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From Freud to a Modern Understanding of Behavioral, Physiological, and Brain Development

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Abstract

Seymour Levine's first "early experience" experiments were inspired by Freud. Yet, Levine's lifetime of work, and the work of his colleagues and scientists who followed, unveiled a myriad of early experience effects that even Freud himself could not have imagined. Related to and extending beyond his work on early experience, Levine also made important, often seminal, contributions to overlapping and related areas, such as early maternal separation and deprivation, maternal behavior and physiology, sexual differentiation, perinatal malnutrition, attachment in non-human primates, hypothalamic-pituitary-adrenal (HPA) stress reactivity and its adaptive significance, and the development of the HPA system. Moreover, his work spawned new lines of research by investigators active today. The papers contained in this special issue provide a sampling of research demonstrating some of the important directions in which those earliest experiments have led, many with clinical applications.

Keywords

Seymour Levine; early experience effects; hypothalamic-pituitary-adrenal; stress reactivity; maternal-infant; maternal physiology; maternal behavior

At the initial evening session of 40th Annual Meeting of the International Society for Developmental Psychobiology (ISDP), on October 31, 2007, two of us (M.B.H. and J.M.S.) gave a talk in the Past Presidents' Symposium. We both had been postdoctoral fellows in the laboratory of Seymour "Gig" Levine in the 1970s (see Fig. 1 for a photo from that era) and we had looked forward to seeing him in the audience. Although Gig had been planning to participate in this meeting, he became seriously ill; we soon learned that he had died the night of the symposium (see In Memoriam Commentary: Coe, Stern, Hennessy, & Weinberg, 2008). In the next few days, plans were made for a memorial Special Issue of

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Developmental Psychobiology as a tribute to Gig's legacy and major contributions to this field of research. An earlier Special Issue of this journal (Coe, Gunnar, Ursin, & Weinberg, 1997) was based on a 1995 conference held in honor of Gig's retirement from Stanford University (Fig. 2); its editors and contributors had worked with Gig, as a graduate student (J.W.), postdoctoral fellow, or research collaborator. The current Special Issue also includes contributions by those who worked directly with Gig (Coe; Lyons & Schatzberg; Moriceau, & Sullivan), as well as those who never published with him but whose research was influenced by his publications and by the sharing of ideas at conferences and networks (Baram; Heim & Nemeroff; Walker).

Collectively, the papers of this issue represent a selected extension of the broad array of early experiences and outcome variables, behavioral and physiological, which Gig studied in a career spanning close to 60 years. Aspects of early experience effects are included in a large proportion of Levine's well over 400 publications (including seven to date since 2008). Related to and beyond his work on early experience, Gig also made important, often seminal, contributions to overlapping and related areas, such as early maternal separation and deprivation, maternal behavior and physiology (e.g., Stern, Goldman, & Levine, 1973; Thoman & Levine, 1970), sexual differentiation (e.g., Levine, 1966), perinatal malnutrition (Levine & Wiener, 1976), attachment in non-human primates, hypothalamic-pituitary-adrenal (HPA) stress reactivity and its adaptive significance (Levine, 1971), and the development of the HPA system, including the neonatal stress-hyporesponsive period. Moreover, his work spawned new lines of research by investigators active today. Contributions in this current Special Issue illustrate nicely lines of research that Gig's influence helped forge. Certainly the articles printed here do not define the boundaries of Gig's influence. Many other researchers and specific lines of work shaped by Gig's ideas might easily have been included in a larger volume. Note that a Special Section of the journal *Neuroscience and Biobehavioral Reviews* was published recently as a tribute to Gig Levine (Cirulli & Suchecki, 2010).

As a recent Ph.D. (1951, NYU; mentor: Howard Kendler) steeped in the then dominant learning theory, how was it that Gig Levine turned his attention to early experiences? Like many others at that time, Gig was intrigued by Freud's theory that early trauma has long-lasting effects on behavior by forming the basis for primary anxiety (Freud, 1936) and personality development (Freud, 1949). Although this idea had received support from clinical reports, Gig realized that experimental work was needed to flesh out, in a controlled fashion, the host of variables involved and to elucidate the underlying mechanisms. Fifty four years ago, Levine, Chevalier, and Korchin (1956) published the results of experiments examining effects of early-life traumatic experience on adult avoidance learning. Experimental animals were exposed to mild electric shocks daily during the preweaning period. Animals in a control condition received equivalent handling to the shocked animals, being placed in the shock chamber daily but not receiving shock. A second control group received no handling at all, but remained undisturbed in the home cage. To their surprise, it was the non-handled animals which showed deviations in behavior and physiology during subsequent exposure to stressors, whereas the shocked animals and the handled controls both showed seemingly adaptive behavioral and physiological responses and were similar to each other (see later review: Levine, 1960). So was born the phenomenon of "early

handling” or “infantile stimulation” and its beneficial effects on resistance to stress (e.g., Levine, 1957, 1960, 1962), later termed coping (e.g., Levine, 1983; Weinberg & Levine, 1980). Repeated studies confirmed the finding that animals that were handled during the preweaning period typically had an attenuated or better modulated HPA response to stressors, with moderate corticosterone increases to mild stressors and greater increases to more severe stressors, as well as faster recovery to basal hormone levels following termination of stress (Levine, 1960; Weinberg & Levine, 1980). Development in general was also enhanced in the handled animals, which showed earlier eye and ear opening, earlier maturation of motor coordination, and were heavier at weaning (Levine, 1960). The adverse effects of the *absence* of early stimulation (the non-handled group) “was attributed to an increased susceptibility to emotional disturbance resulting from the restriction of experience in infancy” (Levine et al., 1956). Despite this clear disparity with Freud’s views on the role of “trauma,” a legacy of Levine’s work is that early experience—especially stress and altered interactions with the mother—affects development more pervasively than even Freud could have imagined. Of course, Gig was not solely responsible for this progress; many others, notably Victor Denenberg (e.g., 1962) and Robert Ader (e.g., Ader & Friedman, 1965), made enormous contributions to the field. Yet Gig, probably more than any other investigator, pioneered the study of how early events, often innocuous ones, shaped the animal’s habitual biobehavioral response to the challenges it would meet for a lifetime.

An important issue of the early experience literature, conducted mostly on rodents, is whether the results are generalizable to other mammalian species, especially primates. Decades after Gig’s findings on hormonal and behavioral effects of infantile stimulation in neonatal rats (Levine, 1957; Levine et al., 1956) and mice (Levine, 1959), Coe, Hennessy, Lyons, Mendoza, Levine, and others conducted experiments on the long-term effects of brief maternal separations on infant squirrel monkeys. This manipulation was found to be a particularly potent activator of the HPA axis at the time of the separation, and to improve arousal regulation and resilience later in life, paralleling some of the effects of early stimulation in rodents (e.g., Levine & Mody, 2003; Lyons, Martel, Levine, Risch, & Schatzberg, 1999; Levine, 2005). In their present review of subsequent findings, Lyons, Parker, and Schatzberg (2010) show that repeated, brief maternal separations diminish hormonal stress responses to a novel test environment and increase novelty-seeking behavior. The behavioral effect appears to reflect a true increase in curiosity rather than a reduction in anxiety behavior. Unlike the case in laboratory rodents (see discussion below), however, effects appear not to be mediated by the mother. A measure of cognitive control of behavior—response inhibition—also is affected by the earlier intermittent maternal separations. Perhaps most intriguing, the authors use neuroimaging techniques to provide evidence that the cortical region likely underlying the cognitive effect increases in volume and myelination as a result of the early stress, akin to changes seen after environmental enrichment in other animals. These results have important health-related implications for human populations, which the authors go on to discuss.

The very earliest experiences, of course, occur during prenatal development. Levine and his coworkers studied the effects of auditory restriction during pregnancy on offspring survival (Levine & King, 1965), the maternal-fetal adrenal and stress response system in rats (Thoman, Sproul, Seeler, & Levine, 1970; Milkovic et al., 1974), squirrel monkeys Coe,

Murai, Wiener, Levine, and Siiteri (1986), and women (Obel, Hedgaard, Henriksen, Secher, Olsen, & Levine, 2005), and the effects of pre- and postpartum malnutrition in rats (Wiener, Robinson, & Levine, 1983). A notable contribution to this literature on prenatal influences on development is the research report in this issue by Coe, Lubach, Crispin, Shirtcliff, and Schneider (2010) on the assessment, over many years, of 413 infant rhesus monkeys whose mothers were subjected to one of a variety of conditions during pregnancy. Chris Coe worked with Gig for many years (as postdoctoral fellow, research associate, and research assistant professor), including on the behavioral and physiological responses to maternal separation in monkeys (e.g., Coe, Glass, Wiener, & Levine, 1983; Coe, Mendoza, Smotherman, & Levine, 1978; Coe, Rosenberg, & Levine, 1988). Using the comprehensive and sensitive Infant Behavioral Assessment Scale, Coe et al. (2010) found subtle impairments in orientation and sensory, motor, and emotional reactivity in healthy, full-term infants whose mothers drank alcohol in moderate amounts or were administered ACTH or corticoids during part of their pregnancy.

Levine's many studies on the developing HPA system throughout his career included a focus on the rat neonate's stress hyporesponsive period (SHRP). This occurs during the first two weeks of postnatal life (Levine, Glick, & Nakane, 1967; Levine & Dent, 2000), is protective of brain development (Vazquez & Levine, 2005) and is indicative of environmental programming of future coping mechanisms (Dent, Choi, Herman, & Levine, 2007). By examining the effect of removing the mother for 24 hr, termed maternal deprivation, Levine and coworkers were able to show the importance of maternal stimulation for blunting the stress response in preweaning pups (Stanton, Gutierrez, & Levine, 1988), as it is for other developmental outcomes (Hofer, 1987). Replacement of specific forms of maternal stimulation during the deprivation period demonstrated an essential role of both nutrition and tactile contact in maintaining the SHRP (Rosenfeld, Ekstrand, Olson, Suchecki, & Levine, 1993; Suchecki, Rosenfeld, & Levine, 1993). Walker (2010) herein reviews her research that expands on these findings in two ways. She reports that maternal pre- and postpartum high-fat feeding blunts stress responsiveness in neonates, in part mediated by increased circulating levels of leptin in offspring. Moreover, leptin administration to rat pups elicits increased anogenital licking from the mothers compared to that received by pups treated with saline. Given that the early handling paradigm, which elicits increased pup licking, is associated with reduced HPA axis responsiveness in adulthood, it is possible that changes in behavior of the "high fat" females also contributed to the effects observed on their offspring's later HPA activity. Walker further shows that the effects of modest, repetitive pain (formalin injection in rear paw) in the first weeks of life, that is, acute stress responsiveness and paw inflammation and adult sensitivity to thermal pain, are reduced by high natural levels of maternal licking or artificial tactile stimulation. These studies add significantly to our understanding of the maternal factors and early influences that are so critical in determining the infant's physiology and behavioral repertoire.

The paper by Moriceau, Roth, and Sullivan (2010) also builds on Gig's research over the years on the SHRP and its relationship to infant attachment. Gig often viewed the mother's ability to reduce infant glucocorticoid levels in terms of filial attachment (Levine, 2001). For instance, his experiments with Mark Stanton on older pups carefully documented the role of somatosensory and olfactory cues from mothers in blunting stress reactivity (Stanton &

Levine, 1990; Stanton, Wallstrom, & Levine, 1987). Moriceau et al. (2010) also examine the relation of attachment and the HPA axis, but from a different perspective. Rather than focusing on how attachment-related stimuli affect HPA activity, they recount recent findings from their laboratory that document profound influences of the HPA system on filial attachment. Low glucocorticoid levels—whether due to the SHRP or to the mother’s presence during a limited window after the SHRP—promotes approach to the mother, regardless of her treatment of the young. This behavior appears adaptive for the very young pup, before significant sensory and motor maturation has occurred. Later in the neonatal period, rising corticosterone concentrations prompt the emergence of more adult-like behavior associated with aversive conditioning. In short, the termination of the SHRP leads to a concatenation of neural effects that, in turn, reorganize the behavior of the growing pup in synchrony with its changing needs and capabilities. The fine tuning of this process may depend on the mother’s treatment of the pup as the SHRP wanes.

Gig’s original studies on the early handling phenomenon immediately prompted speculation about the mechanisms involved in translating touch by the experimenter into relatively permanent and often seemingly beneficial changes in such basic biological processes as the neuroendocrine stress response. In 1969 Levine suggested that the effects of infantile stimulation could be attributed to alterations in circulating adrenal steroids during sensitive periods of development, that is, early handling has direct stimulatory effects on the pup. Further, increased corticosterone levels that occur with handling were suggested to permanently modify the organization of the central nervous system and result in different patterns of adrenocorticotrophic hormone (ACTH) secretion. Thus, by causing frequent variations in the concentration of corticosterone in the infant, handling modifies the setpoint of a hypothetical “homonostat” such that it could vary in a graded manner in adulthood (Levine, 1969). Later studies in the Levine laboratory focused on the role of mother–infant interactions in the modulation of HPA activity in the offspring. For example, Smotherman, Brown, and Levine (1977) showed that early exposure to shock or handling alters the stimulus characteristics of the pups. In turn, when pups are returned to the nest, mothers alter their behavior according to the intensity of stimulation that they received; handling enhances mother–pup interaction by provoking bursts of maternal sensory stimulation of the pups immediately after their return to the home cage (Brown, Smotherman, & Levine, 1977), whereas shocked pups receive even more licking, nurse more frequently, and are in the nest with the mother more often compared to handled pups (Smotherman et al., 1977). Because the presence of the mother facilitates a more rapid return of the HPA hormones to basal levels, it was suggested that increases in maternal care may modulate the pup’s HPA response during the preweaning period, with effects that persist into adulthood, thus possibly accounting for the long-term effects of early handling (Smotherman, 1983).

Over the years the question of how early handling effects are mediated, and the role of the mother in this phenomenon, has continued to intrigue and motivate researchers. The paper by Korosi and Baram (2010) beautifully exemplifies the substantial progress that has been made in understanding some of the basic biological mechanisms underlying the long-term effects of early experience. Baram and her coworkers have been examining the molecular cascade bridging maternal care and the enduring consequences of HPA programming. For example, they have shown that with increased maternal care, whether it occurs naturally or is

induced (in the early handling paradigm), levels of CRH messenger RNA in the hypothalamus are reduced, whereas glucocorticoid receptor (GR) levels in the hippocampus are increased. In support, they found that after a single day of handling the expression of the immediate-early gene Fos was induced in the bed nucleus of the stria terminalis (BnST) and the central nucleus of the amygdala (ACe), regions that generally augment CRH expression in the hypothalamic paraventricular nucleus (PVN), while repeated handling induced Fos in the thalamic paraventricular nucleus, which can inhibit the ACe. Thus, an effect of early experience may be to alter the balance of excitatory and inhibitory influences on CRH neurons in the PVN. The authors conclude by referring to possible clinical significance of these findings via use of pharmacological interventions.

The important clinical implications of the early experience literature are the focus of the paper by Heim, Shugart, Craighead, and Nemeroff (2010), in which they comprehensively review the effects of early-life trauma—including early sexual and physical abuse, neglect, and parental loss—on vulnerability to mental health problems in later life. These authors note that Gig's studies provided the first “proof of principle” that early experiences can shape behavior and physiology of systems relevant to stress, and that their clinical studies on the long-term consequences of early life trauma build on this legacy. In his later years, Gig himself increasingly collaborated on studies focusing on the clinical implications of early experience effects (Bruce, Fisher, Pears, & Levine, 2009; Corbett, Mendoza, Abdullah, Wegelin, & Levine, 2006; Corbett, Mendoza, Baym, Bunge, & Levine, 2008; Corbett, Mendoza, Wegelin, Carmean, & Levine, 2008; Dozier, Peloso, Lewis, Laurenceau, & Levine, 2008; Kobak, Zajac, & Levine, 2009; Schiffman et al., 2003).

Heim et al. (2010) first discuss the epidemiological evidence demonstrating a significant prevalence rate of early traumatic experiences. A review of clinical studies then provides evidence that child abuse and neglect are nonspecific risk factors for various psychiatric syndromes, with a particularly strong link between childhood trauma and the mood and anxiety disorders. It is suggested that early life traumatic events induce a persistent sensitization of stress-responsive neural circuits, resulting in increased vulnerability to subsequent stressors, and in turn, an increased incidence of mental health problems. Numerous rodent and non-human primate studies are then discussed to highlight persistent neurobiological consequences of early-life trauma, with particular effects on central CRH circuitry and altered HPA activity and feedback. Importantly, both preclinical and clinical data suggest that later life circumstances can ameliorate or reverse some of the long-term adverse effects of early-life stress. The clinical data, for example, show that the availability of positive supports and optimal subsequent caregiving experiences can have significant protective effects. Further, the well-known finding that women are twice as vulnerable to major depression as are men is discussed in terms of many sex-related experiential and biological interactions. Translational research into the effects of early experience on brain development and behavior, such as those by Heim, Nemeroff, and coworkers, are critical for elucidating specific mechanisms by which early life trauma increases risk for adult psychopathology, which in turn will guide the development of more effective and specific treatments. While the authors do not consider traditional Freudian psychoanalysis, they review the efficacy of various modern, and briefer, forms of psychotherapy, such as Cognitive Behavioral Therapy (CBT) and Emotion Focused Therapy, as well as

pharmacotherapy, and the combination of psychotherapy and pharmacotherapy. A reanalysis of a report from their group led to the conclusion that for depressed patients with a history of childhood trauma, a form of CBT alone was more effective than treatment with an antidepressant (nefazodone) alone, and the antidepressant added no further benefit to treatment with CBT. They also recommend individualized treatment options.

In conclusion, the legacy of Gig Levine, originally inspired by the writings of Sigmund Freud, is a rich, and ever increasing, understanding of the many ways in which early experiences affect our lives.

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FIGURE 1.

Some of the participants at a conference, “Growing Points in Developmental Psychobiology,” held in honor of Dr. Seymour “Gig” Levine held at Tanque Verde, Tuscon, AZ, October 6–8, 1995, and organized by Christopher Coe, Megan Gunnar, Stephen Suomi, and Joanne Weinberg. From left, Top Row: Chris Coe, Barbara Levine, *Gig Levine, and Nellie Laughlin; Middle Row: Sally Mendoza, Megan Gunnar, Holger Ursin, Mark Stanton, and *Evelyn Satinoff; Bottom Row: Judy Stern, Joanne Weinberg, Mike Hennessy, and Bruce Overmier. *Deceased.

FIGURE 2.
Dr. Seymour “Gig” Levine. Photo taken on a fishing trip with Mike Hennessy, ca. 1977.