and during proestrus. Together, these studies suggest that stressful life events alter dendritic structures in relatively crude and nonspecific ways; these changes in anatomy can easily alter the response to new experience since the same structures or set of structures are being affected.

9. Neurogenesis and the learning experience

What about neurons themselves, and in particular new neurons? Could they be involved in shaping new responses after exposure to significant life events? For decades, it was assumed that the adult brain did not produce new neurons, at least to any great extent (Altman & Das, 1965; Rakic, 2002). However, numerous studies now demonstrate that adult brain, including the human, continues to produce new neurons throughout life (Cameron, Woolley, McEwen, & Gould, 1993; Eriksson et al., 1998; Gould, Tanapat, Hastings, & Shors, 1999). Most of these cells seem to be produced in the hippocampal formation, a brain structure intimately involved in some aspects of learning, notably those related to formation of declarative or episodic memory (Fortin, Agster, & Eichenbaum, 2002; Squire & Zola, 1996). Thousands of cells are produced each day in the rat hippocampus, although the numbers vary according to the behavioral state (Fig. 6). For example, different types of stressful experiences decrease cell proliferation (Cameron & Gould, 1994), as does normal aging (Cameron & McKay, 1999). These cell are also sensitive to sex differences, at least to the extent that they are regulated by the presence of estrogen and are produced in greater numbers during proestrus, when estrogen levels are high (Tanapat, Hastings, Reeves, & Gould, 1999). Their production is increased in the presence of some psychotropic medication, most notably the antidepressant Prozac (Malberg, Eisch, Nestler, & Duman, 2000; Santarelli et al., 2003).

These few examples illustrate how amazingly sensitive these new cells are to experience and stage of life. However, changes in cells production do not necessarily reveal the function of the new cells. What could be the function of these new cells? Since they are so prevalent in the hippocampus and given its role in learning, we asked whether they were affected by experiences of learning. One of the more interesting features of these cells is that most die within just a few weeks of being born (Fig. 6A). What might be the purpose of such a response and more specifically, would a learning experience keep them from dying? To address this question, we injected BrdU, a compound that labels cells as they are produced (Gould, Beylin, Tanapat, Reeves, & Shors, 1999). One injection will label the cells born in the next few hours. A week later and as most cells would be in the process of dying, the animals were trained on various learning tasks. Animals were trained on the classically conditioned eyeblink response using the hippocampal-dependent trace memory task as well as a hippocampal-independent delay task. After receiving 4 days of training, the animals were sacrificed and the cells were counted. Animals that learned the hippocampal-dependent task had nearly twice as many cells remaining in their hippocampus when compared to the numbers remaining in naïve animals. Also, animals that were training on the delay task which does not require the hippocampus retained no more cells than naïve animals. Moreover, animals exposed to unpaired stimuli retained no more cells than did naïve animals. Thus, it appears that something about this type of learning experience can rescue these new neurons from death. Moreover, once the

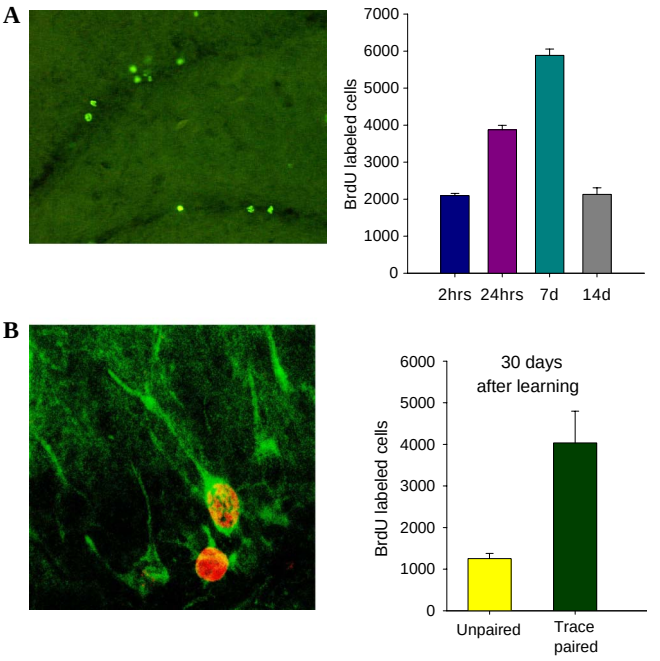

Fig. 6. Neurogenesis in the adult hippocampus is affected by learning experiences. (A) The hippocampus produces new cells throughout life, as shown in cells labeled with bright green. Most of these new cells will become neurons. The graph depicts the number of new cells in the hippocampus of rats that were injected with one dose of BrdU, a marker which labels newly generated cells. The number of cells increased from 2 h to 1 week later. However, most of the new cells died between 1 and 2 weeks of birth (Gould, Beylin et al., 1999). (B) Within a few weeks, the new cells acquire characteristics associated with neurons. The cells here are labeled with a marker that is specific to neurons. After exposure to a learning experience of trace conditioning, many more of these neurons survive. Once rescued from death, they can survive for months. The graph depicts the number of BrdU labeled cells that continue to reside in the hippocampus 1 month after a learning experience (Leuner Mendolia-Loffredo & Kozorovitskiy et al., 2004a).

cells are rescued from death, they remain in the hippocampus for at least 2 months (Fig. 6B) (Leuner Mendolia-Loffredo & Kozorovitskiy et al., 2004a). Together, these studies indicate that new neurons in the hippocampus are sensitive to some types of new learning experiences. More generally, they illustrate that acute experiences can alter the lifespan of thousands of cells at a time, again suggesting a relatively nonspecific effect of experience on cellular anatomy in the brain. Presumably, these gross changes in brain anatomy will affect the ways in which information is processed in the future and thus is yet another example of how a significant life experience might alter the shape of memories to come.

10. Hormonal regulation of experience

Returning to the question posed in the introduction: how does an experience in one situation and phase of life make an impression on our brains that extend into the future to affect new learning? I will propose here that hormones are the major effector and that they induce broad structural changes in the brain, which in turn alter future responses to new experience (Fig. 8). But before doing so, I should present the evidence that hormones regulate the effects of experience on new learning. I begin with estrogen since the evidence is so overwhelming.

Recall that females acquire the classically conditioned response faster than do males but that their learning abilities are reduced by stressful experience. Both of these effects are dependent on the presence of estrogen (Wood & Shors, 1998). In other words, females that are ovariectomized do not emit more responses than males and they do not show any learning deficits after stress. Thus, both sex differences in learning and the stress effects on conditioning depend on the presence of ovarian hormones (Fig. 7A). Similarly, exposure to an estrogen antagonist prevents the effects of stress on conditioning, again implicating estrogen as a critical factor in these effects of stress on learning in females. The contribution of estrogen to these effects is also evident across the lifespan. Recall that there is no observable effect prior to puberty, one emerges during puberty but is expressed as an enhancement. The deficit in conditioning after stress is first evident in adult females as they establish a functional estrous cycle. It is still evident during pregnancy but suppressed during the postpartum period. All of these stages of female life are marked by changes in endogenous levels of estrogen. But do they relate to the effects of stress on conditioning? It seems so. The effects of stress on conditioning are evident in adult cycling females and even in females that are pregnant. However, they are suppressed and indeed absent during the postpartum period. These effects of stress reemerge if the mother becomes separated from her offspring and ceases lactation. Overall, most data suggest that when estrogen levels are high, stress impairs conditioning and when estrogen levels are lower, there is less of an effect on conditioning, if one at all.

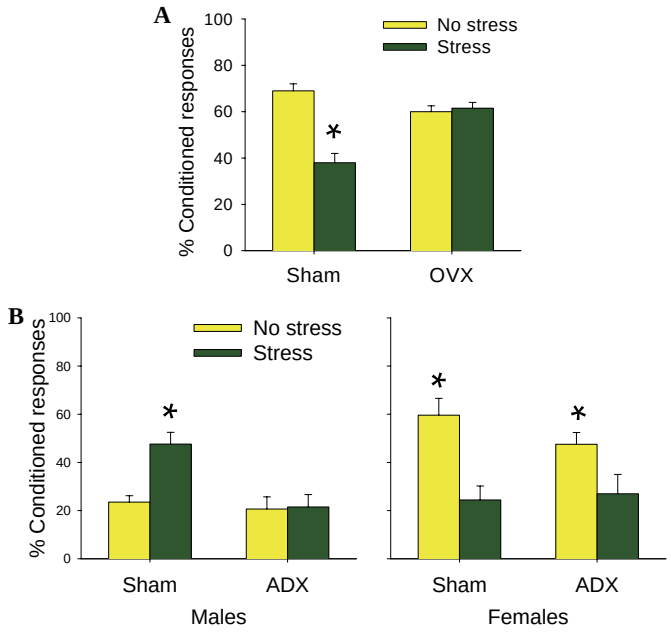

Fig. 7. Hormonal manipulations later the effects of experience on new learning. (A) The ovaries were removed from adult females. They were then exposed to an acute stressful event and trained 24 h alter on the classically conditioned eyeblink response. Females without ovarian hormones did not respond to the stressful event (Wood & Shors, 1998). (B) The adrenal glands were removed from male and female rats. In the absence of stress hormones, they were exposed to an acute stressful event and 24 h later trained on the classically conditioned eyeblink response. Males without adrenal hormones did not respond with more conditioned responses as did the males with adrenal hormones (Beylin & Shors, 2003). In contrast, females without adrenal hormones responded to the stressor with fewer conditioned responses, as did females with their adrenal glands intact (Wood et al., 2001).

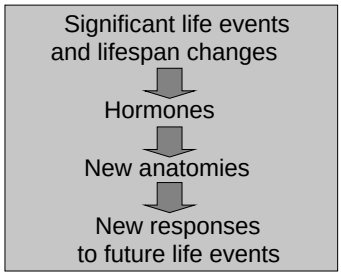

Fig. 8. It is hypothesized that significant life events in the presence of hormones induce broad changes in anatomical structures in the brain. These modifications present a new structure for learning, one that allows different and presumably adaptive responses to emerge during future life events.

The other major hormonal system to consider is the glucocorticoid response to stress, since it occurs in response to nearly all significant life events, good and bad. In a series of experiments, we evaluated how animals would respond to stress in the absence of this system. To do that, we simply removed the adrenal gland, which removes all endogenous level of glucocorticoids and prevents the HPA response to stressful experience. After adrenalectomy (ADX), male and female rats were stressed and trained the next day on the classically conditioned eyeblink response. As shown in

Fig. 7B, ADX prevented the enhancing effect of stress on learning in males but did not alter the effect of stress in females (Beylin & Shors, 2003; Wood et al., 2001). Thus, exposure to the acute stressful event not only affects new learning in opposite ways in males versus females, but each effect is mediated by a different hormonal system. These data represent yet another situation in which males and females respond quite differently to stress and appear to do so through the influence of hormones.

11. The shape of memories to come

In this final section, I propose one way that significant life events might alter our responses to future events that are seemingly unrelated to the initial event. During stressful and/or memorable life events, hormonal systems are activated and release these substrates throughout the nervous system. The "purpose" of these hormones is to alter anatomy in a relatively crude and extensive way. This change in anatomy then modifies and in many cases dictates what an animal can and cannot do (Fig. 8). At this point, I should state that this is not necessarily a new idea and is rather established in the field of hormones and behavior, particularly in the ways that hormones regulate sexual behavior. It is also prominent among those studying song- and spatial-learning systems in avian species (Nottebohm, 2002; Sartor & Ball, 2005). However, I do not think that this particular idea has been proposed in a formal way with respect to processes directly involved in learning and memory. With that said, I will present a study that is not about learning but nonetheless encapsulates this idea. It was conducted by VanderHorst and Holstege and reported in the *Journal of Neuroscience* in 1997 (VanderHorst & Holstege, 1997). In it, they were evaluating the role of estrogen in the sexual behavior of cats. They found that exposure to estrogen establishes connections between neurons that are involved in very specific sexual behaviors, in particular those associated with sexual receptivity. These behaviors include lordosis which involves elevation of the lower back, rhythmic treading of the hindlimbs and deviation of the tail to the side of the animal. As you might imagine, these behaviors serve several functions, one is to alert the male to the fact that the female is receptive and likely ovulating, but also to assist in the process of intromission itself. These behaviors are remarkably specific and the motor neurons and muscles involved are likewise specific. For example, motor neurons used for lordosis do not, for the most part, overlap with motor neurons and muscles used for daily activity such as walking or jumping. Thus, these neurons represent the anatomy that allows a specific behavior to be expressed at a specific time in life. This behavior is under the direct control of estrogen. Consequently, when estrogen levels are enhanced, these behaviors are expressed. According to the authors (VanderHorst & Holstege, 1997), the release of estrogen induces the axons to extend and make functional connections with the specific motor neurons used in these sexual behaviors. The point here is that estrogen does not "modulate" behavior, but rather determines whether or not a specific behavior can be expressed. Indeed, this connection ensures that a very specific set of behaviors will occur.

The proliferative power of estrogen cannot be overestimated. To illustrate, note the findings shown in Fig. 9, as collected from ovariectomized females. After just two injections of estradiol, their uterus weighed nearly twice as much (Fig. 9) (Leuner, Mendolia-Loffredo, & Shors, 2004b). The effects of estrogen on brain structures are really no less profound. In the case of dendritic spines, exposure to estrogen increases their density by more than 20% and does so similarly during proestrus (Shors et al., 2001; Woolley et al., 1990). In the case of the new neurons, these too are sensitive to estrogen. Production is increased in the presence of estrogen and similarly during proestrus when compared to other stages of estrus (Tanapat et al., 1999). I would imagine that these few examples represent a small percentage of structures affected by estrogen. Similarly, glucocorticoids have dramatic and relatively nonspecific effects on brain structure. They can decrease dendritic branching, an even more basic anatomical change than that of dendritic spines (Galea et al., 1997). They also can induce cell death and suppress the production of new neurons in the hippocampus (Gould, Woolley, & McEwen, 1991; Sapolsky, 1992). Other hormones are not exempt. A recent study found that castration reduced the density of dendritic spines by as much as 50%, again those located in the hippocampal formation (Leranth, Petnehazy, & MacLusky, 2003). In summary, the structures that are most associated with the consequences of stress and learning, neurons and dendrites, are apparently supersensitive to hormonal exposure.

Why would these brain structures be so sensitive to changes in hormones, especially given the profound changes in hormones that occur across the lifespan?

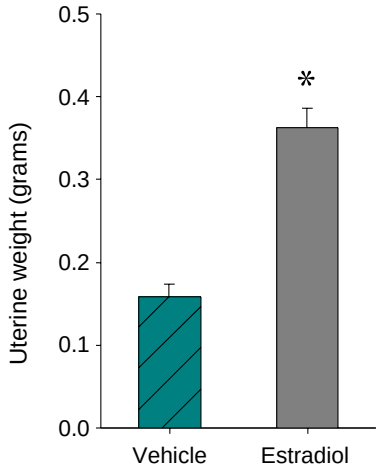

Fig. 9. Estrogen increases the weight of the uterus. The graph depicts the mean weight of the uterus in females. Females were ovariectomized and then treated with two doses of estradiol or a vehicle injection over 2 days (Leuner et al., 2004b).

Could it be that these changes in neuroanatomy are used to alter responses to future events in a relatively nonspecific but presumably adaptive way? Based on these data, it seems possible. So how would this system work with respect to dendritic spines? It would have to be less dramatic than that used for the expression of lordosis, simply because reproductive behaviors should be relatively stable and invariable whereas those related to learning cannot be all or none; they should be more flexible and less dependent on anatomy. For example, recall that exposure to a stressful and presumably memorable event persistently increases a male rat's ability to associate a tone with a brief shock to the eyelid. This enhancing effect occurs over several days and probably reflects the likelihood that an animal will face new and potentially threatening experiences in the near future—after all, it just experienced one. Recall also that exposure to the same type of stressful event reduced this type of conditioning in females. We also found that stress increased spine production in the hippocampus of males but reduced it in females. These data suggest a positive correlation between the presence of spines and the likelihood that an animal will learn a conditioned response. Thus, with respect to the theory proposed here, the male brain would respond to the stressful event by producing more spines in anticipation that they would become useful for new learning experiences. The female brain responds in the opposite direction, producing few spines and reducing the likelihood that she will learn that particular type of association. On the face of it, the female response seems maladaptive but regardless, the system is organized so that the anatomical structures are already present when the animal encounters the new learning situation. This is one way that an animal can prepare itself for new experiences without knowing exactly what those experiences will entail.

Recall that treatment with Prozac prevents the negative effects of stress on learning in females (Fig. 4). Interestingly enough, there was a recent report that treatment with the antidepressant increases the density of spines in CA1 pyramidal cells in the hippocampus (Hajszan, MacLusky, & Leranth, 2005). These are the same spines that are affected by stress and learning. If a reduction in dendritic spines in response to stress somehow modulates subsequent responses to learning events, it may be that the restoration of spines lessens the impact of the stressful stimulus and thereby prevents the reduction in conditioning. Of course, Prozac has numerous effects other than those on spines, but these relatively crude effects on neuroanatomies are one way that these drugs can change the architecture and thereby alter responses to learning situations in the future.

A similar scenario could be proposed for the phenomenon of neurogenesis in the adult brain. Many experiences in life alter the production of new neurons, including stress, exposure to alcohol, exercise, antidepressants, and drugs of abuse (Eisch, Barrot, Schad, Self, & Nestler, 2000; Jang et al., 2002; Kempermann, Kuhn, & Gage, 1997; van Praag, Kempermann, & Gage, 1999). The effects of life experience on cell density could over time lead to functionally relevant changes in brain structure. In fact, much of the enthusiasm surrounding neurogenesis in the adult brain concerns its potential role in depression. It has been observed that depressed humans often possess a smaller hippocampus than non-depressed humans (Campbell, Marriott, Nahmias, & MacQueen, 2004; Neumeister et al., 2005). It is also known that antidepressants increase the production of new neurons (Malberg et al., 2000), suggesting a link between neurogenesis and depressed behaviors. One might imagine that the presence of hormones, in this case a persistent exposure to glucocorticoids, reduces the production of these cells to the point that the structure (and the animal) responds differently to events in its future. The data presented earlier could reflect just such a process. In these studies, learning in females that were chronically treated with the antidepressant Prozac was unaffected by the stressful event where untreated females were learning impaired. In this instance, a short exposure would not alter the anatomy sufficiently to immunize the system, but rather a prolonged exposure would induce structural changes that "protect" the organism from experiencing the stressful event in the same way. The effects of this type of manipulation would not be specific and would not necessarily reflect any role that they might play in learning (Shors, 2004b); rather this effect would simply reflect a nonspecific process with unintended but presumably adaptive consequences.

12. Conclusion

I began this review by discussing those most unusual cases of K and R, whose life tapes were essentially spliced, leaving them without a decade or so of remembered experience. You might ask how these examples relate to the theme of this review. Recall that their memory loss went back to times in life associated with stressful and traumatic events. In the case of K, his memory loss went back to when his family house burned down and his family became destitute. In the case of R, her loss went back to when she become pregnant with a married man's baby. That these significant life events were associated with the beginning (or end, depending on how you look at it) of the memory deficit suggests that their brains were anatomically altered during those eventful times. Presumably, these two people experienced hormonal changes during these events, which would in turn alter anatomical structures within their brains. Decades later, their brain traumas simply revealed the underlying anatomies into which these memories of life were carved. Under normal circumstances, these anatomies would alter the shape of memories to come.

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