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Once a mother, always a mother: Maternal experience protects females from the negative effects of stress on learning

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Abstract

Women experience profound hormonal fluctuations throughout their reproductive lives. They are especially susceptible to disturbances in mood and cognition during the transition from pregnancy into postpartum and motherhood (Brummelte & Galea, 2010). Their behavioral and hormonal responses to stressful stimuli are also altered during this time. These changes are not limited to humans but occur in many mammalian species. Virgin female rats express a severe learning deficit in associative eyeblink conditioning after a stressful life event (Wood & Shors, 1998; Wood et al., 2001), but lactating females or those that are caring for young learn well even after the stressor (Leuner & Shors, 2006). However, we do not know whether maternal experience persistently alters learning after a stressful event. Here we hypothesized that females that had been maternal at some time in their lives would learn well even after exposure to a stressful event. To test this hypothesis, females that had at least one brood of young and expressed a normal estrous cycle were exposed to an acute stressful event that reliably impairs learning in virgin females. Animals were trained 24 h later with classical eyeblink conditioning. Exposure to the stressor suppressed learning in virgins but not in females that had been mothers at some time in their lives. These data suggest that maternal experience induces a protective mechanism in mothers, which promotes associative learning long after the offspring have left their care.

Keywords

acute stress; maternal experience; eyeblink conditioning; postpartum

Introduction

Women face drastic changes in mood and cognition as they progress through the different stages of their reproductive lives, especially during pregnancy and the postpartum period (Brummelte & Galea, 2010). Indeed, several studies report that new mothers are better able to learn to navigate in their environment, a behavior that would more often than not have

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positive consequences for survival of the offspring (Kinsley et al., 1999; Lemaire et al., 2006). We have also noted enhanced learning as a consequence of motherhood. In this case, the act of maternal behavior itself prevents a learning deficit that occurs in virgins after exposure to a stressful life event (Wood & Shors, 1998; Wood et al., 2001; Bangasser & Shors, 2004; Leuner et al., 2004; Maeng et al., 2010; Leuner & Shors, 2006). Moreover, the suppression is likewise absent in females that are simply induced to behave as mothers, i.e. they are sensitized to learn to care for young that are not their own and thus become “maternal virgins” (Leuner & Shors, 2006). Together, these data suggest that maternal behavior itself, and not lactation following pregnancy *per se*, protects females from the negative effects of stress on learning.

Considering these data, one might ask whether the “protective” effect of maternal behavior persists beyond the time of maternal care. To answer this question, we assessed associative learning in females that had been pregnant and given birth at least once in their lifetimes. They were not pregnant or nursing at the time of the study and were in fact expressing a normal estrous cycle. These females were tested along with age-matched virgin females. Half of each group was exposed to an acute stressor and trained one day later with classical eyeblink conditioning.

Methods

Subjects

Virgin female Sprague Dawley rats (60-90 days of age) from a breeding facility at Rutgers University were housed in shoebox-style plastic bins in groups of 3-4. They were maintained on ad libitum food and tap water and on a 12 h:12 h light:dark cycle. They were handled and age-matched to postpartum females (9-12 months old) at the time of experimentation. Postpartum parous females were selected from our colony once they had given birth to at least one litter of pups, all of whom were weaned more than 28 days after being born (standard weaning period that typically occurs 3-4 weeks after birth). Therefore, the postpartum females in this study were not caring for young or lactating. One of the mothers had only delivered one litter whereas all of the other mothers delivered at least two. The time from birth of the first litter to behavioral testing ranged from 5 to 9 months. This experiment was conducted with full compliance to the rules and regulations specified by the Public Health Service (PHS) Policy on Humane Care and Use of Laboratory Animals and the Guide for the Care and Use of Laboratory Animals.

Experimental Procedure

All rats were anesthetized with sodium pentobarbital (40mg/kg, i.p.), as previously described (Waddell et al., 2008; Maeng et al., 2010). Two electrodes were used to deliver a periorbital stimulation as the unconditioned stimulus and two electrodes were used to record electromyographic activity from the eyelid as an indicator of eyeblinks. Estrous cycles were monitored daily, as described (Shors, 1998; Bangasser & Shors, 2004; Leuner & Shors, 2006; Waddell et al., 2008; Maeng et al., 2010). It has been previously demonstrated that the stress effect is most pronounced when females are stressed in diestrus 2 and trained 24 h later in proestrus (Shors et al., 1998). Therefore, all females used in this study were lavaged daily after at least a week of recovery after surgery, stressed in diestrus, and trained in proestrus, when estrogen levels were increasing (Shors et al., 1998; Wood et al., 2001). Animals that did not exhibit a normal estrous cycle were excluded from the study.

Four groups of female rats were trained: virgin/unstressed (N=6), virgin/stressed (N=5), parous/unstressed (N=5), and parous/stressed (N=5). After seven days of recovery, rats were acclimated to the conditioning chamber (60 min), and spontaneous blinks were recorded.

Unstressed rats were returned to their home cages. Stressed animals were transferred to another context (different from that in which training occurred) and placed into a dark soundproof chamber. In this chamber, they were loosely restrained and exposed to 30 low-intensity (1 mA, 60 Hz, 1 sec) stimulations to the tail. This degree of stimulation is sufficient to suppress classical eyeblink conditioning in rats (Shors & Servatius, 1997; Shors, 2004).

The next day, rats were returned to the conditioning chamber and exposed to ten white noise stimuli alone (250 ms, 80 dB, ITI 25 ± 5 s) before the first session. This procedure was used to determine whether the females were emitting sensitized responses to the CS before any training had occurred (blinks during first 100 ms of the CS) (Servatius & Shors, 1994). The rats were then trained with 400 trials (100 trials/day) of delay conditioning in which an 80-dB, 850 ms burst of white noise CS overlapped and co-terminated with a 100 ms, 0.5 mA periorbital stimulation of the eyelid (US). Eyeblinks were assessed by analyzing change in the magnitude of the electromyographic (EMG) response recorded from the eyelid muscles. Muscle activity that exceeded a length of 10 ms and amplitude of at least 0.3 mV (and > 4 standard deviations) when compared to activity within the 250 ms pre-CS baseline recording period were considered indicative of an eyeblink. Those that occurred within 250 ms prior to the US were classified as conditioned responses (CRs).

Results

Independent measures were stress (stressed versus unstressed) and maternal experience (parous versus virgin). Anticipatory conditioned responses (CRs) prior to the US were counted and averaged across blocks of 100 trials (Figure 1). A 2 × 2 repeated measures ANOVA revealed an interaction between stress and maternal experience [$F(1, 17)=5.79$, $p<0.05$]. A Neuman-Keuls *post hoc* analysis confirmed that the age-matched virgin females that were stressed emitted fewer conditioned responses than all other groups ($p<0.05$). Females that had given birth and cared for young prior to the stressor exposure performed similarly to the unstressed groups of females ($p>0.05$). Therefore, exposure to the stressful event did not alter conditioned responding in females that had given birth at least once in their lifetimes, whereas exposure to the stressor suppressed responding in virgins.

Overall, the number of responses increased for all groups across sessions [$F(3, 51)=14.02$, $p<0.01$], as expected during classical conditioning. However, one-way repeated measures analysis of each group suggested that the virgin females did not increase their responding across sessions [$F(3, 12)=0.56$, $p>0.05$]. These results suggest that stressor exposure suppressed any evidence of associative learning within the number of trials provided. A one-way repeated measures analysis of the mothers also indicated no change in responding across sessions [$F(3, 12)=1.97$, $p>0.05$], but this was for a very different reason. In this case, the females expressed many conditioned responses within the first day of training and apparently reached asymptote within the first 100 trials. This is not unusual when training with delay eyeblink conditioning, especially in females (Wood & Shors, 1998). To note, there were no differences among the groups with respect to spontaneous blink activity, [$F(1, 17)=0.02$, $p>0.05$] and no interaction between stress exposure and maternal experience in sensitized responding to the CS [$F(1, 17)=2.35$, $p>0.05$]. In other studies, we observed no observable changes in these measures as a function of stress, including those related to changes in the unconditioned response (Leuner & Shors, 2006; Bangasser & Shors, 2004).

A learning criterion of 60% conditioned responding during any session of training was used to assess how well individual animals learned the association. All animals in the unstressed groups, and most stressed parous females, reached criterion, whereas only one of the stressed females did (Figure 2). These results support the idea that maternal experience has a lasting effect on classical conditioning, which permits learning even after a stressful life experience.

Discussion

The goal of this experiment was to determine whether the experience of motherhood persistently protects females from the negative effects of stress on learning. Classical conditioning of the eyeblink response was assessed in females that were no longer lactating or caring for young but had given birth at least once in their lives. Those that were stressed prior to training quickly learned to emit the CR prior to the onset of the US. Indeed, they responded similarly to those females that were not stressed and had been mothers. In contrast, virgin age-matched females did not learn to emit the CR after exposure to the stressor. Thus, associative learning was suppressed in virgin females that had been exposed to an acute stressful event one day earlier but not in those that had been pregnant and nursed offspring at least once in their lifetimes. These data suggest that maternal experience has a persistent and protective effect on learning abilities in females after stress even long after they have cared for their offspring.

It has been reported that motherhood, in and of itself, can improve learning ability and may do so throughout the lifespan (Lemaire et al., 2006; Kinsley et al., 1999; Pawluski et al., 2006). Kinsley and his colleagues have conducted numerous studies on this topic. In one, it was reported that two weeks after weaning, multiparous rats outperformed nulliparous cohorts when trained to navigate using spatial cues (Kinsley et al., 1999). Primiparous (first pregnancy) and multiparous rats emitted fewer errors and performed better than nulliparous females, and this effect persisted even one month after their pups had been weaned (Pawluski et al., 2006). Pawluski et al. (2006) assessed whether pregnancy or motherhood was responsible for the lasting effect on spatial learning. Pregnant-only females had their pups removed 24 h after birth to isolate the experience of pregnancy. The pregnant-only females failed to complete the task and also required more training in order to learn. Maternal sensitization did not radically modify performance in the maze. Based on these findings, the authors suggest that a combination of pregnancy and maternal care was necessary to persistently enhance processes related to spatial learning and working memory in this context.

The effects reported here suggest that motherhood may induce a long-term influence on learning that can protect females against traumatic events later in life. It is well-established that pregnant and lactating female animals, including women, are less responsive to stress, especially as measured by activation of the HPA axis (Brummelte & Galea, 2010; Douglas et al., 2003; Douglas et al., 1998; Neumann et al., 1998; Slattery & Neumann, 2008; Altemus et al., 1995). However, others find that exposure to a stressor during gestation, or pregnancy, suppresses learning and can even eliminate the protective effects of maternal experience on learning later in life. Specifically, parous female rats tested two weeks after weaning learned significantly better than nulliparous or parous females that experienced stress during the last week of pregnancy. Interestingly, this effect persisted for 16 months after weaning and close to the end of their lifespan (Lemaire et al., 2006). The mechanisms through which this protective effect occurs are not yet known. With the limited information we have currently, it is evident that there are biological as well as environmental factors that come with motherhood that reprogram the female brain to become less responsive to stressful life events.

It seems likely that changes in reproductive hormones contribute to the protective effect of motherhood reported here. Learning is suppressed when estrogen levels are high (pregnancy) and is not when estrogen levels are low (postpartum) (Shors et al., 1998). The learning impairment does not emerge until females reach sexual maturity; in fact, before puberty, they learn better after stressor exposure (Hodes & Shors, 2005). Most convincing, however, is the observation that ovariectomy or estrogen antagonists prevent the stress effect on learning from being expressed (Wood & Shors, 1998). Another possible mediator is progesterone, a sex steroid hormone that fluctuates throughout the female lifespan and interacts with estrogen. For instance, allopregnanolone, a progesterone metabolite, directly blocks HPA axis activity during pregnancy and influences the stress response (Brunton & Russell, 2010; Brunton & Russell, 2011). The neuropeptide oxytocin also interacts with estrogen and progesterone to produce milk as well as the immediate expression of maternal behavior after childbirth (Slattery & Neumann, 2008; Douglas & Russell, 2001). Some studies also report increases in oxytocin levels after stress (Brunton & Russell, 2010; Bale et al., 2001). However, it has been demonstrated that the deficit in learning is not expressed by virgin females that are induced to behave maternally (Leuner & Shors, 2006). Since these females do not lactate, lactation itself is not necessary for the protective effect. It remains possible that maternal behavior itself induces this long-term protection from stress. To assess this, it would be important to determine whether the sensitized females can learn if they are stressed long after they ceased caring for offspring. If so, this would suggest that maternal behavior and not lactation itself is responsible for inducing a *persistent* resistance to stress, at least as assessed during associative learning.

Human studies on this topic are few in number and have reported contradictory results. Some describe impairments or no change in cognitive ability after delivery (Macbeth & Luine, 2010). For example, pregnant women do not perform as well as they do during postpartum on an episodic verbal memory task (Buckwalter et al., 1999). The women in another study were evaluated based on performance in a “naturalistic” prospective memory task in which they were asked to log in at specific times during the day while conducting normal daily life activities (Rendell and Henry, 2008). Non-pregnant women performed significantly better than pregnant women (between-subjects comparison), who either missed responses entirely or emitted late responses. Women performed poorly while pregnant as they did while in postpartum (within-subjects comparison) on this same time-logging task. Unfortunately, but for obvious reasons, the study did not include a pre-pregnancy baseline measure. Nonetheless, there were potentially important differences in the types of errors. While pregnant, women often forgot to carry out the activity, whereas during postpartum, they did remember, but only after a significant delay. Another human study reported deficits in verbal recall from pregnancy into parturition with minimal, if any, deficits in recognition or working memory (Glynn, 2010). It has been suggested that hormonal and/or neuronal changes during pregnancy place greater demands on executive processing which lead to deficits in performance. These early effortful experiences may, in turn, produce more positive responses later in life. Indeed, one study reported enhanced verbal, semantic, and working memory two years after giving birth when compared to performance during pregnancy and early postpartum (Buckwalter et al., 2001). These findings are generally consistent with the positive effects of motherhood on learning reported here and by others (Lemaire et al., 2006; Kinsley et al., 1999; Pawluski et al., 2006).

The new mother must abruptly acquire new behaviors and take on more responsibilities along with feelings of love, happiness, and anxiety. Therefore, it is not uncommon for women to experience mood disturbances during this postpartum period. As many as ~80% of new mothers experience postpartum blues that can develop into postpartum depression (PPD), which affects 10%-15% of mothers within the first year of giving birth (Seyfried & Marcus, 2003; O’Hara et al., 1990). Furthermore, women with PPD often complain of cognitive disturbances, which are exacerbated by stressful situations (Goodman, 2007). Interestingly, there is a considerable amount of overlap among brain structures involved in depression and motherhood (Barrett & Fleming, 2010). For example, the prefrontal cortex is preferentially activated in depressed women (Beauregard et al., 1998) and in mothers by infant cues (Barrett & Fleming, 2010). The region is also critically engaged during the stressor to reduce learning in virgin females (Maeng et al., 2010). If the mechanisms within those regions are shared, one might imagine therapies that could target these regions and thereby protect women from the negative consequences of stressful life experience on their thoughts and behaviors.

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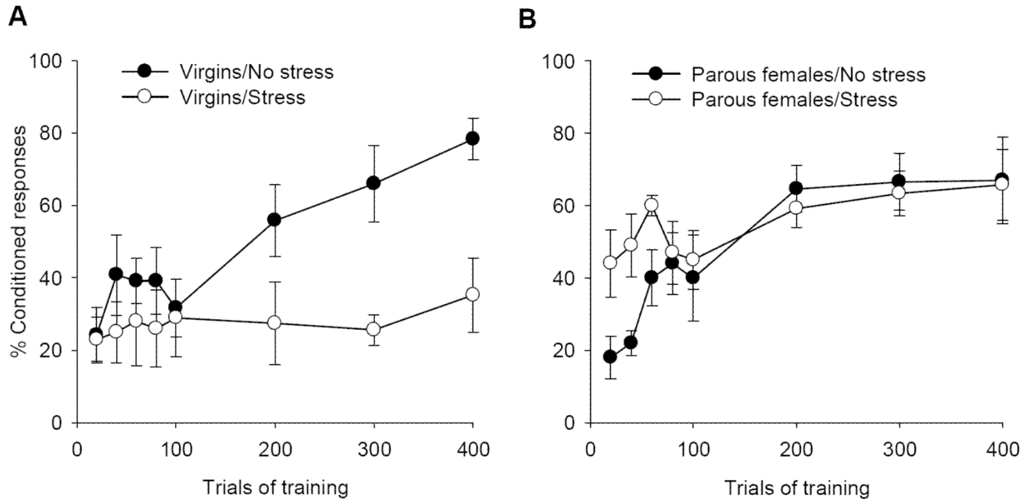

Figure 1.

Age-matched virgin females and parous females (mothers who have given birth at least once) were either stressed in diestrus or unstressed. 24 h later, they were trained with delay eyeblink conditioning for four consecutive days, 100 trials per day. ***A***. Virgin females that were stressed did not perform as many conditioned responses (CRs) as their unstressed counterparts ($p<0.05$). ***B***. Stressed females with prior maternal experience (parous females) learned as well as both the unstressed virgins and parous females ($p>0.05$). These data suggest that maternal experience at one point in the female lifespan persistently protects her from detrimental effects of acute stress on eyeblink conditioning.

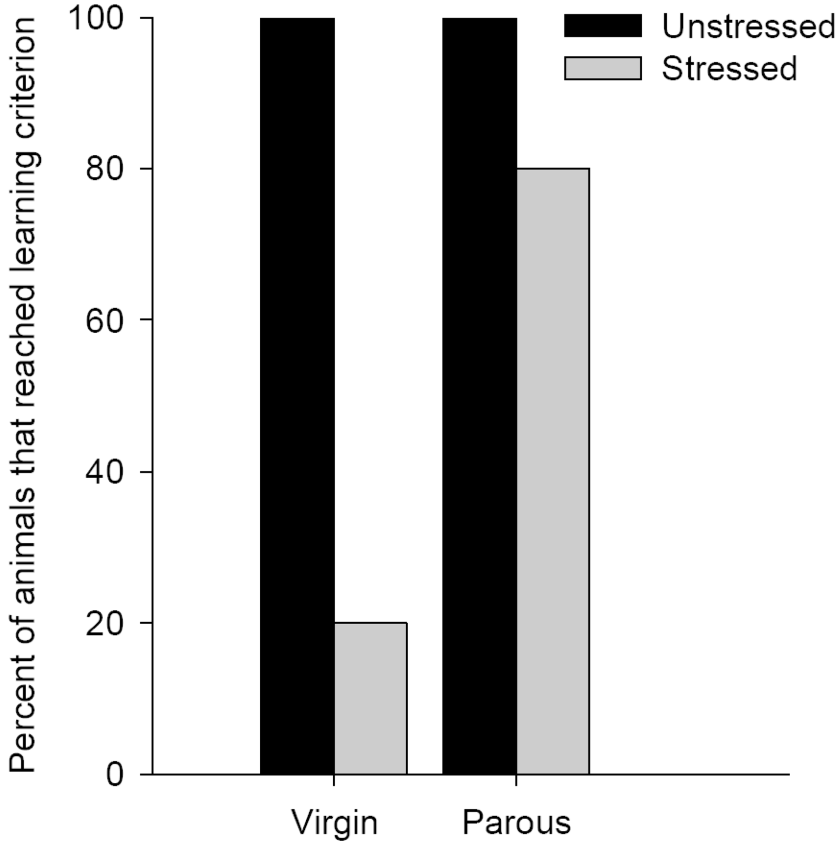

Figure 2.

Animals that learned the conditioned eyeblink response well reached a learning criterion of 60% conditioned responses. Most or all of the unstressed virgin, stressed postpartum, and unstressed postpartum females reached this learning criterion, whereas almost all of the virgin stressed females did not. Therefore, these data indicate that learning was suppressed after a stressful experience only in virgin females but was not negatively affected in parous females that had been mothers at some time in their lives.