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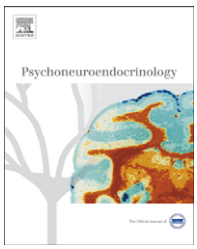

# Behavioral and physiological effects of an infant-neglect manipulation in a bi-parental, twinning primate: Impact is dependent on familial factors

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**Summary**
Experimental animal studies and epidemiological and clinical human studies demonstrate that atypical infant-caregiving can exert short- and long-term effects on offspring phenotype, including increased long-term risk of affective disorders. Whilst the early environment is therefore a major determinant of behavioral, physiological and neurobiological phenotypes, the effects of early adversity exhibit individual variation, presumably due to differences in environment–genotype interactions. Twin studies provide a powerful model with which to study such interactions. However, human twin studies rarely include analysis of genotype–environment interactions or of individuals exposed to extreme environments, and rat studies have rarely attempted to utilize littermates (i.e. dizygotic twins) to investigate environment–genotype interactions. Here, we report on the effects of repeated deprivation of caregiving in the common marmoset, a primate that exhibits dizygotic twinning and bi-parental care. Breeding pairs each contributed early deprived (ED) twins and control (CON) twins, thereby allowing for the study of effects of ED, parentage and ED-parentage interaction. Significant ED × parentage interaction effects were obtained for basal urinary, plasma and cerebrospinal-fluid cortisol titers (infancy–adolescence), and basal levels of social and maintenance behaviors (juveniles); basal urinary cortisol titers during a 2-week period of repeated psychosocial challenge (juveniles), and social and exploratory behavior during psychosocial challenge (juveniles). Significant main effects of ED were obtained for: basal levels of time spent in contact with parents (ED > CON; juveniles) and in locomotor activity (ED < CON; adolescents); basal and psychosocial-stress-related systolic blood pressure (ED > CON; juveniles); time spent in locomotor activity (ED < CON), contact calling (ED < CON) and exploring novelty (ED > CON)

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during psychosocial challenge (juveniles). This study provides evidence for long-term effects of early environment on bio-behavioral traits and states in marmosets specifically, and the importance of including parental factors in developmental studies in mammals generally.


## 1. Introduction

In mammals, infancy is characterized by species-typical interactions with the mother, as well as additional caregivers in some species. These interactions provide specific forms of infant stimulation that ensure survival and promote growth and development under conditions of homeostasis. Therefore, it is widely accepted that whilst complex physiological and neurobiological systems are in a state of marked plasticity in infancy, the necessary dynamics in terms of gene and protein expression on-going in these systems occur against a background of homeostasis. Furthermore, for maintenance of such homeostasis, environmental input in the form of appropriate caregiving is essential. Conversely, this period of dynamic plasticity can also confer increased vulnerability to adverse environmental input, where adversity refers to inputs that lead to stress responses, i.e. loss of homeostasis, with both short- and long-term detrimental effects. By extrapolation, it will be clear that inadequate caregiving, in the form of aggressive over-stimulation or neglectful under-stimulation, either spontaneous or experimental, constitutes the major form of early environmental adversity. There is growing evidence from animal studies that experimental exposure to deprivation of caregiving can induce short-term stress responses in infants (Levine et al., 1992; Sanchez et al., 2001), and can lead to long-term effects on neurobiological, physiological and behavioral phenotypes (Newport et al., 2002; Plotsky et al., 2005; Sanchez et al., 2005) Furthermore, human clinical and epidemiological studies demonstrate that adverse early environments can predispose individuals to develop vulnerability traits for as well as episodes of psychiatric disease, in particular depression and anxiety disorders, across development and into adulthood (De Bellis et al., 1999a, b; Heim and Nemeroff, 2001; Pine and Cohen, 2002; Penza et al., 2003; Teicher et al., 2003).

Neglect is the most frequently identified form of child maltreatment. Defining and applying the term neglect is complex in children, as are the actual measurement of neglect and its relationship to specific outcomes. Broadly, neglect can be categorized into the following subtypes: (a) failure to provide food, medical care, clothing, shelter, hygiene and sanitation, (b) lack of adequate supervision, (c) emotional neglect (Dubowitz et al., 2005; English et al., 2005a). Neglect often co-occurs with poverty (Sedlack and Broadhurst, 1996), maternal depression (Kotch et al., 1999), and other types of maltreatment (Dong et al., 2004), each known to impact on child development directly. It has been reported that neglect is associated directly in the child with impaired social and daily-living skills, externalizing and internalizing behavioral problems, and depression and withdrawal (Aber et al., 1989; Dubowitz et al., 2002, 2005; English et al., 2005b). Spontaneous neglect is rare in well-maintained rodent and primate species in the laboratory, but these species do provide important opportunities for detailed description of typical parental care and offspring development, and for controlled prospective studies based on putative neglect-like manipulations.

The homeostasis-stress systems of the hypothalamic–pituitary–adrenal (HPA) axis and sympathetic autonomic nervous system (sympANS) are proposed to exert central roles in the etiology of these inter-relationships. These systems exhibit (i) acute stress responses in infants exposed to caregiving deprivation, leading to short-term changes in neurobiological plasticity with long-term effects on phenotypic development (Hofer, 1994; Blumberg and Sokoloff, 1998; Zhang et al., 2002; Kippin et al., 2004), and/or; (ii) permanently altered basal activity or stressor reactivity, and thereby continuous influence on neurobiological and behavioral phenotypes throughout development and into adulthood (Weaver et al., 2001, 2004; Ladd et al., 2004; Plotsky et al., 2005). Overall, studies of children experiencing any type of maltreatment provide inconsistent findings in terms of effects on HPA activity (Heim and Nemeroff, 2001; Kaufman and Charney, 2001; Shea et al., 2004). We are not aware of any data on HPA or sympANS activity in neglected children per se. In Romanian orphans that experienced prolonged parental privation (Rutter et al., 2004), basal cortisol levels were high over the daytime hours relative to controls (Gunnar et al., 2001). Maltreated children with affective psychopathology in the form of post-traumatic stress disorder (PTSD) exhibit low peak-basal cortisol levels relative to controls (De Bellis et al., 1999a; Heim et al., 2004). The evidence is quite consistent for the relationship between early life adversity and childhood sympANS activity, in the direction of increased activation (Glaser, 2000). Maltreated children with PTSD exhibit increased systolic blood pressure (BP) and heart rate (HR) (Perry, 1994). Although understanding of long-term mediating mechanisms is sparse, evidence for short- and long-term responses of the HPA and ANS systems to infant–mother manipulations does exist for rats and monkey species, as summarized below.

In rats, a stress hyporesponsive period (SHRP) in terms of synthesis and release of corticotrophin (ACTH) and corticosterone (CORT) has been described; there are reduced basal levels of plasma ACTH and CORT and reduced reactivity to physical challenges, in pups relative to older conspecifics (Walker et al., 1986; Levine et al., 1992). That the SHRP is dependent on an intact pup–dam relationship, and can be disrupted by various pup–dam manipulations, is probably the most striking evidence to-date for the importance of maternal care to at least short-term homeostasis (e.g. Levine et al., 1992; McCormick et al., 1998). For the ANS, rat pups deprived of maternal care for a 24-h period exhibit altered central levels of norepinephrine,