

David M. Lyons

Karen J. Parker

Alan F. Schatzberg

Department of Psychiatry and Behavioral
Sciences, Stanford University, 1201 Welch
Rd, MSLS P104, Stanford, CA 94305
E-mail: dmlyons@stanford.edu

Animal Models of Early Life Stress: Implications for Understanding Resilience

ABSTRACT: In the mid-1950s, Levine and his colleagues reported that brief intermittent exposure to early life stress diminished indications of subsequent emotionality in rats. Here we review ongoing studies of a similar process in squirrel monkeys. Results from these animal models suggest that brief intermittent exposure to stress promotes the development of arousal regulation and resilience. Implications for programs designed to enhance resilience in human development are discussed. © 2010 Wiley Periodicals, Inc. *Dev Psychobiol* 52: 616–624, 2010.

Keywords: emotion regulation; cognitive control; prefrontal plasticity; HPA axis; curiosity; anxiety; cortisol; squirrel monkey

INTRODUCTION

The negative consequences of early life stress are well recognized in contemporary perspectives on human mental health. Chronic exposure to severe forms of stress has been linked to the development of mood, anger, anxiety, and substance abuse disorders (Anda et al., 2006; Heim, Newport, Mletzko, Miller, & Nemeroff, 2008; Repetti, Taylor, & Seeman, 2002; Turner & Lloyd, 2003). Far less researched, but of equal importance, are indications that early intermittent exposure to stress does not result in vulnerability but instead enhances arousal regulation and resilience. Various described in studies of humans as inoculating, steeling, or toughening (Dienstbier, 1989; Masten, 2001; Mortimer & Staff, 2004;

Rutter, 2006), the notion that intermittent exposure to early life stress induces resilience is rooted in observations that Levine and his colleagues first described in the mid-1950s.

Based on Freud's theory that early life stress contributes to the development of subsequent emotional instability, Levine set out to investigate this hypothesis as described elsewhere in detail (Levine, 1962; Levine, Chevalier, & Korchin, 1956). Levine and his colleagues expected to find that infant rats exposed to intermittent foot shocks sufficient to elicit evasive movements would show signs of subsequent emotional instability in adolescence and adulthood. Results of their experiments were not supportive of Freudian theory and Levine concluded that early intermittent stress "results in the capacity for the organism to respond more effectively when confronted with novel situations or, in other words, to exhibit a diminished emotional response" (Levine, 1962).

Thirty years later, in the Laboratory of Developmental Psychobiology that Levine founded at Stanford University, we began to investigate the long-term effects of brief intermittent mother–infant separations in squirrel monkeys. Squirrel monkeys live in groups comprised of males and females of all ages. In natural and semi-natural conditions, mothers and other group members intermittently leave newly weaned offspring to forage for food beginning at 3–6 months of age (Boinski & Fragaszy, 1989; Lyons, Kim, Schatzberg, & Levine, 1998). Initially, brief intermittent separations studied in controlled

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Correspondence to: David M. Lyons

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experimental conditions (see below) elicit distress peep-calls and increase plasma levels of cortisol with partial habituation of these measures of arousal observed over repeated intermittent social separations (Coe, Glass, Wiener, & Levine, 1983; Hennessy, 1986). Working on the same misapprehension that beset earlier investigations of postnatal stress in rats, we expected to find that intermittent separations would increase emotional instability. Instead, we found that monkeys exposed to early intermittent separations showed fewer behavioral indications of anxiety, diminished stress-levels of cortisol, and increased sensitivity to glucocorticoid feedback regulation of the hypothalamic–pituitary–adrenal (HPA) axis compared to age-matched monkeys not exposed to intermittent separations (Levine & Mody, 2003; Lyons, Martel, Levine, Risch, & Schatzberg, 1999; Lyons, Yang, Mobley, Nickerson, & Schatzberg, 2000).

Based on these findings, follow-up studies were designed to prospectively test the hypothesis that intermittent separations represent a form of stress inoculation that enhances arousal regulation and resilience. Socially housed squirrel monkeys were randomized to either brief intermittent separations or a nonseparated control condition at 17 weeks of age. For each of 10 total separation sessions, 1 monkey was removed from the natal group for a 1-hr session once a week. In the nonseparated control condition, age-matched monkeys remained undisturbed in their natal groups. After completion of the postnatal protocols at 27 weeks of age, all of the monkeys were maintained in identical conditions. Behavioral and hormonal measures of anxiety were assessed in the presence of each monkey's mother at 9 months of age (Parker, Buckmaster, Schatzberg, & Lyons, 2004). Cognitive control of behavior was examined at 1.5 years of age (Parker, Buckmaster, Justus, Schatzberg, & Lyons, 2005) and exploratory behavior was assessed at 2.5 years of age (Parker et al., 2007). Noninvasive neuroimaging was performed to investigate prefrontal brain development at 3.3 years of age (Katz et al., 2009). Puberty occurs at 2–3 years of age and the average maximum life span is ~21 years. All procedures were conducted in accordance with the NIH Guide and were IACUC approved.

AROUSAL REGULATION, COGNITIVE CONTROL, CURIOSITY, AND RESILIENCE

At 9 months of age, each monkey was tested along with its mother for 30 min on five consecutive days in a novel environment that contained an assortment of foods and various toy-like objects (Parker et al., 2004). Similar test conditions have been used to demonstrate that severe forms of early life stress increase subsequent indications of anxiety in marmoset monkeys and macaques (Andrews

& Rosenblum, 1993; Dettling, Feldon, & Pryce, 2002; Hinde & Spencer-Booth, 1971). Here the novel environment test was used to determine whether intermittent separations enhance the development of arousal regulation and resilience.

In the novel environment stress test, the previously separated and nonseparated monkeys were initially similar but differences emerged over repeated test sessions. Gradually, the previously separated monkeys showed fewer signs of anxiety inferred from decreased maternal clinging and increased exploration compared to monkeys not exposed to intermittent separations. Plasma levels of pituitary–adrenal stress hormones were likewise diminished in monkeys previously exposed to intermittent separations compared to nonseparated controls (Fig. 1).

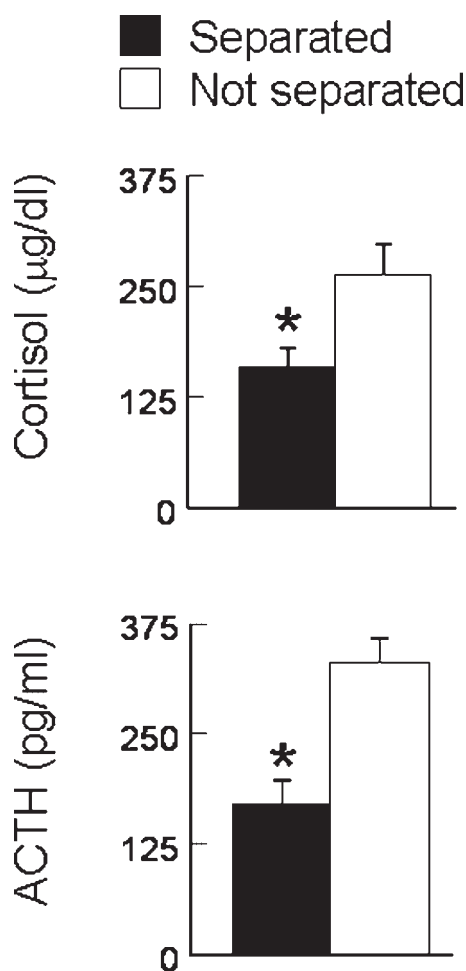


FIGURE 1 Early intermittent separations diminish subsequent pituitary–adrenal responses to a novel test environment. Posttest plasma levels of cortisol (top panel) and adrenocorticotropic hormone (bottom panel) are presented for previously separated and nonseparated monkeys ($n = 9–10$ monkeys per condition; mean \pm SEM). Asterisks signify a significant ($p < .05$) separation effect (adapted from data presented in Parker et al., 2004).

As described elsewhere in greater detail (Parker et al., 2004), these results support the suggestion that intermittent separations represent a form of stress inoculation that enhances arousal regulation and resilience in novel situations.

At 1.5 years of age, all monkeys were administered a behavioral test of cognitive control that specifically focused on response inhibition (Parker et al., 2005). Monkeys were required to inhibit a previously rewarded reaching response in order to efficiently retrieve food treats from a clear plastic box. In marmoset monkeys and macaques, performance on this test 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). Test performance is likewise impaired in a marmoset 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 neuroendocrine stress response (Lyons, Lopez, Yang, & Schatzberg, 2000). Here this test was used to assess whether intermittent separations affect cognitive control of behavior.

The ability to inhibit a previously rewarded behavioral response gradually improved over repeated test trials. At peak levels of performance, however, all of the previously separated monkeys successfully completed all test trials whereas fewer than half of the monkeys not exposed to intermittent separations achieved similar levels of success (Parker et al., 2005). These and related findings suggest that early intermittent separations enhance cognitive control of behavior.

At 2.5 years of age, all monkeys were administered a test to examine curiosity in a stress-free condition (Parker et al., 2007). Each monkey was provided free access to explore a familiar or a novel toy-like object secured to the wall of a compartment affixed to the monkey's home cage. Similar test conditions have been used to demonstrate that severe forms of early life stress diminish subsequent exploratory tendencies in macaques (Hinde & Spencer-Booth, 1971; Roder, Timmermans, & Vossen, 1989; Sackett, 1972). Here exploration of novelty was used to determine whether intermittent separations induce subsequent differences in curiosity and exploratory behavior.

All previously separated and all but one of the nonseparated monkeys approached the compartment and subsequently peered inside. More of the previously separated monkeys left the home cage to enter the compartment, and they entered faster, with greater frequency, and spent more time inside the compartment compared to nonseparated monkeys (Parker et al., 2007). Inside the compartment, more previously separated than nonseparated monkeys explored both objects, and the previously separated monkeys showed a significant

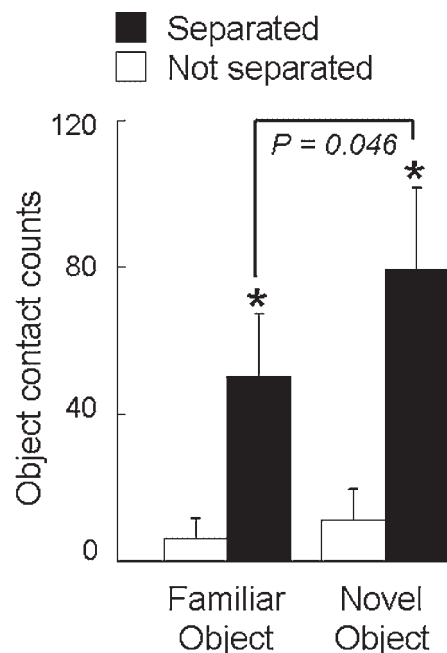


FIGURE 2 Early intermittent separations increase subsequent novelty-seeking behavior. Measures of familiar versus novel object exploration are presented for previously separated and nonseparated monkeys ($n = 9-10$ monkeys per condition; mean \pm SEM). Asterisks signify separation effects ($p < .05$) and the bracket shows that previously separated monkeys preferred to interact with the novel toy-like object (adapted from data presented in Parker et al., 2007).

preference for the novel object compared to the familiar object (Fig. 2).

In the earlier novel environment test conducted at 9 months of age, significantly more object exploration was also observed in the previously separated compared to nonseparated monkeys (Parker et al., 2004). Object exploration in the earlier study was assessed, however, in stressful conditions that involved involuntary removal of monkeys from the home cage. Both the previously separated and nonseparated monkeys in the earlier study had higher plasma levels of pituitary–adrenal hormones after the novel environment test compared to baseline levels measured in undisturbed home cage conditions (Parker et al., 2004). Moreover, posttest plasma levels of pituitary–adrenal hormones were significantly higher in the nonseparated compared to separated monkeys (Fig. 1). Differences in pituitary–adrenal activity were therefore confounded with differences in exploratory behavior assessed at 9 months of age.

In the study conducted at 2.5 years of age, exploratory behavior was examined by providing free access to a compartment attached to each monkey's home cage (Parker et al., 2007). To further reduce the potentially stressful nature of the test situation, each monkey was

acclimated to all test procedures prior to the start of the study. Posttest cortisol levels at 2.5 years of age were not significantly different from baseline levels measured in undisturbed home cage conditions. Moreover, neither baseline nor posttest cortisol levels at 2.5 years of age correlated with exploratory behavior in the stress-free test condition. Individual differences previously observed in object exploration at 9 months of age were, however, correlated with differences in test compartment entries and total time spent inside the compartment at 2.5 years of age (Lyons & Parker, 2007). Individual differences previously observed in cognitive control at 1.5 years of age were also correlated with test compartment entries and total time spent inside the compartment at 2.5 years of age. Taken together, these findings suggest that early intermittent separations induce broad and enduring trait-like transformation in cognitive, motivational, and emotional aspects of arousal regulation and resilience (Lyons, Parker, Katz, & Schatzberg, 2009).

MATERNAL MEDIATION

Stress inoculation-induced resilience in monkeys resembles the effects of early intermittent “postnatal handling” that Levine and his colleagues identified 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 diminished emotionality, increased exploration, improved learning, and diminished HPA axis activation compared to rats raised in standard undisturbed laboratory conditions (Fernandez-Teruel et al., 2002; Levine, 1957, 2000; Levine, Alpert, & Lewis, 1957; Meaney et al., 1996).

In rats, these outcomes appear to partially reflect the effects of maternal behavior directed toward pups that are briefly separated and then returned to the nest (Denenberg, 1999; Smotherman & Bell, 1980). Brief intermittent separations increase arched-back nursing after reunions (Pryce, Bettschen, & Feldon, 2001) and in some studies high levels of maternal care persist throughout early development (Lee & Williams, 1974). Importantly, the neuroendocrine indications of resilience observed in rats exposed to intermittent separations can be replicated in nonmanipulated offspring that naturally receive high levels of maternal care (Liu et al., 1997). That increased maternal care is sufficient to induce 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). Maternal mediation might therefore explain Levine’s observation that pups removed intermittently from the nest and exposed to brief foot shock show subsequent signs of diminished emotionality as adults (Levine, 1962; Levine et al., 1956).

To determine whether resilience in monkeys exposed to early intermittent separations is maternally mediated, we examined maternal behavior and subsequent neuroendocrine measures of resilience in monkeys that were randomized to three postnatal conditions (Parker, Buckmaster, Sundlass, Schatzberg, & Lyons, 2006). In one condition, each monkey was separated from its mother and the natal group for 10 weekly 1-hr sessions. In the second condition, each monkey and its mother were removed together as a pair and separated from the natal group for 10 weekly 1-hr sessions. Both of these social separation conditions elicit locomotor agitation, distress vocalizations, and HPA axis activation with baseline measures of arousal restored soon after reunion with members of the natal group (Coe et al., 1983; Jordan, Hennessy, Gonzalez, & Levine, 1985). In the third treatment condition, nonseparated monkeys remained undisturbed in their natal groups.

Neither separation condition induced long-lasting changes in maternal care (Parker et al., 2006). Moreover, the transient changes observed in maternal behavior did not correspond with differences in the development of arousal regulation and resilience. Monkeys exposed along with their mother to intermittent separations received less maternal care in the home cage as mothers direct their attention toward re-integration with the group. Yet both intermittent separation conditions induced neuroendocrine indications of resilience compared to control monkeys not exposed to intermittent separations (Fig. 3). Specifically, monkeys separated alone or separated along with their mother exhibited diminished cortisol responses to a subsequent novel environment stress test compared to monkeys not exposed to either separation condition (Parker et al., 2006). These and related findings suggest that arousal regulation and resilience correspond more closely to prior stress exposure than to separation-induced changes in maternal care. Similar conclusions have been reported in recent investigations of developmental plasticity and early life stress in rats (Macri & Wurbel, 2006; Tang, Akers, Reeb, Romeo, & McEwen, 2006).

PREFRONTAL NEUROPLASTICITY

Based on our findings that early intermittent separations enhance arousal regulation and improve prefrontal-dependent cognitive control of behavior, noninvasive neuroimaging was used to examine separation effects on prefrontal brain development. Monkeys randomized to

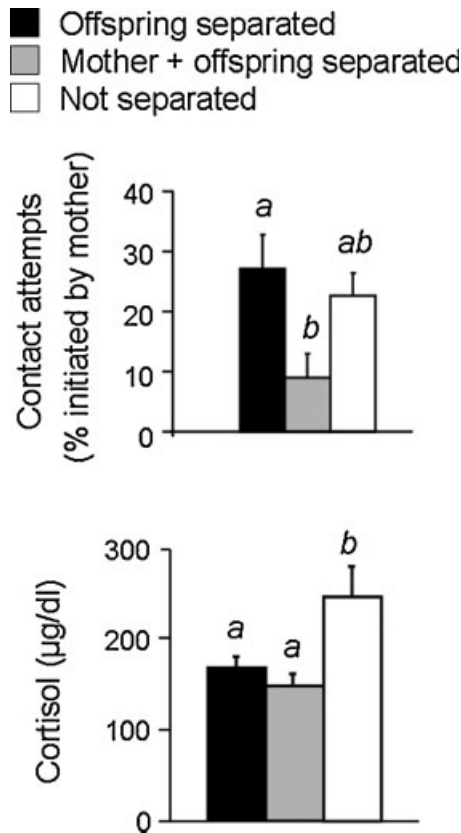


FIGURE 3 Early intermittent separation-induced changes in neuroendocrine indications of resilience are not maternally mediated. The percentage of contact attempts initiated by mothers in the home cage (top panel) and plasma cortisol levels after exposure to a novel environment stress test (bottom panel) are presented for 9–11 monkeys in each treatment condition (mean \pm SEM). Treatment conditions without shared superscript letters differ significantly from one another ($p < .05$) and conditions with shared letters do not (adapted from data presented in Parker et al., 2006).

brief intermittent separations or a nonseparated condition were initially studied as described above and then neuroimaging was performed at 3.3 years of age (Katz et al., 2009). In keeping with previous evidence (Lyons, Afarian, Schatzberg, Sawyer-Glover, & Moseley, 2002) we found that monkeys exposed to early intermittent separations had larger ventromedial but not larger dorsolateral prefrontal cortical volumes compared to monkeys not exposed to intermittent separations (Fig. 4). Larger volumes do not reflect increased cortical thickness but instead represent surface area expansion of ventromedial prefrontal cortex (Katz et al., 2009).

These findings are of interest because increased ventromedial prefrontal size in humans predicts diminished impulsivity (Matsuo et al., 2009), lower harm avoidance (Yamasue et al., 2008), and greater retention of

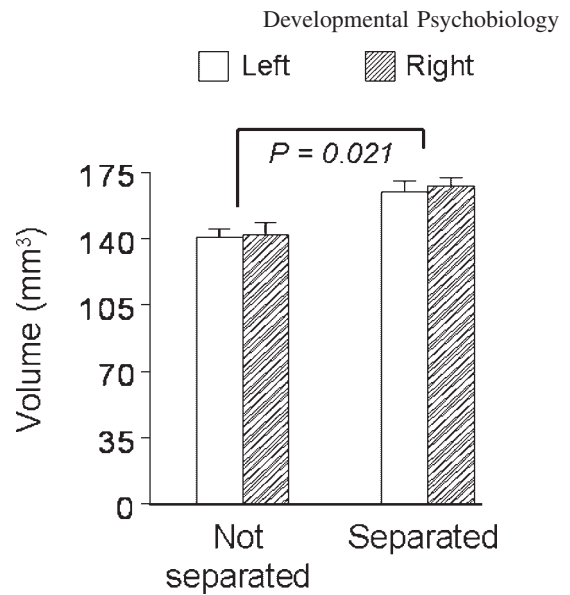


FIGURE 4 Early intermittent separation-induced adaptations in prefrontal cortex. Ventromedial prefrontal cortical volumes are larger in monkeys exposed to early intermittent separations compared to nonseparated controls ($n = 9$ – 10 monkeys per condition; mean \pm SEM). Separation effects were not discerned in dorsolateral prefrontal cortex (data not shown) and the separation-by-brain side interactions were not statistically significant (adapted from data presented in Katz et al., 2009).

learned extinction of fear (Milad et al., 2005). Recent neuroimaging studies of humans support results from animal research confirming that learned extinction of fear is mediated by prefrontal downregulation of arousal via inhibitory connections that diminish neural output from the amygdala (Delgado, Nearing, Ledoux, & Phelps, 2008; Quirk & Mueller, 2008). Additional evidence likewise suggests that differences in the balance between top-down prefrontal regulation and arousal inducing amygdala activation may account for trait-like differences in coping with intermittent stress (Bishop, 2007; Drabant, McRae, Manuck, Hariri, & Gross, 2009).

Despite evidence that coping with stress depends on myelinated prefrontal cortical and subcortical (e.g., amygdala) interconnections, myelination is seldom considered in discussions of neural plasticity as a mechanism for experience-dependent resilience. In the study described above, magnetic resonance diffusion tensor imaging was used to examine prefrontal myelination in terms of fractional anisotropy (Katz et al., 2009). Fractional anisotropy represents water proton diffusion directionality on a scale from zero to one. A value of zero indicates that diffusion is unrestricted in all directions, whereas a value of one indicates that diffusion is completely restricted along a single direction. High values of fractional anisotropy occur when tissue microstructure restricts diffusion directionality as exemplified

by myelination of axons in white matter. Myelination increases nerve conduction velocities and facilitates synchronous firing of neurons by reducing travel distance effects in distributed networks (Fields, 2008). Coordination of firing inputs to maximize temporal summation at postsynaptic neurons is the foundation for a key concept in neuroplasticity and development—neurons that fire together, wire together. In children, myelination of prefrontal connections determined by fractional anisotropy increases with age (Barnea-Goraly et al., 2005) and maturation of prefrontal-dependent functions (Casey et al., 2007).

In monkeys, exposure to early intermittent separations increases ventromedial but not dorsolateral prefrontal white matter measures of fractional anisotropy (Fig. 5). This difference coincides with the difference in ventromedial and not dorsolateral prefrontal cortical volumes described above. White matter measures of fractional anisotropy in ventromedial but not dorsolateral regions correlate with their respective volumes of prefrontal cortex (Katz et al., 2009). These findings suggest that the learning-like process of coping with early intermittent stress increases prefrontal myelination and expands a region of cortex that broadly controls arousal regulation and resilience.

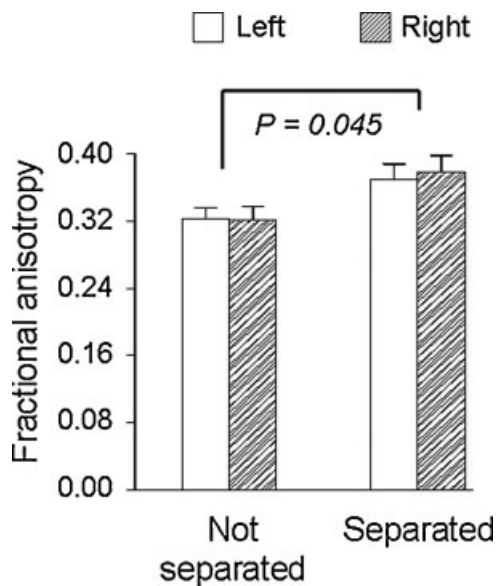


FIGURE 5 Early intermittent separation-induced adaptations in prefrontal white matter. Ventromedial prefrontal white matter fractional anisotropy is greater in monkeys previously exposed to early intermittent separations compared to nonseparated controls ($n=9-10$ monkeys per condition; mean \pm SEM). Separation effects were not discerned in the white matter region underlying dorsolateral prefrontal cortex (data not shown) and the separation-by-brain side interactions were not statistically significant (adapted from data presented in Katz et al., 2009).

The effect size for these neuroadaptations is similar to that observed in studies of environmental enrichment in marmoset monkeys (Kozorovitskiy et al., 2005) and rats (Rosenzweig, 2003). Enrichment entails repeated exposure to novel inanimate and social stimulation (Fox, Merali, & Harrison, 2006) that elicits neuroendocrine indications of stress coping in rats (Moncek, Duncko, Johansson, & Jezova, 2004). After exposure to enrichment, however, rats show diminished indications of anxiety, increased exploration, and enhanced prefrontal-dependent cognitive control compared to nonenriched rats (Fox et al., 2006; Schrijver, Pallier, Brown, & Wurbel, 2004). These findings combined with our studies suggest that enrichment effects may be mediated, in part, by the process of coping with stress.

ENHANCING HUMAN RESILIENCE

Controlled exposure to stress-related cues is a key feature of resiliency training for people that work in conditions where performance in the face of adversity is required, for example, medical and military personnel, aviators, police, firefighters, and rescue workers (Meichenbaum, 2007; Stetz et al., 2007). A similar process also occurs during cognitive behavior exposure therapies for stress-induced psychopathologies. Intermittent exposure to relevant stressors is thought to induce a learning-like process that modifies erroneous psychobiological conditions that impair mental health (De Raedt, 2006; Foa & Kozak, 1986).

Although resiliency training and exposure psychotherapies are generally administered by psychologists and psychiatrists, these interventions build on a process that appears to spontaneously occur in most humans without professional training or formal guidance (Epstein, 1983). Adult humans, for example, tend to cope better with spousal loss, illness, and accidents if they have previously experienced and coped with stress in childhood (Khoshaba & Maddi, 1999). Work-related stress likewise has fewer deleterious mental health effects in adults previously exposed to work stress in adolescence (Mortimer & Staff, 2004). These and related investigations of infants (Tronick, 2006) and young children (Ellis, Essex, & Boyce, 2005; Gunnar, Frenn, Wewerka, & Van Ryzin, 2008) suggest that a spontaneous learning-like stress coping process promotes arousal regulation and resilience.

The public health impact of understanding how spontaneous stress coping promotes resilience is potentially quite high. According to the World Health Organization, stress-related health disorders will be the second leading cause of disabilities by the year

2020. The American Institute of Stress has determined that 75–90% of all medical visits are stress-related and cost the nation 42 billion dollars each year. Levine's seminal observation that early intermittent exposure to stress does not increase vulnerability, but instead promotes the development of resilience warrants renewed attention in programs designed to improve human health.

NOTES

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