Journal of Traumatic Stress, Vol. 20, No. 4, August 2007, pp. 423–433 (© 2007)

Stress Inoculation-Induced Indications of Resilience in Monkeys

David M. Lyons and Karen J. Parker
Department of Psychiatry and Behavioral Sciences, Stanford University Medical Center, Stanford, CA

The negative consequences of stress are well-recognized in mental health research. Exposure to early life stressors, for example, increases the risk for the development of mood, anger, anxiety, and substance abuse disorders. Interestingly, however, early life stressors have also been linked to the subsequent development of resilience. Variously described as inoculating, immunizing, steeling, toughening, or thriving, the hypothesis that early life stressors provide a challenge that, when overcome, induces adaptations that enhance emotional processing, cognitive control, curiosity, and neuroendocrine regulation is examined in this review of squirrel monkey research.

Early exposure to severe forms of stress is a risk factor for the development of subsequent psychopathology (Agid et al., 1999; Davidson, Stein, Shalev, & Yehuda, 2004; Foa, Stein, & McFarlane, 2006; Heim, Plotsky, & Nemeroff, 2004). Far less researched, but of equal importance, are indications that early life stressors may also foster resilience. Adults cope better with spousal loss, illness, and major accidents if they have previously experienced and coped with stressors in childhood (Forest, 1991; Khoshaba & Maddi, 1999). Work-related stressors likewise have fewer depressive effects in adults previously exposed to work-related stressors in adolescence (Mortimer & Staff, 2004). These findings suggest that stressful events that are not overwhelming, but challenging enough to elicit emotional activation and cognitive processing may make subsequent coping efforts more efficient, and therefore easier and more likely to be used later in life (Fergus & Zimmerman, 2005; Garmezy, 1991; Rutter, 1993; Yates, Egeland, & Sroufe, 2003). In this review, we summarize our studies designed to test the hypothesis that early life stressors may foster the development of resilience as modeled in squirrel monkeys.

Monkeys raised in groups comprised of 3–4 mother–infant pairs were initially randomized to a stress inoculation protocol or a no-stress control condition at 17 weeks of age. The stress inoculation protocol consisted of 10 weekly 1-hour social separations (Parker, Buckmaster, Schatzberg, & Lyons, 2004) designed to provide repeated opportunities for emotional activation and cognitive processing while not overwhelming the capacity for coping with adversity. During each 1-hour separation session, each monkey was individually placed in a cage with various toy-like objects, and could see, hear, and smell, but not touch other unfamiliar monkeys. Separations evoked repetitive distress peep-calls, locomotor agitation, and acute elevations in plasma cortisol

Supported by the Nancy Pritzker Network for the Study of Depression, and Public Health Service grants DA16902, MH77884, MH66573, and MH47573. The authors declare no competing interests. All procedures were approved by Stanford University's Administrative Panel on Laboratory Animal Care and were carried out in accordance with the NIH Guide for the Care and Use of Laboratory Animals.

Correspondence concerning this article should be addressed to: David M. Lyons, Psychiatry Neuroscience, Stanford University Medical Center, 1201 Welch Road, MSLS P104–Mail Code 5485, Stanford, CA 94305-5485. E-mail: dmlyons@stanford.edu.

 DOI: 10.1002/jts.20265

levels with baseline measures restored soon after each social reunion with the natal group (Coe, Glass, Wiener, & Levine, 1983; Hennessy, 1986; Stanton & Levine, 1985). Separations were scheduled at weekly intervals to allow ample time for recovery at an age when squirrel monkeys are typically developing physical and psychosocial independence (Boinski & Fragaszy, 1989; Rosenblum, 1968). The transition from filial, mother-directed behavior (e.g., clinging and nursing) to exploratory, other-directed behavior (e.g., object exploration and social play) presents important learning opportunities that are thought to promote the development of psychosocial functions (Lyons, 1993; Mason, 1971).

EMOTIONAL AND PSYCHOSOCIAL INDICATIONS OF RESILIENCE

At 9 months of age, each monkey was tested along with its mother for 30 minutes on 5 consecutive days in a novel environment that contained an assortment of foods and objects (Parker et al., 2004). Similar test conditions have been used to demonstrate that prior exposure to overwhelming postnatal stressors increases indications of anxiety-related psychopathology in marmoset monkeys and macaques (Andrews & Rosenblum, 1993; Dettling, Feldon, & Pryce, 2002; Hinde & Spencer-Booth, 1971). Here the novel environment stress test was used to assess stress inoculation-induced indications of resilience.

The behavior of stress inoculated and noninoculated monkeys was initially similar, but differences emerged over repeated test sessions in the novel environment (Figure 1). Gradually, stress-inoculated compared to noninoculated monkeys appeared to become less anxious as inferred by decreased maternal clinging and increased object exploration. As described elsewhere in greater detail (Parker et al., 2004), these results indicate that stress inoculated monkeys more readily self-regulate arousal and engage in more exploration than noninoculated monkeys. This conclusion is consistent with earlier findings from different cohorts of stress-inoculated monkeys that responded to the removal of mothers at weaning with fewer distress peep-

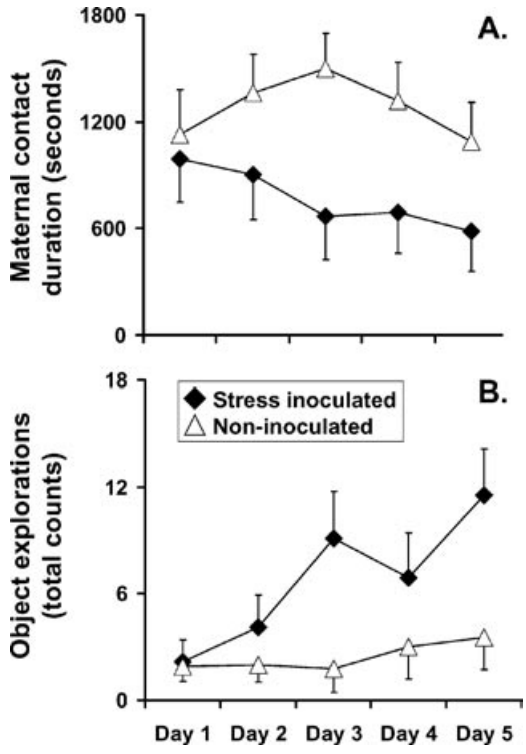

Figure 1. Emotional and psychosocial indications of resilience are enhanced by stress inoculation. Measures of (A) time spent clinging to mother and (B) frequency of object exploration during repeated novel environment test sessions are presented for stress inoculated ($n = 11$) and noninoculated ($n = 9$) monkeys ($M + SEM$). A significant postnatal stress inoculation treatment-by-test session interaction ($p < .05$) was discerned for both measures (adapted from data presented in Parker et al., 2004).

calls and more time spent near peers (Levine & Mody, 2003; Lyons, Martel, Levine, Risch, & Schatzberg, 1999).

Cognitive Indications of Resilience

At 1.5 years of age, the stress inoculated and noninoculated monkeys were administered a test to examine prefrontal-dependent cognitive control of behavior described elsewhere in detail (Parker, Buckmaster, Justus, Schatzberg, & Lyons, 2005). Briefly, a clear Plexiglas box with one open side was baited with a favorite food treat. When the box opening was oriented straight toward the monkey, food

retrieval was achieved by reaching straight into the box. When the box was rotated 90 degrees so the opening was oriented toward either side, inhibition of straight-reaching and a detour-reach around either side was required to retrieve food from the clear baited box. Reaches aimed straight toward the center of the box when the opening was oriented toward either side were scored as response inhibition errors.

Inhibitory control of the reaching response in marmoset monkeys and rhesus macaques is impaired by lesions of prefrontal cortex (Diamond, 1990; Dias, Robbins, & Roberts, 1996; Wallis, Dias, Robbins, & Roberts, 2001), but not lesions of the hippocampus (Diamond, Zola-Morgan, & Squire, 1989). Response inhibition assessed on this test is also impaired in a marmoset monkey model of parental neglect (Pryce, Dettling, Spengler, Spaete, & Feldon, 2004), and in squirrel monkeys treated with cortisol according to a protocol that simulates a chronic stress response (Lyons, Lopez, Yang, & Schatzberg, 2000). Here this test of cognitive control was used to assess stress inoculation-induced indications of resilience. As indicated below, prefrontal-dependent cognitive control likely plays a role in emotion regulation and resilience.

Initially, each monkey was administered 10 trials per day for 7 consecutive days with the box opening always oriented straight toward the monkey subject. Food retrieval was achieved by reaching straight into the center of the box. These 70 trials served to reinforce as prepotent the straight-reaching response. Thereafter, each monkey was administered 10 trials per day for 14 consecutive days with the orientation of the box opening systematically varied to assess inhibitory control of the straight-reaching response. The stress inoculated and noninoculated monkeys performed equally well on all trials except for those that required inhibitory control of the straight-reaching response. Performance on the side-facing trials improved gradually over repeated test days (Figure 2), but at peak levels of performance all stress-inoculated monkeys successfully completed all response inhibition trials whereas fewer than half of the noninoculated monkeys achieved similar levels of success.

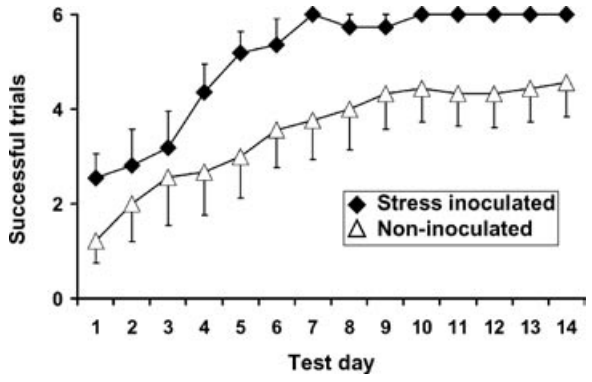

Figure 2. Prefrontal-dependent cognitive response inhibition is enhanced by stress inoculation. Stress inoculated monkeys ($n = 11$) completed more successful test trials with the box opening oriented toward either side compared to non-inoculated monkeys ($n = 9$) examined over successive test days (mean + SEM). Maximum score is 6 successful trials per day. A significant postnatal stress inoculation treatment main effect ($p < .05$) was discerned over repeated test days. From "Prospective Investigation of Stress Inoculation in Young Monkeys," by K. J. Parker, C. L. Buckmaster, A. F. Schatzberg, and D. M. Lyons, 2004, Archives of General Psychiatry, 61, 933–941. Copyright 2004 by the American Medical Association. Adapted with permission.

These results are in keeping with evidence that postnatal stress inoculation stimulates the development of larger prefrontal cortical volumes without affecting hippocampal volumes determined in squirrel monkeys by high-resolution magnetic resonance imaging (MRI; Lyons, Afarian, Schatzberg, Sawyer-Glover, & Moseley, 2002; Lyons, Yang, Sawyer-Glover, Moseley, & Schatzberg, 2001). Prefrontal corticolimbic circuits play a key role in cognitive control of behavior in humans and monkeys (Garavan, Ross, & Stein, 1999; Konishi, Nakajima, Uchida, Sekihara, & Miyashita, 1998; Lyons et al., 2000; Miller & Cohen, 2001; Ridderinkhof, Ullsperger, Crone, & Nieuwenhuis, 2004). Increased prefrontal activation, for example, corresponds with diminished amygdala activation, and with increased cognitive control of emotion in humans studied by functional MRI (Ochsner & Gross, 2005; Taylor, Eisenberger, Saxbe, Lehman, & Lieberman, 2006; Urry

et al., 2006). In ongoing research we plan to assess whether stress inoculation enhances prefrontal inhibition of amygdala activity in monkeys.

CURIOSITY AND EXPLORATION-BASED INDICATIONS OF RESILIENCE

At 2.5 years of age, the stress-inoculated and noninoculated monkeys were administered a test to examine curiosity and the exploratory behavior it elicits. This was accomplished by monitoring exploration of novel and familiar objects presented in a stress-free condition (Parker et al., 2007). Briefly, a familiar and a novel object were each secured to the back wall of a test compartment. The compartment was affixed to the monkey's home cage 5 minutes before the start of each test, after which time a sliding door was removed and the monkey had free access to the test compartment. Test sessions lasted 30 minutes in duration, and each monkey was tested on 5 consecutive days. Similar test situations have been used to demonstrate that prior exposure to overwhelming postnatal stressors reduces exploration of novelty in macaque monkeys (Hinde & Spencer-Booth, 1971; Roder, Timmermans, & Vossen, 1989; Sackett, 1972). Here exploration of novelty was used to assess stress inoculation-induced indications of resilience. As described below, information-seeking and sensory types of curiosity play a role in the maintenance of life-long resilience.

All stress inoculated and all but one of the noninoculated monkeys approached the test compartment and looked inside. However, more stress inoculated than noninoculated monkeys entered the compartment, and stress inoculated monkeys entered faster, with greater frequency, and spent more time inside the test compartment compared to noninoculated monkeys (Figure 3). In addition, more stress-inoculated than noninoculated monkeys explored the objects inside the compartment, and stress-inoculated monkeys preferred to explore the novel compared to the familiar object (Parker et al., 2007).

In the earlier novel environment stress test conducted at 9 months of age, inoculated monkeys also showed significantly more object exploration compared to noninoculated monkeys (Figure 1). Object exploration in the earlier study was assessed, however, in inescapable conditions that involved involuntary separation of monkeys from the home

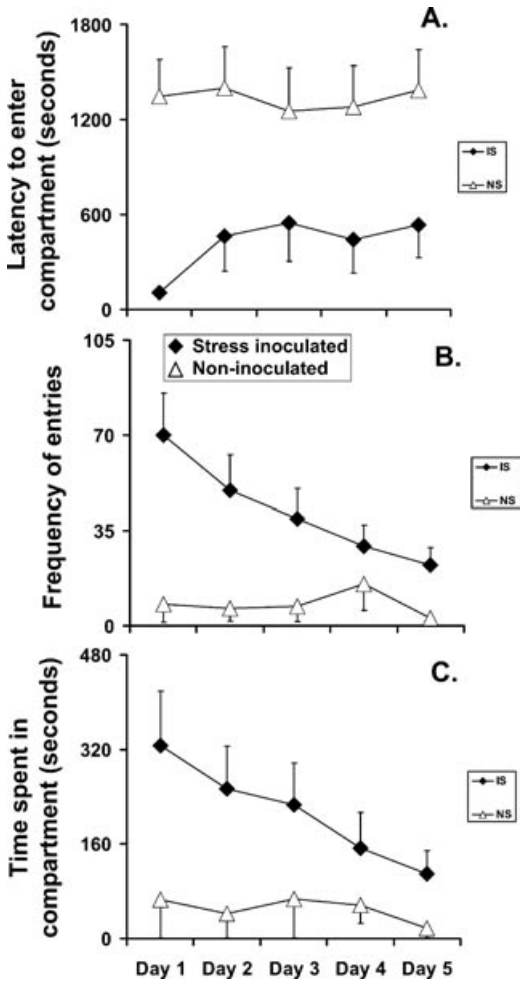

Figure 3. Curiosity and exploratory behavior are enhanced by stress inoculation. Measures of (A) latency to enter the test compartment, (B) frequency of entries into the compartment, and (C) duration of time spent inside the compartment across repeated test sessions are presented for stress inoculated ($n = 11$) and noninoculated ($n = 9$) monkeys ($M + SEM$). A significant postnatal stress inoculation treatment main effect ($p < .05$) was discerned across repeated test sessions for all three measures of behavior. From "Early Life Stress and Novelty Seeking Behavior in Adolescent Monkeys," by K. J. Parker, K. L. Rainwater, C. L. Buckmaster, A. F. Schatzberg, S. E. Lindley and D. M. Lyons, 2007, Psychoneuroendocrinology, in press. Copyright 2007 by Elsevier Ltd. Adapted with permission.

cage. Both stress inoculated and noninoculated monkeys in the earlier study presented with significantly higher cortisol levels immediately after the novel environment stress test compared to baseline levels measured in undisturbed home cage conditions (Parker et al., 2004). Moreover, because posttest levels of cortisol were significantly lower in stress inoculated compared to noninoculated monkeys, differences in objection exploration in the earlier study were confounded with differences in stress-related anxiety.

In the study conducted at 2.5 years of age, exploratory behavior was assessed in the test compartment attached to each monkey's home cage. To further reduce the potentially stressful nature of the test situation, each monkey was extensively acclimated to the procedures and test compartment prior to the start of the study. Stress hormones measured immediately after Test Sessions 1 and 5 confirmed that posttest cortisol levels were not significantly different from baseline levels in undisturbed home cage conditions at 2.5 years of age. Moreover, neither baseline nor posttest cortisol levels correlated with measures of exploration in the stress-free conditions at 2.5 years of age. Individual differences previously observed in object exploration at 9 months of age were, however, correlated with the rank order of individual differences in test compartment entries, $r_s = .41$, $p < .05$, and total time spent in the test compartment, $r_s = .51$, $p < .05$, at 2.5 years of age. Individual differences previously observed in cognitive control of behavior at 1.5 years of age were also correlated with test compartment entries, $r_s = .48$, $p < .05$, and total time spent in the test compartment, $r_s = .42$, $p < .05$, at 2.5 years of age.

Taken together, these data suggest that postnatal stress inoculation affects interrelated aspects of cognitive control, emotion regulation, and curiosity consistently expressed over time and across situations. Exploration of novelty reflects more than diminished anxiety because stress-inoculated monkeys are more curious than noninoculated monkeys when tested in the absence of adrenocortical or behavioral indications of anxiety. Exploration of novelty and curiosity does not, in turn, reflect impulsivity because stress-inoculated monkeys more readily exercise cognitive control and successfully inhibit impulsive behavior compared to noninoculated monkeys. Information-seeking and sensory types of curiosity motivate individuals to seek new opportunities for action (Reio, Petrosko, Wiswell, & Thongsukmag, 2006). Engagement in new situations that entail challenging, but not overwhelming stress may further induce neuroadaptations that enhance cognitive control and emotional self-regulation. According to this conceptual working model (Figure 4), curiosity thereby plays a role in the life-long maintenance of stress inoculation-induced resilience.

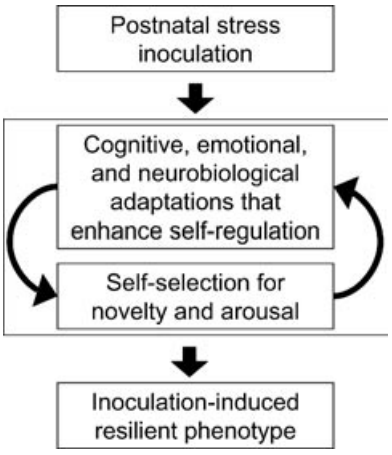

Figure 4. Conceptual model of how stress fosters the development of resilience.

IS STRESS INOCULATION-INDUCED RESILIENCE MATERNALLY MEDIATED?

Stress inoculation-induced resilience in monkeys resembles the effects of postnatal handling in studies of rats. Neonatal rats removed from the nest and briefly separated from nest-related cues respond with behavioral and physiological indications of arousal (Hofer, 1996; Lyons & Banks, 1982). When studied as adults, these rats then display increased exploration, diminished emotionality, improved learning and memory, and diminished activation of the hypothalamic–pituitary–adrenal (HPA) axis by various stressors relative to

rats that are raised in undisturbed conditions (Fernandez-Teruel et al., 2002; Levine, 2000; Meaney et al., 1996).

In rats, these outcomes seem to reflect the effects of maternal behavior directed toward pups that are briefly separated and returned to the nest (Denenberg, 1999; Smotherman & Bell, 1980). Brief intermittent separations increase maternal licking and grooming not only immediately after reunion, but also throughout postnatal development (Lee & Williams, 1974). Importantly, the neuroendocrine indications of resilience observed in rats exposed to brief intermittent postnatal separations can be replicated in unmanipulated offspring that naturally receive high levels of maternal care (Liu et al., 1997). That increased maternal care is sufficient to produce resilience in rats is corroborated by evidence that the amount of maternal stimulation received by pups during development is negatively correlated with later stress-induced activation of the HPA axis (Liu et al., 1997; Rosenberg, Denenberg, & Zarrow, 1970).

To determine whether the development of resilience in monkeys exposed to intermittent separations is maternally mediated, we recently examined maternal behavior and subsequent neuroendocrine measures of resilience in 30 monkeys randomized to three postnatal treatment conditions (Parker, Buckmaster, Sundlass, Schatzberg, & Lyons, 2006). In one condition, each juvenile monkey was separated from its mother and the natal group for 10 weekly sessions that each lasted 1-hour in duration. In the second condition, each juvenile monkey and its mother were removed together from the group for 10 weekly 1-hour sessions. Both of these two conditions elicit distress peep-calls, locomotor agitation, and transiently activate the HPA axis with baseline measures restored soon after reunion with the natal group (Coe et al., 1983; Jordan, Hennessy, Gonzalez, & Levine, 1985). In the third condition, nonseparated monkeys remained in their natal groups.

The maternal mediation hypothesis predicts that juvenile monkeys exposed alone to repeated separations will receive consistently more maternal care than age-matched undisturbed monkeys. Conversely, the repeated removal of both mothers and offspring will diminish maternal behavior as stressed mothers direct their attention toward reintegration with the natal group. The maternal mediation hypothesis thus predicts that offspring removed along with their mother will not develop resilience due to diminished levels of maternal care. In contrast, the stress-inoculation hypothesis predicts that resilience will develop in monkeys exposed to either intermittent separation condition because both conditions elicit acute anxiety and transiently activate the HPA axis.

Unlike brief separations in rats, neither separation condition in monkeys caused a permanent increase in levels of maternal behavior (Parker et al., 2006). Moreover, group differences in maternal behavior did not correspond with the development of neuroendocrine indications of resilience. Juvenile monkeys exposed with their mother to repeated separations received less maternal care in the home cage throughout development compared to juveniles separated alone, or juveniles from undisturbed groups. Yet both separation conditions induced in juvenile monkeys subsequent neuroendocrine indications of resilience compared to juveniles not exposed to either separation condition. Specifically, juveniles separated alone or separated along with their mother exhibited diminished cortisol responses to a subsequent novel environment stress test compared to monkeys that were not previously exposed to either of the two separation conditions (Parker et al., 2006).

LONG-LASTING NEUROENDOCRINE EFFECTS OF STRESS INOCULATION

The findings described above suggest that the development of resilience corresponds more closely to prior stress exposure than to differences in the quantity or quality of maternal care. A follow-up experiment confirmed this conclusion in a different cohort of squirrel monkeys exposed from 10–22 weeks of age to a high-demand foraging condition or a low-demand foraging control. During the 12-week high-demand condition, squirrel monkey mothers stopped carrying their juvenile offspring at earlier ages and spent more time foraging for food (Lyons, Kim, Schatzberg, & Levine, 1998). Plasma cortisol levels were intermittently higher in high-demand compared to low-demand offspring, but

foraging demands did not affect postnatal growth, nursing behavior, or amounts of solid-food consumed.

By selectively reducing certain aspects of maternal care, squirrel monkey mothers seem to protect their offspring from the full impact of the stressful foraging task (Lyons et al., 1998). A similar process appears to occur in studies of bonnet macaques. Whereas unpredictable variable-demand foraging conditions impair emotional (Rosenblum & Andrews, 1994) and neurobiological (Coplan et al., 2006) aspects of development, consistently predictable high-demand foraging does not appear to adversely affect development in bonnet macaques (Rosenblum & Paully, 1984).

Based on these findings, we studied squirrel monkeys raised in consistently high- versus low-demand foraging conditions for subsequent differences in neuroendocrine indications of resilience (Parker et al., 2006). The maternal mediation hypothesis predicts that diminished levels of maternal care induced by high-demand foraging will increase subsequent HPA axis responses to stress in monkeys previously raised in the high- versus low-demand condition. Conversely, if early life stressors foster the development of resilience, then HPA axis responses to subsequent stressors in adulthood should be diminished in the monkeys raised in high- versus low-demand foraging conditions.

In midlife adulthood at ~8 years of age, restraint stress tests were administered to squirrel monkeys raised from 10–22 weeks of age in high- versus low-demand conditions. Restraint is a well-studied psychological stressor in animal biomedical research (Glavin, Pare, Sandbak, Bakke, & Murison, 1994). An intramuscular injection of saline was given 60 minutes before initiation of the first 30-minute restraint stress. Seven days later, an intramuscular injection of exogenous cortisol (i.e., 2.5 mg/kg hydrocortisone sodium succinate) was given 60 minutes before the second and otherwise identical restraint stress test. This dose of hydrocortisone was used to assess glucocorticoid feedback, and is known to suppress stress-induced increases in squirrel monkey adrenocorticotropic hormone (ACTH; Lyons, Yang, Eliez, Reiss, & Schatzberg, 2004). Plasma levels of ACTH were determined 0, 30, and 60 minutes after completion of each restraint stress test, and analyzed as an index of HPA axis activation because endogenous cortisol cannot be distinguished from exogenous hydrocortisone (Lyons et al., 2004).

A significant postnatal foraging condition-by-hydrocortisone pretreatment interaction was discerned in postrestraint measures of ACTH with baseline levels controlled as a statistical covariate. Subsequent analysis of simple main effects confirmed that monkeys from the high-demand condition responded with diminished activation of the HPA axis determined by smaller increases in postrestraint ACTH levels compared to monkeys from the low-demand condition after pretreatment with saline (Figure 5). As expected, hydrocortisone suppressed postrestraint stress levels of ACTH, but enduring postnatal effects were not discerned when restraint was preceded by hydrocortisone to test for differences in sensitivity to glucocorticoid feedback.

In rodents, neuroendocrine indications of resilience are induced by maternal stimulation and mediated, in part, by enhanced sensitivity to glucocorticoid feedback (Liu et al., 1997; Meaney et al., 1996). In monkeys, we failed to find evidence for maternal mediation or enhanced sensitivity to glucocorticoid feedback. Our finding that increased maternal stimulation is not required to foster resilience does not, however, diminish the role of parenting in primate development. In our studies (Lyons et al., 1998), mother–infant attachment relationships were established well before onset of the postnatal protocols and all monkeys received more than the typical levels of maternal care experienced in naturalistic conditions (Boinski & Fragaszy, 1989). Psychosocial support derived from attachment relationships promotes coping skills in humans (Cohen & Wills, 1985) and nonhuman primates (Harlow & Suomi, 1974; Mason & Capitanio, 1988), and a minimal threshold of maternal care is likely required for the development of stress inoculation-induced resilience.

SUMMARY AND CONCLUSIONS

The studies reviewed above suggest that repeated exposure to early life stressors that are challenging, but not overwhelming foster the development of interrelated

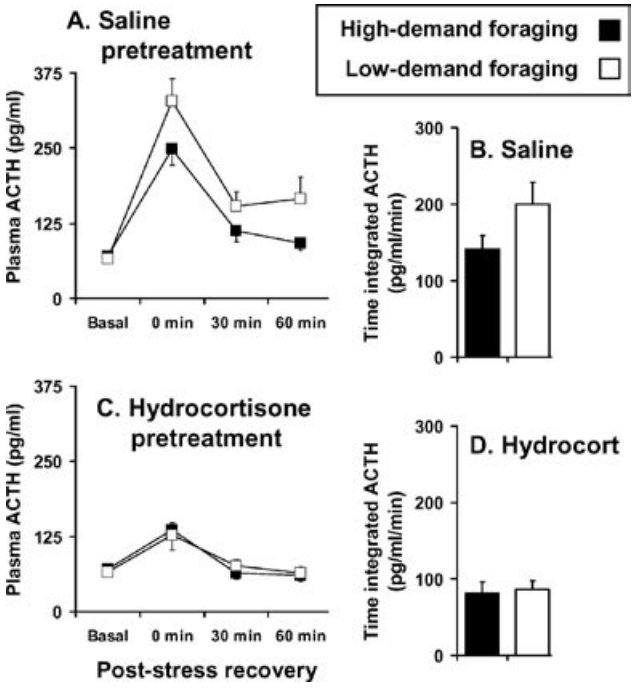

Figure 5. Neuroendocrine indications of resilience are enhanced by stress inoculation. Postrestraint stress levels of ACTH at successive 30-minute intervals after pretreatment with (A) saline or (C) hydrocortisone, and the corresponding time-integrated levels (B and D), are presented for 6–7 adult male monkeys from each postnatal foraging demand condition (mean + SEM). Significant postnatal foraging demand treatment main effects ($p < .05$) were discerned for postrestraint measures of ACTH after pretreatment with saline, but not hydrocortisone. From "Maternal Mediation, Stress Inoculation, and the Development of Neuroendocrine Stress Resistance in Primates," by K. J. Parker, C. L. Buckmaster, K. Sundlass, A. F. Schatzberg, and D. M. Lyons, 2006, Proceedings of the National Academy of Sciences USA, 103, 3000–3005. Copyright 2006 by the National Academy of Sciences USA. Adapted with permission.

aspects of emotion regulation, cognitive control, curiosity, and diminished HPA axis activation induced by exposure to stress. Based on these findings, primate research is now well positioned to bridge the gap between psychosocial studies of human resilience reviewed elsewhere (Fergus & Zimmerman, 2005; Masten, 2001; Yates et al., 2003) and rodent research focused on cellular and molecular explanations of stress resistance (Maier, Amat, Baratta, Paul, & Watkins, 2006; Meaney & Szyf, 2005). Differences in prefrontal neuroanatomy limit prospects for rodent research (Ongur & Price, 2000; Preuss, 1995), and access to human brain tissue occurs less often than in other fields of medicine where tissue biopsies are performed. In the rare case where human brain tissue is made available for biomedical research, the absence of prior psychosocial measures precludes direct comparisons between molecular, cellular, psychological, and social indications of resilience. In this regard, nonhuman primates offer attractive opportunities to provide cross-disciplinary explanations for the development of stress-inoculation induced resilience. A better understanding of stress inoculation through repeated exposure to stressors is important because of concerns that reexperiencing stressors may impede recovery instead of fostering the development of resilience (Bisson, Jenkins, Alexander, & Bannister, 1997; Foa, Zoellner, Feeny, Hembree, & Alvarez-Conrad, 2002; Hembree et al., 2003; Mayou, Ehlers, & Hobbs, 2000).

REFERENCES

Agid, O., Shapira, B., Zislin, J., Ritsner, M., Hanin, B., Murad, H., et al. (1999). Environment and vulnerability to major psychiatric illness: A case control study of early parental loss in major depression, bipolar disorder and schizophrenia. Molecular Psychiatry, 4, 163–172.

Andrews, M. W., & Rosenblum, L. A. (1993). Assessment of attachment in differentially reared infant monkeys (Macaca radiata): Response to separation and a novel environment. Journal of Comparative Psychology, 107, 84–90.

Bisson, J. I., Jenkins, P. L., Alexander, J., & Bannister, C. (1997). Randomised controlled trial of psychological debriefing for victims of acute burn trauma. British Journal of Psychiatry, 171, 78–81.

Boinski, S., & Fragaszy, D. M. (1989). The ontogeny of foraging in squirrel monkeys, Saimiri oerstedi. Animal Behaviour, 37, 415–428.

Coe, C. L., Glass, J. C., Wiener, S. G., & Levine, S. (1983). Behavioral, but not physiological, adaptation to repeated separation in mother and infant primates. Psychoneuroendocrinology, 8, 401–409.

Cohen, S., & Wills, T. A. (1985). Stress, social support, and the buffering hypothesis. Psychological Bulletin, 98, 310–357.

Coplan, J. D., Smith, E. L., Altemus, M., Mathew, S. J., Perera, T., Kral, J. G., et al. (2006). Maternal–infant response to variable foraging demand in nonhuman primates: Effects of timing of stressor on cerebrospinal fluid corticotropin-releasing factor and circulating glucocorticoid concentrations. Annals of the New York Academy of Sciences, 1071, 525–533.

Davidson, J. R., Stein, D. J., Shalev, A. Y., & Yehuda, R. (2004). Post-traumatic stress disorder: Acquisition, recognition, course, and treatment. Journal Neuropsychiatry and Clinical Neuroscience, 16, 135–147.

Denenberg, V. H. (1999). Commentary: Is maternal stimulation the mediator of the handling effect in infancy? Developmental Psychobiology, 34, 1–3.

Dettling, A. C., Feldon, J., & Pryce, C. R. (2002). Repeated parental deprivation in the infant common marmoset (Callithrix jacchus, primates) and analysis of its effects on early development. Biological Psychiatry, 52, 1037–1046.

Diamond, A. (1990). Developmental time course in human infants and infant monkeys, and the neural bases of, inhibitory control of reaching. Annals of the New York Academy of Sciences, 608, 637–676.

Diamond, A., Zola-Morgan, S., & Squire, L. R. (1989). Successful performance by monkeys with lesions of the hippocampal formation on AB and object retrieval, two tasks that mark developmental changes in human infants. Behavioral Neuroscience, 103, 526–537.

Dias, R., Robbins, T. W., & Roberts, A. C. (1996). Primate analogue of the Wisconsin Card Sorting Test: Effects of excitotoxic lesions of the prefrontal cortex in the marmoset. Behavioral Neuroscience, 110, 872–886.

Fergus, S., & Zimmerman, M. A. (2005). Adolescent resilience: A framework for understanding healthy development in the face of risk. Annual Reviews of Public Health, 26, 399–419.

Fernandez-Teruel, A., Gimenez-Llort, L., Escorihuela, R. M., Gil, L., Aguilar, R., Steimer, T., et al. (2002). Early-life handling stimulation and environmental enrichment. Are some of their effects mediated by similar neural mechanisms? Pharmacology, Biochemistry and Behavior, 73, 233–245.

Foa, E. B., Stein, D. J., & McFarlane, A. C. (2006). Symptomatology and psychopathology of mental health problems after disaster. Journal of Clinical Psychiatry, 67(Suppl. 2), 15–25.

Foa, E. B., Zoellner, L. A., Feeny, N. C., Hembree, E. A., & Alvarez-Conrad, J. (2002). Does imaginal exposure exacerbate PTSD symptoms? Journal of Consulting and Clinical Psychology, 70, 1022–1028.

Forest, K. B. (1991). The interplay of childhood stress and adult life events on women's symptoms of depression. Dissertation Abstracts International, 51, 3237.

Garavan, H., Ross, T. J., & Stein, E. A. (1999). Right hemispheric dominance of inhibitory control: An event-related functional MRI study. Proceedings of the National Academy of Sciences USA, 96, 8301–8306.

Garmezy, N. (1991). Resilience in children's adaptation to negative life events and stressed environments. Pediatric Annals, 20, 463–466.

Glavin, G. B., Pare, W. P., Sandbak, T., Bakke, H. K., & Murison, R. (1994). Restraint stress in biomedical research: An update. Neuroscience and Biobehavioral Reviews, 18, 223–249.

Harlow, H. F., & Suomi, S. J. (1974). Induced depression in monkeys. Behavioral Biology, 12, 273–296.

Heim, C., Plotsky, P. M., & Nemeroff, C. B. (2004). Importance of studying the contributions of early adverse experience to neurobiological findings in depression. Neuropsychopharmacology, 29, 641–648.

Hembree, E. A., Foa, E. B., Dorfan, N. M., Street, G. P., Kowalski, J., & Tu, X. (2003). Do patients drop out prematurely from exposure therapy for PTSD? Journal of Traumatic Stress, 16, 555–562.

Hennessy, M. B. (1986). Multiple, brief maternal separations in the squirrel monkey: Changes in hormonal and behavioral responsiveness. Physiology and Behavior, 36, 245–250.

Hinde, R. A., & Spencer-Booth, Y. (1971). Effects of brief separation from mother on rhesus monkeys. Science, 173, 111–118.

Hofer, M. A. (1996). Multiple regulators of ultrasonic vocalization in the infant rat. Psychoneuroendocrinology, 21, 203–217.

Jordan, T. C., Hennessy, M. B., Gonzalez, C. A., & Levine, S. (1985). Social and environmental factors influencing mother–infant separation–reunion in squirrel monkeys. Physiology and Behavior, 34, 489–493.

Khoshaba, D. M., & Maddi, S. R. (1999). Early experiences in hardiness development. Consulting Psychology Journal: Practice and Research, 51, 106–116.

Konishi, S., Nakajima, K., Uchida, I., Sekihara, K., & Miyashita, Y. (1998). No-go dominant brain activity in human inferior prefrontal cortex revealed by functional magnetic resonance imaging. European Journal of Neuroscience, 10, 1209–1213.

Lee, M. H., & Williams, D. I. (1974). Changes in licking behaviour of rat mother following handling of young. Animal Behaviour, 22, 679–681.

Levine, S. (2000). Influence of psychological variables on the activity of the hypothalamic-pituitary-adrenal axis. European Journal of Pharmacology, 405, 149–160.

Levine, S., & Mody, T. (2003). The long-term psychobiological consequences of intermittent postnatal separation in the squirrel monkey. Neuroscience and Biobehavioral Reviews, 27, 83–89.

Liu, D., Diorio, J., Tannenbaum, B., Caldji, C., Francis, D., Freedman, A., et al. (1997). Maternal care, hippocampal glucocorticoid receptors, and hypothalamic–pituitary–adrenal responses to stress. Science, 277, 1659–1662.

Lyons, D. M. (1993). Conflict as a constructive force in social life. In W. A. Mason & S. P. Mendoza (Eds.), Primate social conflict (pp. 387–408). Albany, NY: State University of New York Press.

Lyons, D. M., Afarian, H., Schatzberg, A. F., Sawyer-Glover, A., & Moseley, M. E. (2002). Experience-dependent asymmetric variation in primate prefrontal morphology. Behavioural Brain Research, 136, 51–59.

Lyons, D. M., & Banks, E. M. (1982). Ultrasounds in neonatal rats: Novel, predator and conspecific odor cues. Developmental Psychobiology, 15, 455–460.

Lyons, D. M., Kim, S., Schatzberg, A. F., & Levine, S. (1998). Postnatal foraging demands alter adrenocortical activity and psychosocial development. Developmental Psychobiology, 32, 285–291.

Lyons, D. M., Lopez, J. M., Yang, C., & Schatzberg, A. F. (2000). Stress-level cortisol treatment impairs inhibitory control of behavior in monkeys. Journal of Neuroscience, 20, 7816–7821.

Lyons, D. M., Martel, F. L., Levine, S., Risch, N. J., & Schatzberg, A. F. (1999). Postnatal experiences and genetic effects on squirrel monkey social affinities and emotional distress. Hormones and Behavior, 36, 266–275.

Lyons, D. M., Yang, C., Eliez, S., Reiss, A. L., & Schatzberg, A. F. (2004). Cognitive correlates of white matter growth and stress hormones in female squirrel monkey adults. Journal of Neuroscience, 24, 3655–3662.

Lyons, D. M., Yang, C., Sawyer-Glover, A. M., Moseley, M. E., & Schatzberg, A. F. (2001). Early life stress and inherited variation in monkey hippocampal volumes. Archives of General Psychiatry, 58, 1145–1151.

Maier, S. F., Amat, J., Baratta, M. V., Paul, E., & Watkins, L. R. (2006). Behavioral control, the medial prefrontal cortex, and resilience. Dialogues in Clinical Neuroscience, 8, 397–406.

Mason, W. A. (1971). Motivational factors in psychosocial development. In W. J. Arnold & M. M. Page (Eds.), Nebraska symposium on motivation (pp. 35–67). Lincoln, NE: University of Nebraska Press.

Mason, W. A., & Capitanio, J. P. (1988). Formation and expression of filial attachment in rhesus monkeys raised with living and inanimate mother substitutes. Developmental Psychobiology, 21, 401–430.

Masten, A. S. (2001). Ordinary magic. Resilience processes in development. American Psychologist, 56, 227–238.

Mayou, R. A., Ehlers, A., & Hobbs, M. (2000). Psychological debriefing for road traffic accident victims. Three-year follow-up of a randomised controlled trial. British Journal of Psychiatry, 176, 589–593.

Meaney, M. J., Diorio, J., Francis, D., Widdowson, J., LaPlante, P., Caldji, C., et al. (1996). Early environmental regulation of forebrain glucocorticoid receptor gene expression: Implications for adrenocortical responses to stress. Developmental Neuroscience, 18, 49–72.

Meaney, M. J., & Szyf, M. (2005). Environmental programming of stress responses through DNA methylation: Life at the interface between a dynamic environment and a fixed genome. Dialogues in Clinical Neuroscience, 7, 103–123.

Miller, E. K., & Cohen, J. D. (2001). An integrative theory of prefrontal cortex function. Annual Reviews of Neuroscience, 24, 167–202.

Mortimer, J. T., & Staff, J. (2004). Early work as a source of developmental discontinuity during the transition to adulthood. Development and Psychopathology, 16, 1047–1070.

Ochsner, K. N., & Gross, J. J. (2005). The cognitive control of emotion. Trends in Cognitive Sciences, 9, 242–249.

Ongur, D., & Price, J. L. (2000). The organization of networks within the orbital and medial prefrontal cortex of rats, monkeys and humans. Cerebral Cortex, 10, 206–219.

Parker, K. J., Buckmaster, C. L., Justus, K. R., Schatzberg, A. F., & Lyons, D. M. (2005). Mild early life stress enhances prefrontal-dependent response inhibition in monkeys. Biological Psychiatry, 57, 848–855.

Parker, K. J., Buckmaster, C. L., Schatzberg, A. F., & Lyons, D. M. (2004). Prospective investigation of stress inoculation in young monkeys. Archives of General Psychiatry, 61, 933–941.

Parker, K. J., Buckmaster, C. L., Sundlass, K., Schatzberg, A. F., & Lyons, D. M. (2006). Maternal mediation, stress inoculation, and the development of neuroendocrine stress resistance in primates. Proceedings of the National Academy of Sciences USA, 103, 3000–3005.

Parker, K. J., Rainwater, K. L., Buckmaster, C. L., Schatzberg, A. F., Lindley, S. E., & Lyons, D. M. (2007). Early life stress and novelty seeking behavior in adolescent monkeys. Psychoneuroendocrinology, in press.

Preuss, T. M. (1995). Do rats have prefrontal cortex? The Rose–Woolsey–Akert program reconsidered. Journal of Cognitive Neuroscience, 7, 1–24.

Pryce, C. R., Dettling, A., Spengler, M., Spaete, C., & Feldon, J. (2004). Evidence for altered monoamine activity and emotional and cognitive disturbance in marmoset monkeys exposed to early life stress. Annals of the New York Academy of Sciences, 1032, 245–249.

Reio, T. G., Jr., Petrosko, J. M., Wiswell, A. K., & Thongsukmag, J. (2006). The measurement and conceptualization of curiosity. Journal of Genetic Psychology, 167, 117–135.

Ridderinkhof, K. R., Ullsperger, M., Crone, E. A., & Nieuwenhuis, S. (2004). The role of the medial frontal cortex in cognitive control. Science, 306, 443–447.

Roder, E. L., Timmermans, P. J., & Vossen, J. M. (1989). Effects of rearing and exposure condition upon the acquisition of phobic behaviour in cynomolgus monkeys. Behaviour Research and Therapy, 27, 221–231.

Rosenberg, K. M., Denenberg, V. H., & Zarrow, M. X. (1970). Mice (*Mus musculus*) reared with rat aunts: The role of rat-mouse contact in mediating behavioural and physiological changes in the mouse. Animal Behaviour, 18, 138–143.

Rosenblum, L. A. (1968). Mother–infant relations and early behavioral development in the squirrel monkey. In L. A. Rosenblum & R. W. Cooper (Eds.), The squirrel monkey (pp. 207–233). Orlando, FL: Academic Press.

Rosenblum, L. A., & Andrews, M. W. (1994). Influences of environmental demand on maternal behavior and infant development. Acta Paediatrica, 397(Suppl.), 57–63.

Rosenblum, L. A., & Paully, G. S. (1984). The effects of varying environmental demands on maternal and infant behavior. Child Development, 55, 305–314.

Rutter, M. (1993). Resilience: Some conceptual considerations. Journal of Adolescent Health, 14, 626–631, 690–626.

Sackett, G. P. (1972). Exploratory behavior of rhesus monkeys as a function of rearing conditions and sex. Developmental Psychology, 6, 260–270.

Smotherman, W. P., & Bell, R. W. (1980). Maternal mediation of early experiences. In R. W. Bell & W. P. Smotherman (Eds.), Maternal influences and early behavior (pp. 201–210). New York: Spectrum Publications.

Stanton, M. E., & Levine, S. (1985). Brief separation elevates cortisol in mother and infant squirrel monkeys. Physiology and Behavior, 34, 1007–1008.

Taylor, S. E., Eisenberger, N. I., Saxbe, D., Lehman, B. J., & Lieberman, M. D. (2006). Neural responses to emotional stimuli are associated with childhood family stress. Biological Psychiatry, 60, 296–301.

Urry, H. L., van Reekum, C. M., Johnstone, T., Kalin, N. H., Thurow, M. E., Schaefer, H. S., et al. (2006). Amygdala and ventromedial prefrontal cortex are inversely coupled during regulation of negative affect and predict the diurnal pattern of cortisol secretion among older adults. Journal of Neuroscience, 26, 4415–4425.

Wallis, J. D., Dias, R., Robbins, T. W., & Roberts, A. C. (2001). Dissociable contributions of the orbitofrontal and lateral prefrontal cortex of the marmoset to performance on a detour reaching task. European Journal of Neuroscience, 13, 1797–1808.

Yates, T. M., Egeland, B., & Sroufe, A. (2003). Rethinking resilience: A developmental process perspective. In S. S. Luthar (Ed.), Resilience and vulnerability. Adaptation in the context of childhood adversities (pp. 243–266). New York: Cambridge University Press.