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Biological perspectives on the effects of early psychosocial experience

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ABSTRACT

There is much current interest in how adverse experiences early in life might affect certain elements of physiological, behavioral, and psychological functioning across the lifespan. Recent conceptual frameworks for studying the effects of early experience have involved constructs such as experience-expectant, experience-dependent, and experience-adaptive plasticity. The latter construct is related to comparative models of developmental programming which posit the persistence of biological adjustments to the early caregiving environment. We briefly review such models and their translational implications. We then turn to human development and focus on the effects of large changes in children's life courses as tests of hypotheses related to early experience effects. In particular, the effect of early institutionalization on children's brain and behavioral development after changes to adoptive families or foster care is used as an example of a research area in which programming hypotheses have been proposed.

Introduction

Although some theorists have appropriately questioned the utility of the concept of experience as a distinct, external influence on the developing individual (e.g., Overton, 2004), the last few decades have continued to see vigorous debates among developmental scientists concerning the role of early experiences in shaping perceptual, cognitive, and social development. The issue of particular relevance in the current review concerns the extent to which exposure to certain aspects of the early rearing environment affects later outcomes. Following a brief overview of this broad area, we focus on two main questions. First, how current work on developmental programming relates to more established

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constructs such as experience-expectant and experience-dependent plasticity. As part of this, we also consider how rodent models of the biology of early experiences might inform studies of human development. Second, we discuss one particular paradigm for studying the effects of early adverse psychosocial experience in humans: examining the effect of drastic changes in the environments of children who had previously experienced institutional care. In doing so, we focus on two particular sequelae of early institutionalization: cognitive impairment and indiscriminate approach behavior.

In the mid-twentieth century, the principal viewpoints concerning the effects of early psychosocial experience were framed through the psychoanalytic and behaviorist paradigms, both of which were characterized by the notion that the effects of early experience were long-lasting and difficult, if not impossible, to reverse (for review see Kagan, 1998). However, consistent with wider changes within psychology at the time, the 1970s saw a move toward less deterministic approaches in the study of early experience. More dialectical viewpoints emerged which emphasized continual change and plasticity of behavior across the lifespan, in part based on descriptions of remarkable recoveries of individuals from early adverse conditions, once those conditions had been remediated (e.g., Clarke & Clarke, 1976). However, this broad questioning of persistent early experience effects was supplanted by research in the 1980s and 1990s which showed increasing evidence for early psychosocial risk factors for later psychopathology (for review see Rutter, 1999). In contrast to earlier deterministic approaches, this work was influenced by an increasing awareness of the heterogeneity of the effects of early adverse experience, both within individuals (i.e., that different capacities were affected in different ways) and between individuals, with work on the latter focusing on the concept of resilience. Importantly, this work also focused interest on mechanisms which indirectly promote the long-term effects of early experiences, primarily through a chain of interactive effects (Sroufe & Rutter, 1984).

While wider contextual influences remained an important consideration (Bronfenbrenner, 1977), developmental psychopathologists began to examine how proximal psychological mechanisms, such as attentional biases or information processing styles, may mediate the persistent effects of early adverse experience (e.g., Dodge, Bates, & Pettit, 1990). In line with recent trends towards a more integrative approach to understanding the relation of neurobiological processes to behavior and cognition (Marshall, 2009), there has also been increasing interest in the role of neuroscience in evaluating the continuity between early experience and later outcome (Cicchetti & Curtis, 2006; Gunnar, 2003; Pollak, 2005). Part of this interest has come through the establishment and consolidation of an extensive psychobiological literature on the neural changes accompanying various types of environmental experiences in various mammalian species (e.g., Rosenzweig & Bennett, 1996) including the physiological concomitants of early social experiences such as maternal separation (e.g., Levine, 2001; Polan & Hofer, 1999) as well as the effects of natural variations in maternal behavior on offspring later in life (e.g., Meaney, 2001). This comparative literature has been particularly influential in shaping current research and theory on the biology of early experience effects. A cogent illustration is the work of Greenough and colleagues (e.g., Greenough, Black, & Wallace, 1987), whose concepts of experience-expectant and experience-dependent processes are based in the comparative literature and continue to be invoked in many contemporary discussions of the effects of early experience. These constructs are discussed in more detail below, followed by a consideration of the more recent, hybrid construct of experience-adaptive programming.

Experience-expectant, experience-dependent, and experience-adaptive processes

Resembling the concept of critical periods, experience-expectant models of development posit that appropriate stimulation within a specific time frame is required for species-typical development to proceed (Greenough et al., 1987). The expected experience is usually characterized as having features with survival value that would be common to all individuals in that species. Thus, the typical consideration of experience-expectant programming is that development is likely to be permanently and adversely affected when exposure during a critical period is outside the typical range of environmental variation, with subsequent exposure to typical environments having no effect. As with critical period models, individual differences in outcome are not expected or considered, since all individuals would be equally affected by the adverse experience.

In humans, strong evidence for the operation of experience-expectant processes in the form of prototypical critical periods is hard to find, since "humans retain significant plasticity throughout development" (MacDonald, 1985, p. 180). In contrast, critical periods for certain aspects of behavioral development in other species have been well documented. These include birdsong in oscine songbirds (e.g., Nottebohm, 2005) and auditory localization in the barn owl (e.g., Knudsen & Knudsen, 1990), as well as the classic neurobiological work on the mammalian visual system by Wiesel and Hubel (1965). The latter authors noted the permanent effects of early monocular deprivation on the behavioral and neuroanatomical manifestations of ocular dominance in the mammalian visual system. One guiding principle from this work is that, in contrast to partial deprivation which provides aberrant sensory input, behavioral and anatomical changes resulting from complete deprivation (i.e., the complete absence of any stimulation) are more readily modified by the later restoration of typical sensory input. This reinforces the "expectancy" component of experience-expectant plasticity, such that if no relevant experience is present, the offset of critical periods may be extended (see Hensch, 2004; Knudsen, 2005). An additional point here concerns the problem of specifying what is meant by experience. In discussing their construct of experience-expectant plasticity in the context of human development, Greenough et al. (1987) note that "we suspect that some types of 'expected' experience may rely largely on the infant to produce them" (p. 545). This relates to one particular issue that is prevalent in work on early experience, which is a tendency to pit the individual against their environment, a dichotomous approach that is not supported by current thinking in developmental systems theory (Marshall, 2009; Overton, 2006). We will not explore this issue in detail here, although it is clear that it has a great deal of importance for understanding developmental processes more generally.

In contrast to experience-expectant processes, experience-dependent processes are less reminiscent of the critical period concept. Experience-dependent processes optimize "individual adaptation to specific and possibly unique aspects of the individual organism's environment" (Black & Greenough, 1986, p. 14), with an emphasis on lifespan plasticity and individual differences. Rather than stressing the importance of particular experiences in a specific time frame, experience-dependent processes involve sequential dependencies where mastering one skill is dependent on having previously learned other skills. As such, experience-dependent processes are seen as promoting plastic adjustment or adaptation to current environments across the lifespan.

In addition to the constructs of experience-expectant and experience-dependent plasticity, a third construct has recently emerged which combines elements of both these processes. With origins in diverse literatures concerning the influence of the prenatal and early postnatal environment on later health outcomes (Barker, 1994) as well as in developmental evolutionary psychology (Belsky, Steinberg, & Draper, 1991), the concept of experience-adaptive programming posits another mechanism by which early experience may have persistent effects (Rutter, 2002). As with experience-expectant models, experience-adaptive models propose that experience within a certain time frame has a persistent effect on the development and maintenance of a particular behavior, with a limited level of subsequent plasticity in response to a later change in the environment. However, drawing on the concept of experience-dependent models, models of experience-adaptive programming also involve a strong consideration of individual differences. Specifically, experience-adaptive models emphasize the adjustment of individual functioning to the specific characteristics of the early environment, but with less emphasis on continuing plasticity than in experience-dependent processes.

It should be noted that the three constructs outlined above are not necessarily distinct, and as such they only provide a loose framework for models of early experience. For instance, it could be argued that there is an adaptive component to experience-expectant processes, with early changes in sensory and perceptual systems serving as adjustments to the idiosyncrasies of the individual's environment and their own physical makeup. However, we argue here that the concept of experience-expectant plasticity (or critical periods) has usually been considered in the context of the binary (all-or-nothing) effects of deprivation that are well outside the range of environments that might be typically encountered (MacDonald, 1985). In contrast, the construct of experience-adaptive plasticity is more closely related to the construct of developmental programming and has placed individual differences to the fore, in the context of a wider range of environmental conditions (Rutter, O'Connor, & The ERA Study Team, 2004).

Early experience and developmental programming: comparative perspectives

The concept of experience-adaptive programming is closely related to a particular model of developmental programming in which early exposure to adverse physiological environments influences the development of various bodily systems, with implications for health across the lifespan. This link has been extensively discussed in the realm of prenatal development, especially with regard to the consequences of fetal undernutrition. Drawing on evidence that low birth weight in term infants is associated with a range of increased health risks throughout life, Barker (1994) proposed that the nutritional environment experienced by the fetus programs the homeostatic set points of physiological systems responsible for various key metabolic functions. One implication of such experience-adaptive programming models is that if the environment changes later in development, the organism may not be well equipped to meet the challenges of the new setting. For instance, if an individual who had experienced undernourishment in utero is exposed to a large change in the nutritional environment (e.g., a large increase in dietary intake) postnatally, their metabolic systems may be unable to adjust to this change, resulting in an increased likelihood of adverse health outcomes such as diabetes (Barker, 1999). This lack of a capacity for later change is often referred to as reflecting the early programming of metabolic systems, although Bateson (2007) has suggested that the use of the term "programming" obscures the notion that that this form of developmental plasticity is environmentally elicited.

Although the original focus of the developmental programming work was on the lasting effect of early prenatal nutritional deficiency, there has been much recent interest in the potential role of psychological influences, such as maternal anxiety, in the prenatal programming of certain biological systems related to stress regulation (e.g., Talge, Neal, & Glover, 2007; Weinstock, 2008). These programming models primarily involve the effects of early maternal stress on the development of the hypothalamic–pituitary–adrenal (HPA) axis (Seckl & Meaney, 2004). The concept of programming of HPA axis functioning by early psychosocial experience has also been applied to the effects of postnatal rearing experiences (Meaney, Szyf, & Seckl, 2007). Indeed, this concept is the basis of a large literature within psychiatry and clinical psychology on the effects of early stress (e.g., Anda et al., 2006; Bremner & Vermetten, 2001; Kaufman, Plotsky, Nemeroff, & Charney, 2000). Much of this work is based around programming models of early psychosocial experience derived from the comparative literature, which we will now briefly discuss.

There is much current interest in how comparative work might inform links between early adversity and later outcomes in humans. While this question is certainly under debate (see Gottlieb & Lickliter, 2004), it provides a starting point for our discussion of the possible biological processes that may link early experience with later outcomes. One of the areas of particular interest in this review is the effect of early psychosocial adversity on later cognitive functioning. In this respect, one relevant line of comparative work has found that the pups of rat mothers that attend to them less tend to have deficits in various learning tasks in later development (Bredy, Humpartzoomian, Cain, & Meaney, 2003; Fenoglio et al., 2005; Liu, Diorio, Day, Francis, & Meaney, 2000; Vallee et al., 1999). Such variations in early maternal care have been associated with a number of neurobiological changes in the offspring that may mediate the effects on later cognitive abilities, including alterations in neurotransmitter or hormone receptor numbers and changes in certain aspects of hippocampal development (Champagne et al., 2008; Liu et al., 2000). For our purposes it is also important to note that this model has been framed in the context of experience-adaptive plasticity, with deficits in the early caregiving environment seen as a signal for the long-term need for an upregulated stress response system in the offspring. From this perspective, deficits in learning seen in the offspring may partly be an epiphenomenon related to the neurotoxic effects of stress hormones on certain aspects of brain functioning.

Another area of particular interest throughout this review is the effect of the early caregiving environment on later social approach behaviors. In the comparative literature, relevant rodent models have examined alterations in social behavior associated with variations in the early rearing environment (e.g., Branchi, 2009). Natural variations in the maternal care of rat pups have been linked to differences in social interactions such as play fighting in juvenile males (Parent & Meaney, 2008).

Furthermore, altering standard laboratory rearing in which a single male and female are paired to a communal nesting in which one male and three females are placed together alters the social behavior, but not cognitive abilities, of the pups when they become adults (D'Andrea, Alleva, & Branchi, 2007). Specifically, communal nesting results in adults that engage in more social interactions than those reared in standard laboratory conditions (Branchi, D'Andrea, Fiore et al., 2006; D'Andrea et al., 2007). These changes in social behavior are accompanied by various biological alterations such as increased levels of growth factors in various brain regions and increased neurogenesis in the hippocampus (Branchi, D'Andrea, Fiore et al., 2006; Branchi, D'Andrea, Sietzema et al., 2006).

In the rodent literature, one prominent physiological mechanism linking what rats experience as pups and behavioral outcomes in adulthood is the epigenetic modification of regions of the genome that control the expression of genes involved in the regulation of various biobehavioral systems (Cameron et al., 2008; Champagne & Curley, 2009; Meaney & Szyf, 2005). This modification occurs through alterations to the genome that do not alter the underlying genetic sequence but influence how the genome interacts with other molecules. Such epigenetic modifications have been found to influence the long-term effects of early experience on diverse behaviors such as stress responses (Meaney & Szyf, 2005; Weaver et al., 2004) and female reproductive strategies (Cameron et al., 2008). In terms of stress responses, serotonin and corticotropin-releasing factor are thought to be involved in mediating the effects of maternal behavior on the epigenetic modifications of glucocorticoid receptor gene expression in pups which appear to result in altered adult stress reactivity (Fenoglio et al., 2005; Korosi & Baram, 2008; Meaney & Szyf, 2005; Weaver et al., 2007). Other relevant models are currently being developed in mice (Rice, Sandman, Lenjavi, & Baram, 2008) in part to allow the use of powerful genetic manipulation techniques that are not typically used in rat models.

Understanding how the findings from the rodent literature translate to humans is clearly not straightforward (Gottlieb & Lickliter, 2004). However, recent work has suggested that variation in epigenetic modification across the lifespan plays a role in risk for psychopathology in humans. Epigenetic modifications appear to accumulate over the human lifetime and may be involved in the development of various psychological disorders (Fraga et al., 2005; Mill et al., 2008; Rosa et al., 2008). Concerning early experience more specifically, both maternal mood during pregnancy and the experience of abuse during childhood have been associated with epigenetic alterations in the regulatory region of a glucocorticoid receptor gene thought to play a role in later stress reactivity (McGowan et al., 2009; Oberlander et al., 2008).

An additional perspective provided by comparative work is to illuminate potential processes through which aspects of the early environment may be transduced into long-lasting epigenetic modifications. For instance, just as the serotonergic system is thought to partly mediate the effects of maternal behavior on epigenetic modifications in a glucocorticoid receptor gene in the rat pup (Meaney & Szyf, 2005; Weaver et al., 2007), recent findings in the human literature suggest that polymorphisms in the regulatory region of the serotonin transporter gene (5-HTTLPR) may interact with early environmental factors to confer increased susceptibility to depression (Brown & Harris, 2008). Although there is much to be worked out, it is clear that the comparative literature can provide considerable fodder for generating hypotheses concerning mechanisms related to possible programming effects in humans. However, it remains to be seen whether the translation of such models to human development can move beyond fairly general notions (Kaffman & Meaney, 2007), although recent work suggests that it can (McGowan et al., 2009). At the heart of this translation, however, there remain a number of difficulties. Some of these difficulties concern the vastly different cognitive and social capacities of humans in terms of how people construct their own experiences as well as the human capacity to reflect on one's own experiences (Rutter, 2007a). Another set of difficulties comes when we attempt to account for the multifaceted nature of early adversity that typifies studies of early development in humans. We now examine some of these difficulties in more detail.

Testing early experience effects in human development

In contrast to the highly controlled nature of much of the comparative work, testing hypotheses related to the possible programming effects of early psychosocial adversity in humans presents a vari-

ety of methodological and conceptual problems (Repetti, Taylor, & Saxbe, 2007). We will discuss a number of such problems, all of which conspire to present translational difficulties for extrapolating from the comparative work. One of the main obstacles to inference about the persisting effects of early adverse experience is that negative outcomes in children living in environments high in psychosocial risk could be due to the cumulative effects of adversity, rather than any special effects of early experience per se (Clarke & Clarke, 2000; Schaffer, 2000). Early adverse experiences during infancy often tend to be followed by adverse experiences during childhood, such that the effects of the early experience cannot be teased apart from the cumulative effects of experience over the entire time span. A related but often overlooked problem is that it is also difficult to show that a particular experience (of a positive or negative nature) has greater effects on later development when it occurs earlier in life as opposed to at a later age. In this respect it is challenging to definitively show that early experience has specific effects, rather than experience which occurs for a similar duration but which begins later (Ames & Chisholm, 2001; Bruer, 2002).

Despite the conceptual issues mentioned above, there are a variety of ways of exploring causation in developmental studies on early psychosocial risk (Rutter, 2007b; Rutter, Pickles, Murray, & Eaves, 2001). One strategy of particular interest here is to examine situations in which a large discontinuity arises in a child's environment, such as adoption or entry into long-term foster care following early experience in an adverse environment (O'Connor, 2003; Rutter, 2007b). In the case of children coming from severely deprived backgrounds, such a life change provides an opportunity to examine whether early adverse experience has persisting effects once the caregiving environment improves. Although there are various examples of such life changes, our focus here is primarily on a small number of recent studies examining the development of formerly institutionalized children (mostly from Eastern Europe) who were either placed into family care through international adoption or who entered into foster care within their home country. While being relevant to broader questions of early intervention and social policy (Millum & Emanuel, 2007; Nelson et al., 2007), such studies have also provided researchers with a unique opportunity to examine various theories concerning the effects of early adverse experience. One focus of this work has been whether early experience in an institutional environment has persistent effects on certain aspects of cognitive and social development. After briefly introducing this question, we examine some current models of continuity and change in behavior and cognition after early life changes in children exposed to early adversity.

Persistent effects of early adversity: the example of institutionalization

Across multiple countries and cultures, institutions have historically been a prevalent form of care for children who have been orphaned or abandoned. While there is a good deal of variability in the quality of institutional environments, common characteristics include low levels of environmental stimulation and a lack of consistent individualized attention from specific caregivers, sometimes accompanied by deficits (of varying degrees) in nutrition as well as exposure to a variety of pathogens (for review see Johnson, 2000). Studies of life changes of institutionalized children (e.g., placement into family care) are of particular interest since they allow contrasting models of early experience to be tested. Such studies also have the potential for a lasting impact on applied issues, ranging from the treatment of behavioral problems in post-institutionalized children (Gunnar & van Dulmen, 2007) and the improvement of current institutional environments (The St. Petersburg—USA Orphanage Research Team., 2008) through to policy decisions concerning institutionalization (Millum & Emanuel, 2007; Wolff & Fesseha, 2005) – issues that seem particularly pressing given the large number of children worldwide who are destined to grow up in institutional settings.

A view of early experience which stresses experience-dependent learning puts an emphasis on plasticity, and predicts that a drastic improvement of a child's environment after adversity (e.g., adoption following institutionalization) will be associated with a high level of recovery of functioning across a variety of domains (Clarke & Clarke, 1976; Clarke & Clarke, 2000). In contrast, models emphasizing experience-expectant or experience-adaptive programming would predict more persistent effects of the early institutional experience on later behavior. In particular, the experience-adaptive model would suggest that behaviors reflecting adaptation to certain aspects of the early institutional

environment may persist after a life change such as adoption, even if such behaviors are no longer appropriate for current circumstances. Building on prior work on institutionalization (e.g., Dennis, 1973; Goldfarb, 1945; Provence & Lipton, 1962; Skeels, 1966; Spitz, 1947; Tizard & Tizard, 1971), a number of research programs over the last two decades have attempted to study these issues from a scientifically rigorous standpoint using the natural experiment of institutionalized children who have been placed into family environments (for reviews see Gunnar, 2001; MacLean, 2003). Here we focus a small number of research programs concerning the effects of early institutionalization on two domains of development: cognitive functioning and social approach behavior (Rutter, 2006). While other persistent and dose-dependent effects of institutionalization have been noted (e.g., inattention/overactivity and quasi-autistic symptoms; Rutter, 2006), we chose to focus on cognitive deficits and social approach behaviors in part for the sake of brevity and in part because they may be associated with quite different underlying processes. Indeed, one key finding to emerge from work on post-institutionalized children is that different domains of development may be impacted in quite different ways by early experience, possibly reflecting the operation of different kinds of plasticity-related processes.

The effects of early institutionalization on generalized cognitive functioning

In their ongoing research program, Rutter and his colleagues in the English and Romanian Adoptees (ERA) study team have monitored the development of children who were internationally adopted into the United Kingdom from Romania (e.g., Rutter, 1998; Rutter, 2006; Rutter, Colvert et al., 2007; Rutter, Kreppner, & O'Connor, 2001; Rutter, O'Connor, & The ERA Study Team, 2004). In the ERA study, retrospective reports of children's abilities upon entry into the UK (which occurred at up to 42 months of age) suggested that a significant degree of cognitive impairment was present at the time of adoption (Rutter, O'Connor, & The ERA Study Team, 2004). In terms of the recovery of cognitive function following placement into families, most children showed dramatic improvements after adoption, with significant catch-up even in the group of most severely impaired children (e.g., between 6 and 11 years – Beckett et al., 2006). However, assessments at 4, 6, and 11 years showed that some degree of cognitive impairment persisted for a significant proportion of post-institutionalized children (Beckett et al., 2006; O'Connor et al., 2000; Rutter, 2006; Rutter, Beckett et al., 2007; Rutter, O'Connor, & The ERA Study Team, 2004). One particularly notable finding from this project has been that children adopted before the age of 6 months had significantly improved cognitive outcomes compared with children adopted after this age point (Beckett et al., 2006; Rutter, O'Connor, & The ERA Study Team, 2004).

The second research program considered here also concerns Romanian children who had experienced institutional care in their early development. The Bucharest Early Intervention Project (BEIP, Zeanah et al., 2003) was aimed at gathering scientific data to inform policy concerning the care of abandoned children (for study overviews and ethical considerations, see Millum & Emanuel, 2007; Nelson et al., 2007; Zeanah, Koga et al., 2006; Zeanah et al., 2003) and it employed a radically different methodology than prior adoption studies. This study implemented a design in which young children living in institutions in Bucharest, Romania (mean age 21 months, age range 7–33 months) were randomly assigned to one of two conditions: (1) moving to foster care that was provided by the BEIP infrastructure; (2) a "care as usual" condition in which children's situations took the natural course of caregiving arrangements for institutionalized children in Bucharest at the time. While some children in the latter group remained in institutions over the course of the study, many did not, instead being adopted within Romania, returned to their biological parents, or placed in an alternative care setting (e.g., government foster care). In this sense, the BEIP study examined the impact of a high-quality foster care intervention for previously institutionalized children in comparison to the natural course of placement changes for children living in institutions at the time of the study onset (Nelson et al., 2007).

Smyke and colleagues reported on the developmental status of the BEIP sample (then aged 6–33 months) prior to randomization (Smyke et al., 2007). Compared with a group of typical children living in the local community, institutionalized children as a group showed moderate levels of cognitive impairment as assessed using the Bayley Scales of Infant Development. Analysis of follow-up data

showed that children placed into foster care showed higher overall intellectual functioning at 42 and 54 months of age, compared with those in the care as usual group (Nelson et al., 2007). In addition, children placed into foster care between 7 and 24 months of age tended to have improved cognitive outcomes compared to those placed later, although even in these early-placed children, mean test scores did not attain the levels of the community comparison group.

While both the ERA and BEIP studies revealed a good deal of heterogeneity in children's responses to life course changes, these findings suggest some degree of persistent, dose-dependent effects of institutionalization on overall cognitive functioning, a notion which is also supported by other work in this area (for reviews see Gunnar, 2001; MacLean, 2003). From the perspective of this review, a key question concerns the biological processes involved in the association of early institutionalization with persistent cognitive deficits. One candidate model is based on the programming models that have been developed in the comparative literature (described above) and which emphasizes the lasting effects of early rearing experience on bodily stress response systems.

Early psychosocial stress as a mechanism for effects on cognitive development

One suggestion has been that cognitive deficits in post-institutionalized children are result of early exposure to neurotoxic levels of glucocorticoids as a result of chronically activated bodily stress responses. For instance, Chugani et al. (2001) made this suggestion based on their PET imaging findings from a group of ten children who had spent their first three years residing in very depriving institutions in Romania before being adopted into the US. Chugani and colleagues suggested that the behavioral and cognitive issues seen in this small group of children may be related to the hypometabolism that was observed in the medial temporal lobe and the inferior temporal cortex. The suggestion of Chugani et al. (2001) that dysfunction in these brain regions was due to the adverse effects of chronic stress responses is consistent with a literature concerning the deleterious physiological effects of high levels of glucocorticoids on neural functioning (Sapolsky, Romero, & Munck, 2000). A more recent suggestion that the cognitive and behavioral outcomes in post-institutionalized children may be related to HPA axis dysfunction triggered by early adversity comes from Stevens et al. (2008), who speculate that one mechanism behind persistent problems with inattention in post-institutionalized children in the ERA study "relates to the long term negative down-stream effects on neuro-transmitter branches. . ..and brain circuits. . . of early stress-related dysregulations of the hypothalamic-pituitary-adrenal axis" (p. 398).

The premise that early adversity leads to dysfunction of the HPA axis with subsequent adverse effects on brain and behavior occupies a central place in biological perspectives on childhood stress and maltreatment (Cicchetti & Walker, 2001). Early life adversity, such as parental loss or maltreatment, has been suggested to be linked to increased levels of stress reactivity and depression in adults (Heim & Nemeroff, 2001; Luecken & Lemery, 2004), with the mechanism behind this effect being a highly reactive or chronically activated HPA system (Essex, Klein, Cho, & Kalin, 2002). This perspective would propose that the cognitive deficits in institutionalized children who have experienced severe deprivation are partly a result of early and persistent HPA axis dysfunction, resulting in sub-optimal levels of glucocorticoids that may ultimately influence cognitive function. In this respect there are clear conceptual links to the comparative programming models of early discussed earlier, which also tend to emphasize characteristics of the early caregiving environment in relation to hypothesized dysfunctions of the HPA axis. In the following section we ask if such a model could be applied to the study of cognitive functioning in post-institutionalized children, and what the limitations of such an application might be.

Evaluating the model of psychosocial stress and cognitive deficits

In trying to relate early psychosocial stressors to HPA axis dysfunction and later cognitive deficits in post-institutionalized children, one relevant set of findings from the child development literature suggests that low levels of maternal responsiveness and insecure attachments are associated with increased cortisol levels in infants and young children (Bugental, Martorell, & Barraza, 2003; Nachmias, Gunnar, Mangelsdorf, Parritz, & Buss, 1996) and that sensitive caregiving buffers the reactivity of the

HPA system in mildly stressful situations. Similar findings across a range of ages and contexts support a notion that under typical conditions, bodily stress responses are buffered by the early caregiving environment (Gunnar & Quevedo, 2007). This buffering by sensitive caregiving may help maintain a long period of hyporesponsivity of the stress response from childhood through adolescence during which it is quite difficult to elicit significant cortisol elevations using mild stressors (Adam, Klimes-Dougan, & Gunnar, 2007).

A related view of potential stressors in institutional environments relates to the notion that seeking out and relating to attachment figures is an adaptive mechanism for promoting survival (Baumeister & Leary, 1995; Bowlby, 1969). Evolutionary psychology views "protective care" as one of a number of distinctive domains, each of which relates to an adaptive problem and which has been subject to evolutionary selection. From this perspective, "children may be thought of as designed by their evolutionary history to expect social interaction as a whole and parental care in particular" (Beaulieu & Bugental, 2007, p. 78). From an attachment perspective, the lack of sensitive caregiving as well as the lack of opportunities for forming an organized attachment – which are both common in institutional environments – would be considered severe stressors, since over evolutionary history, such situations would have represented a threat to children's survival. In turn, these stressors would be associated with a chronically active stress response.

According to a model of early psychosocial influences on stress responses, institutionalized children's physiological stress systems would be chronically reactive, since there may be little or no buffering of this reactivity by sensitive or responsive caregiving. In addition, the deficits in opportunities for forming consistent early attachments would also be considered a severe stressor. Such an account would also suggest that this chronically active or reactive stress system would be associated with cognitive delays, through the neurotoxic effects of elevated glucocorticoid levels on learning and memory abilities. Outside the context of institutionalization, a recent study proposed that chronic physiological stress responses in response to suboptimal caregiving were a possible mechanism behind children's reduced scores on cognitive tasks tapping memory abilities that are dependent on medial temporal lobe functioning (Farah et al., 2008). In this respect, it is notable that even within institutional environments of very poor overall quality, variation in caregiving quality (often in addition to the duration of institutionalization) is associated with children's cognitive status (Castle et al., 1999; Hunt, Mohandessi, Ghodssi, & Akiyama, 1976). One key observation comes from the BEIP study, with the finding that within institutions in Bucharest, observed variation in quality of caregiving (indexed by measures of sensitivity, stimulation of development, and positive affect towards the child) was positively associated with children's cognitive status (Smyke et al., 2007). Admittedly, it is difficult to know the directionality of this effect, because more cognitively advanced children may elicit higher quality care. Nonetheless, the effect on cognitive development of caregiving quality in this particular study was stronger than the effect of duration of institutionalization.

A psychosocial stress-based account of persistent cognitive deficits may also predict that the absence of an organized attachment in young children would be associated with cognitive deficits. In support of this, work with non-institutionalized samples has shown that children who do not show a coherent attachment behavioral strategy to their primary caregiver during reunions following brief separation (i.e., children classified as insecure/other) tend to have lower scores on standardized cognitive tests (Moss & St-Laurent, 2001; O'Connor and McCartney, 2007). O'Connor and McCartney (2007) suggest that since these children were unable to get their attachment needs met, "their continually activated attachment systems appear to impede their cognitive skill development" (p. 471). These authors further suggest that this continual activation of the attachment system inactivates exploratory systems and is associated with stress and anxiety. In samples of institutionalized children, where the lack of opportunities for establishing attachments is extreme, relations between cognitive status and attachment are not particularly clear. In the BEIP study, Zeanah, Smyke, Koga, and Carlson (2005) found that among infants and young children (6–31 months) living in institutions, cognitive status was not associated with measures of attachment organization, although the fact that any form of attachment organization was so rare in this sample suggests that the range may have been too restricted to see effects on cognitive development. Interestingly, in a follow-up assessment of the BEIP sample at 42 months of age, positive associations emerged between the presence of organized attach-

ment in institutionalized children and their cognitive status (Smyke, Zeanah, Fox, Nelson, & Guthrie, in press).

In terms of evaluating a model based on the lasting effects of early psychosocial stressors, it is quite difficult to parse out which aspects of institutional life (e.g., unresponsive caregiving vs. lack of opportunity for attachment) are most important in terms of influencing later cognitive abilities. One particular issue is the high correlation between multiple, potentially negative aspects of the institutional caregiving environment. For instance, it is difficult to parse out the influence of unresponsive caregiving *per se* from a high rate of turnover of caregivers (i.e., the lack of sustained contact with individual caregivers which would prevent the development of organized attachments), since both frequently co-occur in institutional environments. In addition, unresponsive caregiving and high caregiver turnover are also likely to be associated with other detrimental factors such as those noted in the institutional histories of children in the ERA study (e.g. a lack of toys, impersonal feeding of inadequate food, being confined to beds or cots, and being washed in cold water; see Castle et al., 1999).

With respect to disentangling possible influences on cognitive functioning, there are informative sets of findings from studies of institutionalized children who experienced responsive caregiving but who did not have the opportunity to form enduring attachments. One example of this comes from the classic studies by Tizard and colleagues, who followed the development of adopted children who had spent the early part of their lives in residential nurseries in the United Kingdom (Hodges & Tizard, 1989; Tizard, 1979; Tizard & Hodges, 1977; Tizard & Rees, 1974; Tizard & Rees, 1975). These institutions were characterized by far better environmental conditions than those experienced by children in the ERA or BEIP studies. In the nurseries, infant to caregiver ratios were low, and the infants were well cared for: "considerable efforts were made to stimulate them. . .and the nurses were encouraged to talk and play with them" (Tizard, 1979, p. 197). Toys were high-quality and plentiful, and there was a preschool setting for older children, in which children were read to and often went on outside trips, even sometimes being taken home with nurses on days off or weekends. What is particularly noteworthy about the Tizard studies is that these institutions, through their status as training institutions, were characterized by a very high rate of caregiver turnover. Tizard (1979) estimated that by the age of 4.5 years, an individual child may have been cared for by 50 different nurses (for a week or more at a time). There was therefore very little opportunity for children to form lasting attachment bonds with individual caregivers, and "the care they received, although kindly, was brisk, and certainly not intimate or personalized" (p. 197). Despite these characteristics of the caregiving environment, one key finding from Tizard's work was that children in the institutions were not impaired in their general cognitive functioning. However, it should also be noted that while the children living in Tizard's group homes had test scores in the normal range, on average these scores were lower than those of children who had been adopted out of the institutions at an earlier age point, although the nonrandom nature of these adoptions makes this finding hard to fully interpret (Zeanah, Smyke, & Settles, 2006).

Another relevant example here comes from the careful study of Roy and colleagues, who examined a sample of children growing up in contemporary group homes in the United Kingdom, in which the quality of care provided was relatively high (Roy, Rutter, & Pickles, 2000). The principal findings emerging from this study were that, compared with a group of children with similar backgrounds growing up in foster families, children from institutions showed a profile of attentional and social issues (Roy, Rutter, & Pickles, 2004) that ultimately impacted their academic functioning (Roy & Rutter, 2006). However, what is also notable is that standardized intelligence assessments showed no difference between the foster care and institutionalized groups, with both groups having mean scores in the typical range (Roy et al., 2000).

The main findings from the studies of Tizard and Roy suggest that an account based on the absence of an early, organized attachment may not best explain generalized cognitive deficits in post-institutionalized children. This would be consistent with recent suggestions that young children's stress responses can be buffered by responsive caregivers other than a primary caregiver (Gunnar, 2005). In terms of cognitive development, the suggestion is that institutionalized children who experience appropriate responsiveness by caregivers (albeit from a large number of different caregivers) as well as a relatively stimulating physical environment tend to show much less persistent generalized cognitive impairment than children experiencing more severe levels of deprivation (for further discussion see Gunnar, 2001; Rutter, O'Connor, & The ERA Study Team, 2004; Zeanah, Smyke et al., 2006).

Caveats in applying a psychosocial stress-based model

The biological model of chronic HPA dysfunction related to early psychosocial adversity is a focal point for many biologically-minded scientists interested in the effects of early rearing experience (Bremner & Narayan, 1998). However, there are a number of important caveats related to the translation of models which posit the programming of stress-related neurohormonal systems by early adverse experience.

First, even within the comparative literature there is evidence that early deprivation may not directly impact the HPA axis, except in quite severe conditions (Avishai-Eliner, Gilles, Eghbal-Ahmadi, Bar-El, & Baram, 2001). In addition, it seems likely that the widespread impact of early deprivation is being produced through multiple pathways that produce effects on many brain systems, not only the HPA axis (Meaney & Szyf, 2005). As mentioned earlier, it is also not clear that the early engagement of the HPA axis is solely responsible for the programming of later stress reactivity – the animal literature suggests that other neurotransmitters (e.g., serotonin) may actually mediate the initial effects of the caregiving environment. In human work there also remains a great deal of debate concerning the relations between stress, trauma, and dysfunction of emotional and cognitive brain systems in relation to HPA axis functioning (van Praag, de Kloet, & van Os, 2004). As discussed by Kertes, Gunnar, Madsen, and Long (2008), a close examination of the relations between early deprivation and later HPA axis activity across the human and comparative literatures reveals a complex picture, with discrepancies across species and contexts. For example, the relations between cortisol levels and child maltreatment are complex (Bruce, Fisher, Pears, & Levine, 2009; Cicchetti & Walker, 2003; de Bellis, 2005; Tarullo & Gunnar, 2006) and the relations of HPA dysfunction to cognitive deficits in children who have suffered abuse are not particularly clear (Eisen, Goodman, Qin, Davis, & Crayton, 2007). One important finding appears to be that rather than affecting tonic levels of glucocorticoids, chronic stressful experiences may be more likely to impact the diurnal rhythms of the HPA system (Gunnar & Vazquez, 2001). In this respect, it is notable that an intervention targeted at children in foster care, who are at risk for cognitive and behavioral problems associated with separation and psychosocial disruptions, was associated with changes in the diurnal rhythm of HPA axis activity (Fisher, Stoolmiller, Gunnar, & Burraston, 2007).

One further question concerning a stress-based account in relation to institutionalization is whether there is evidence of HPA axis dysfunction in institutionalized or post-institutionalized children. There is virtually no information on HPA axis functioning from young children living in institutional environments, although Carlson and Earls (1997) noted disruptions in the diurnal rhythm of cortisol production in 2-year-olds living in a Romanian institution. There is also some indication of HPA axis disruption in post-institutionalized children. Disruptions in the basal levels and rhythms of cortisol production were first noted in a small sample of internationally adopted children who had experienced severe institutional deprivation prior to adoption (Gunnar, Morison, Chisholm, & Schuder, 2001). Since that time, two studies have further examined cortisol levels in post-institutionalized children. Wismer Fries, Shirtcliff, and Pollak (2008) found that young children who had been adopted into the US from Eastern European and Russian institutions had prolonged elevations in cortisol levels after interactions with their adoptive caregiver, and those children who had experienced more severe conditions of neglect prior to adoption also showed elevated basal cortisol levels. To add to this picture, Kertes et al. (2008) examined basal salivary cortisol levels in a sample of internationally adopted children aged 7–11 years who had been adopted into the US at a mean age of 22 months. The children in this sample had experienced a diversity of pre-adoption contexts, and had spent an average of 11 months living in institutions, although there was a good deal of variability between children in this respect. Rather than revealing a main effect of early deprivation on cortisol levels, this study showed an association of delays in physical growth with the level of deprivation experienced prior to adoption. In turn, growth delay predicted aspects of basal cortisol levels (e.g., higher morning levels and larger diurnal decrease). Based on these findings, Kertes et al. (2008) suggest that long-term effects of early adverse psychosocial experience on the HPA axis may only be seen if children had been living under conditions of deprivation that were severe enough to impact physical growth (Kertes et al., 2008). It is important that such deprivation could be predominantly psychosocial: nutritional deprivation is not required to impact key aspects of physical growth, as suggested by

findings from the ERA sample that institutional deprivation had a persistent effect on brain growth (as indexed by head circumference) even in the absence of subnutrition (Sonuga-Barke et al., 2008).

Given that there is at least some evidence for HPA axis dysfunction in post-institutionalized children, what might be the mechanisms associated with such dysfunction? One suggestion here is that a focus on stressors that are directly related to caregiving tends to underplay the role of exposures that institutionalized children have to pathogens of various kinds as well as their increased likelihood of exposure to environmental contaminants (Johnson, 2000). For instance, it is well known that chronic middle ear infections are common in institutional settings, which may organize linguistic input in an aberrant fashion. Given the high rates of various kinds of infections, it is also important to note that the early immune response to infection involves the release of cytokines, which exert strong effects on the bodily stress response systems, especially the HPA axis (Maier & Watkins, 1998). This suggests that a focus on caregiving deficits and lack of attachment organization as being the primary sources of stress (as indexed by HPA activation) would be difficult to justify, especially since immune system function is also tightly tied to psychosocial functioning (Coe & Laudenslager, 2007). One particularly interesting study in this respect comes from the recent work of Shirtcliff, Coe, and Pollak (2009), who found evidence for persistent alterations in immune functioning (specifically, a high level of herpes simplex virus antibodies) in post-institutionalized children. This finding is particularly striking given that the children in this study were aged between 9 and 14 years, and had lived with adoptive parents in the US for between 3.5 and 13 years.

Caregiving quality, stimulation, and stress

While the above caveats do raise a number of important questions, a psychosocial stress account of cognitive deficits in institutionalized children has the advantage of being linked to a large and influential literature in biological psychiatry and comparative psychology. However, from a biological perspective, one other limitation of a stress-based account focusing on HPA axis dysfunction is that it tends to focus attention on learning and memory capacities that are mediated by medial temporal lobe structures (e.g., the hippocampus) which are thought to be particularly vulnerable to high levels of glucocorticoids (Sapolsky et al., 2000), an emphasis that comes from the adult literature on stress, depression (van Praag et al., 2004) and trauma (Bremner & Narayan, 1998). However, the cognitive deficits seen in institutionalized children appear to encompass multiple domains (Smyke et al., 2007; Zeanah, Smyke et al., 2006), including language development (Windsor, Glaze, Koga, & The BEIP Core Group, 2007), and not just those that would be mediated by the hippocampus or associated structures. Of interest here is a recent study by Farah and colleagues who found that in a (non-institutionalized) sample of young children living in poverty in the United States, parental nurturance predicted memory development, while general environmental stimulation (e.g., the presence of books/toys in the home) predicted language development (Farah et al., 2008). Thus, while stress-based mechanisms are likely to be one piece of the puzzle, a complementary proposal relates to the notion that the scaffolding for cognitive development occurs in the context of social interactions and interactions with the physical environment. Such a perspective would also suggest that a lack of stimulation is also an important contributing factor in institutionalized children's cognitive deficits. This idea is somewhat consistent with the findings from the studies of Tizard and Roy outlined earlier, which suggested that cognitive development is less impaired in institutional environments in which there are higher levels of environmental stimulation. However, in most cases, a highly routinized environment with little opportunity for child-directed play or contingent interactions with caregivers is very characteristic of institutional life (Provence & Lipton, 1962; Smyke et al., 2007; The St. Petersburg—USA Orphanage Research Team., 2005; Tirella et al., 2008).

While the stress/HPA axis account of cognitive deficits is rooted in a large literature in psychobiology and biological psychiatry, much less is known about how generalized deficits in stimulation (e.g., lack of opportunities for contingent communication and play) affect the developing brain. It remains difficult to specify the particular brain systems which may be impacted by a lack of early social stimulation, and our understanding of the biological mechanisms through which early social experience molds human brain development and cognitive development is limited (Thompson & Nelson, 2001). We suggest that part of this problem relates to the fact that cognitive development takes place across

a multiplicity of levels within a social context (Nelson, 2007; Rogoff, 2003; Tomasello & Carpenter, 2007; Vygotsky, 1962). This issue also reflects the predominantly internalist focus within cognitive neuroscience on information processing within individuals, rather than on the joint representations through which social development proceeds (Marshall, 2009; Semin & Cacioppo, 2008). Perhaps for this reason, the neurobiological investigation of social influences on cognitive development has been somewhat neglected, although recent work is beginning to rectify this (see Kuhl, 2007). In addition, the neurobiological processes involved in early social interactions are the focus of a number of research programs (for reviews see Grossmann & Johnson, 2007; Marshall & Fox, 2006). Work in this area has begun to unravel some of the brain systems involved in processing information from social stimuli such as faces (de Haan & Groen, 2006; Nelson, 2001), including the detection of eye gaze, which appears to be critical in fostering joint attentional processes that are an important vehicle for early learning (Van Hecke & Mundy, 2007). However, we still understand little about the development of such systems with respect to variations in early experience, although recent work is suggesting that there may well be experience-adaptive aspects of plasticity in the processing of faces during infancy (Scott, Pascalis, & Nelson, 2007).

Conceptualizing the persistent effects of early institutionalization on cognitive functioning

In summarizing various factors that might be related to persistent cognitive deficits following early adversity, it remains clear that simple explanations will not suffice. In addition, thus far we have glossed over one guiding principle from studies examining the remediation of the effects of early adverse experience by improvements in the rearing environment: that the extent of recovery can vary greatly between children and even between domains of functioning within the same child. In studies of post-institutionalized children, explaining this heterogeneity remains a major undertaking. Clearly, a large part of the issue here is that a variety of overlapping and possibly synergistic mechanisms are at work, something that also presents challenges when trying to develop translational models of early adverse experience which may be based in the much more controlled context of comparative work.

Depending on the specific circumstances, variation in the developmental course of cognitive deficits in institutionalized and post-institutionalized children is likely to be the result of a complex combination of early subnutrition, lack of stimulation, exposure to pathogens and other physical risks, and inconsistent caregiving, all of which would be expected to produce more serious deficits in situations where these factors co-occur, as well as with increasing duration of a child's institutional experience (Gunnar & Kertes, 2005). These factors are in addition to preexisting risk factors such as postnatal and prenatal exposure to neurotoxins (e.g., prenatal alcohol exposure, postnatal lead exposure), adverse perinatal events, as well as potential risk factors relating to genetic load. One related conceptual point here is that any account of the effects of early experience needs to assume transactional interactions between child characteristics and the caregiving environment, which are likely to be important even in the relative deprivation of institutional environments. As noted by Schaffer (2000), the implicit adoption of a unidirectional view of socialization has been an issue in early experience research more generally, a problem that is perhaps compounded when considering institutional contexts. One important contribution here would be to examine gene-environment interactions in the study of early institutionalization.

Given the complex array of influences and factors involved, the heterogeneity in cognitive outcomes for children both within institutions and across different institutional backgrounds is not surprising, although it remains very difficult to isolate individual causal factors (The St. Petersburg—USA Orphanage Research Team, 2005). The cumulative and likely synergistic effect of these multiple factors also helps explain why such large interventions (e.g., foster care, adoption) are needed to produce significant cognitive change in institutionalized children, although there is also evidence that improving certain aspects of institutional life can impact a variety of domains of children's development (Bakermans-Kranenburg, van Ijzendoorn, & Juffer, 2008; Groark, Muhamedrahimov, Palmov, Nikiforova, & McCall, 2005; Muhamedrahimov, Palmov, Nikiforova, Groark, & McCall, 2004), including cognitive status (Hunt et al., 1976).

Finally, one challenge for future investigations of cognitive status in relation to early adversity is to move beyond a focus on IQ as the primary index of cognitive development. The measurement of

general intellectual ability has provided a firm point of reference for investigations of the adverse effects of institutional environments on cognitive development as well as the partial remediation of these effects by placement in alternative care settings (e.g., Nelson et al., 2007). However, in order to unpack the processes involved, more specific measures are needed which tap in the functioning of various aspects of cognitive development. This point also broadly applies to relating biological measures to cognitive status. For instance, in the BEIP study it was possible to relate resting EEG patterns to the cognitive status of post-institutionalized children, but it was not possible to relate changes in cognitive functioning over time to changes in the EEG patterns (Marshall, Reeb, Fox, Nelson, & Zeanah, 2008). One suggestion here is to use tasks which tap more specific cognitive functions to examine changes in brain function that might be associated with institutionalization per se as well as with the extent of subsequent recovery after entry into an improved caregiving environment (Moulson & Nelson, 2009; Moulson, Westerlund, & Nelson, in press; Pollak et al., in press).

The effects of early institutionalization on social approach behavior

Having discussed links between early institutional experiences and generalized cognitive functioning, we now turn to the persistent effect of such experiences on another aspect of children's adjustment, that of social approach behavior. While cognitive deficits in post-institutionalized children are less apparent in conditions where institutions are better quality, indiscriminate behavior appears to be a relatively persistent consequence of the rapid turnover of caregivers that characterizes even higher quality institutions, where children are not undernourished and there is adequate cognitive stimulation. As noted above, while the children in the high quality institutions examined by Tizard did not have persistent issues in terms of their general intelligence and sensorimotor functioning, these children did have problems with response inhibition, inattention, and concentration as reported by their teachers (Tizard, 1979). They were also reported by parents to be overly friendly towards unfamiliar people, a finding which has been confirmed in other studies of post-institutionalized children (Chisholm, 1998; Rutter, Colvert, et al., 2007; Rutter, O'Connor, & The ERA Study Team, 2004). This finding is of particular interest here, since indiscriminate approach behavior towards unfamiliar people has been suggested as reflecting the operation of an experience-adaptive programming mechanism (Rutter et al., 2004).

Rutter's ERA study included assessments of indiscriminate social behavior in children adopted out of institutions into the UK. Compared to a control group, post-institutionalized children were more likely to readily go off with a stranger, and not "check-back" as often in anxiety-provoking situations, a finding that persisted from early childhood into adolescence (Rutter, Colvert, et al., 2007). Two other findings related to this tendency were that the experience of institutionalization lasting beyond six months of age was a strong predictor of later disinhibited behavior (Rutter, Colvert, et al., 2007; Rutter et al., 2004), and that the level of indiscriminate behavior in later childhood was not related to the quality of caregiving in the adoptive home. Although indiscriminate behavior showed less persistence over time than cognitive impairment, Rutter et al. (2004) suggested that the level of indiscriminate behavior found at the early childhood assessment in the ERA sample could represent a form of developmental programming. In discussing these findings, Rutter and colleagues invoked the notion of experience-adaptive programming to suggest the possibility that this persistence reflects "an effect on brain structure and functioning that has come about as a means of adaptation to the environmental circumstances operating at a sensitive period in development." (Rutter, Colvert, et al., 2007, p. 17–18; see also Rutter, 2006). In this formulation, later indiscriminate behavior may reflect a persisting response to early exposure to the high rate of caregiver turnover that characterizes institutional life. In invoking the possibility of such a programming effect, Rutter et al. (2004) proposed that disinhibited behavior "may be adaptive in an institutional environment even if it is clearly maladaptive in the adoptive home" (p. 91) and that "in an institutional environment with a lack of personalized caregiving and a very large number of rotating caregivers, it could be adaptive to seek interactions in a non-selective way in order to make some relationship with the caregivers who come and go." (p. 91–92).

If indeed the nature of early caregiving experiences has a persistent influence on the organization of later social behavior in the post-institutionalized child, what might be some candidate biological processes through which this persistence might be mediated? At this point our understanding is very

limited. Rutter (2006) suggested that the effects of chronic physiological stress responses on neuronal functioning may not explain the persistence of indiscriminate behavior. Instead, he noted the possibility that indiscriminate behavior is a consequence of early programming of neuropeptide systems, specifically those involving oxytocin (OT) and vasopressin (AVP) which have been associated with reproductive, bonding and affiliative processes in a variety of mammalian species (Carter, 1998). There is some suggestion that central OT plays a role in affiliative processes in adult humans (Kosfeld, Heinrichs, Zak, Fischbacher, & Fehr, 2005) as well as in early mother-infant interactions (Feldman, Weller, Zagoory-Sharon, & Levine, 2007). Very little is known, however, about the effects of early social experience on the OT system, although it has been reported that male monkeys who were socially deprived in early development had reduced central levels of oxytocin as adults (Winslow, Noble, Lyons, Sterk, & Insel, 2003).

In terms of developmental work in humans, Wismer Fries, Ziegler, Kurian, Jacoris, and Pollak (2005) measured urinary OT and AVP in a group of children with a mean age of around 4.5 years who had been adopted into the United States from Romanian institutions at an average of 17 months of age. Compared with a comparison group of same-age children, the post-institutionalized children had lower levels of OT after an interaction with their mothers as well as lower baseline levels of AVP. This study represents an important and novel attempt to investigate the neurohormonal correlates of early experience in post-institutionalized children. However, interpretation of peripheral OT and AVP levels is challenging, in part because of challenges with assaying and in part because the levels and neuromodulatory effects of these hormones may be quite different in the periphery compared with the CNS (although see Carter, 2005). Despite such challenges, there remains much interest in these neuropeptides and their possible role in the development and maintenance of early social bonds (Cacioppo et al., 2007) as well as in the effects of early experience on these neurohormonal systems (Meinlschmidt & Heim, 2007). In part, this reflects an intense continued interest in the role of the early caregiving environment in influencing later social development, and the possible mechanisms by which such influence may occur (Feldman, 2007; Fonagy, Gergely, & Target, 2007). However, there remains much work to be done before we have anything more than a cursory understanding of the biology of disinhibited behaviors in institutionalized and post-institutionalized children. For example, the relation of disinhibited approach behaviors to the formation of selective attachment is controversial and not particularly clear (O'Connor and Zeanah, 2003), yet one suggestion from the comparative literature is that similar neurochemical systems are likely to be involved in the formation of selective attachments as well as in the development of affiliation with conspecifics (Nelson & Panksepp, 1998). In addition, the specific brain circuitry that would be impacted by programming effects on the OT and AVP systems needs to be examined – perhaps with an emphasis on links to dopaminergic systems involved in reward (Depue & Morrone-Strupinsky, 2005).

Although there are many questions that need to be addressed, a programming effect on the neurohormonal systems associated with affiliative behavior remains a candidate for explaining the persistent indiscriminate approach in post-institutionalized children. This particular suggestion brings up a number of questions: for example, the original developmental programming hypothesis (concerning low birth weight and later risk for health problems) construed fetal metabolic adjustments to the intrauterine environment as being maladaptive and pathogenic. However, it has also been proposed that such responses to adverse environments may in fact be adaptive in that such phenotypic plasticity has a predictive function (e.g., Gluckman & Hanson, 2006). From this perspective, the early, lasting adjustment of the set points of fetal metabolic systems in response to prenatal undernutrition is a strategic response based on a prediction that an impoverished fetal environment is likely to be followed by an impoverished postnatal environment. This adaptation to the fetal environment (i.e., restriction of fetal growth in response to undernutrition) is therefore thought to position the organism for survival in postnatal conditions (Bateson et al., 2004; Hales & Barker, 2001).

While a predictive element of early adjustments to the fetal environment may be intuitively attractive, it should be noted that it remains controversial whether such long-lasting adjustments to metabolic systems based on the early nutritional environment should be seen as a strategic response of the organism. An alternative possibility is that these adjustments constitute a non-predictive response to current environmental demands that organizes later development in a more experience-dependent fashion (Bogin, Silva, & Rios, 2007; Jones, 2005). In this sense, we suggest that further clarity is needed

when the constructs of experience-adaptive programming or biological programming are used in the context of early psychosocial experiences in humans. There are cases where an evolutionary account of later behavior based on early experiences has been offered, most notably with regard to early familial adversity (e.g., father absence) being associated with earlier onset of menarche in adolescent girls (Belsky et al., 1991; Belsky et al., 2007; Chisholm, Burbank, Coall, & Gemmiti, 2005; Ellis & Essex, 2007). Despite the hormonal mechanisms associated with such an account being poorly understood, this model is more firmly based in an evolutionary account than any of the theorizing about the effects of early experience on previously institutionalized children. For further progress here in relation to indiscriminate social behaviors, it may be helpful to engage more deeply with the question of what the "adaptive" component of experience-adaptive programming hypotheses might refer to.

In considering the biological processes related to deficits in social relatedness in post-institutionalized children, some recent, potentially fruitful work has moved the emphasis away from hormonal systems involved in affiliation to the processes that are involved in social cognition more generally. Bruce, Tarullo, and Gunnar (2009) examined disinhibited behavior in a sample of internationally adopted children aged 6–7 years who had come from either institutional or foster care backgrounds. Interestingly, while disinhibited behavior was increased relative to a non-adopted sample, this type of behavior was also present to a significant extent in children who had been adopted from foster care, the majority of whom had experienced a single foster care placement. Bruce, Tarullo, et al. (2009) suggest that children adopted from foster care have experienced a loss of a consistent caregiver, whereas the institutionalized children had experienced an absence of any consistency in caregiving. Clearly, further work is needed here, especially since the experience-adaptive programming model of disinhibited behavior puts the emphasis on a high rate of caregiver turnover as the driving mechanism behind the persistence of this behavior. Another salient finding from the study of Bruce, Tarullo, et al. (2009) is that disinhibited behavior was related to inhibitory control (as measured using go/no-go and delay of gratification tasks). They suggest that children showing these behaviors "lack the required inhibitory control abilities to regulate their behavior during social interactions. . ..despite awareness of the inappropriateness of their behavior" (p. 168). As noted by Bruce, Tarullo, et al. (2009), it remains puzzling why indiscriminate behavior appears to be a post-institutional syndrome rather than a pattern of behavior which characterizes other groups of children who evince poor inhibitory control (e.g., children with ADHD).

The finding of Bruce, Tarullo, et al. (2009) of a relation between inhibitory control and indiscriminate behavior relates to an influential literature suggesting that the development of inhibitory control may be one important aspect of early social cognition (Carlson & Moses, 2001). Indeed, Tarullo and Gunnar (2005) proposed that the indiscriminate approach behavior frequently seen in post-institutionalized children reflects an insensitivity to social cues, which could reflect problems in mentalizing and perspective-taking. In support of this argument, performance on theory of mind tasks (Tarullo, Bruce, & Gunnar, 2007; Yagmurlu, Berument, & Celimli, 2005) and emotion understanding tasks (Camras, Perlman, Fries, & Pollak, 2006; Vorria et al., 2006) has been found to be impaired in post-institutionalized children. Such issues could have their origins in caregiving experiences in infancy, although there is a complex debate about this issue (Wellman, 2002). Putting aside this debate, perhaps high quality institutional environments such as those studied by Tizard are "good enough" to promote the typical development of general intelligence, but the specific characteristics of such environments are unlikely to completely provide the scaffolding that is thought to be important in the development of social cognition and the understanding of social norms. There is a good deal of evidence that supportive caregiving environments in which mental states are referred to and discussed, as well as the intricacies of narratives between caregiver and child, are important influences in promoting the development of social cognition (Fernyhough, 2008; Nelson, 2007). While part of this influence may lie in the general promotion of language development, which is likely an important factor in mentalizing (Milligan, Astington, & Dack, 2007), recent work suggests that the specific content of language (e.g., the use of mental state terms) is also important (e.g., Meins et al., 2002), content that may well be lacking in institutional environments.

Despite the promising connections outlined above, there remains surprisingly little work on social cognition and its determinants in institutionalized or post-institutionalized children. One exception is the recent analysis by Colvert et al. (2008) who assessed theory of mind and executive function in rela-

tion to indiscriminate social behavior in the ERA sample at 11 years. One finding of note from this study was that higher rates of indiscriminate behavior were associated with poorer performance on the theory of mind and executive function tasks. However, there was no suggestion that problems with theory of mind or executive function mediated the severity of disinhibited behavior. While this is only one study, these findings do present problems for accounts of social approach problems that emphasize a primary role for social cognitive or executive function deficits.

Returning to the general theme of biological processes, there are clearly a number of disparate accounts of indiscriminate behaviors that need to be integrated. While biologically-based accounts of the persistence of approach-related behaviors have tended to emphasize the possible dysfunction of neurohormonal systems thought to be involved in affiliative behavior, other developmental accounts have tended to emphasize deficits in capacities such as executive function and social cognition. There is a good deal of developmental work on the brain systems, particularly those in frontal cortical regions, associated with these latter capacities (Anderson, Jacobs, & Anderson, 2008; Sabbagh, 2006). However, an organization or integration of these accounts with the neurohormonal perspective on affiliation, especially with respect to indiscriminate behavior (although perhaps also social affiliation more generally) would be particularly helpful (Marshall & Fox, 2006).

Conclusions

In the initial part of this review, we noted that comparative work may provide signposts for human work on the effects of early psychosocial experience, although there remain many significant problems that are encountered in translation. Kaffman and Meaney (2007) suggest that there are multiple possibilities for examining the impact of early caregiving on learning that can be addressed at the level of biochemical systems, and that comparative work will aid in generating hypotheses (for a discussion of other translational possibilities, see Gunnar, Fisher, & The Early Experience Stress & Prevention Network, 2006; O'Connor and Cameron, 2006). Among others, one perennial issue here is how to relate highly controlled laboratory experiments to the kinds of multifactorial, dynamic contexts of human studies (Gottlieb & Lickliter, 2004). In our view, a related obstacle to further progress concerns the current lack of knowledge about the neurobiological processes that are associated with sensitive periods for higher cognitive functions and social behaviors in humans. As noted at the beginning of this review, the constructs of experience-expectant and experience-dependent plasticity partly originated in Greenough and Black's classic works from the late 1980s. While originally founded in behavioral neuroscience, over time these constructs have become widely applied, and in the course of this application, have often lost their coupling to neurobiology. This is somewhat unfortunate, but in many ways it reflects the continued lack of understanding of the neural processes involved in the establishment, maintenance, and restriction of sensitive periods in humans. As part of their conclusion, Greenough et al. (1987) made a prediction about neurobiological work on critical periods in humans: using the example of language development, these authors suggest that neuroscience may come to illuminate findings concerning different critical periods for different aspects of language development. Specifically, they note that "after examination of appropriate brain tissue, findings of different time courses or the involvement of other brain regions can reflect back on the original theory" (p. 553). However, while the ensuing two decades have seen developments in our understanding of the nested nature of sensitive periods for language development, the neurobiology of these sensitive periods remains poorly understood, and remains couched in general terms such as "neural commitment" (Kuhl, 2007, p.111).

In the second part of this review, we examined one example of early adverse psychosocial experience in human development – the experience of early institutionalization. In particular, we examined the effects of early institutionalization on generalized cognitive functioning as well as on one aspect of children's later social behavior (indiscriminate approach). The picture with respect to how early institutionalization may become associated with later cognitive and social outcomes is clearly very complex, and although some recent work has begun to hint at the neural systems that might be impacted by early institutional experience, our understanding of the specific processes that might be involved in linking early adverse experiences and later outcomes is still quite limited. While much work is being

directed at this issue, it seems that a good deal of research is still needed. One cautionary note is that for real progress in this domain we may need to embrace a more dynamic, integrative approach that truly embraces collaboration between disciplines. While the literature from biological psychiatry has become a significant force in the area of early adversity, what is often lost here is that at the heart of this area are fundamental questions about plasticity in human development (see Lerner, 2002; Lewis, 1997). In our experience, biological approaches to these questions have sometimes been framed in a particular light, with implications of biological determinism or of a dichotomy between "biological" and "psychosocial" factors in human development. In using those terms in this particular review, we are adopting a pragmatic approach and do not mean to buttress such unhelpful dichotomies (Marshall, 2009). Rather than pitting an individual against his or her environment, more dynamic approaches to human development have embedded the individual within the environment, with a somewhat porous boundary between them (Overton, 2006). We see this wider picture from the area of developmental systems as pointing the way forward for integrative progress in understanding the role of the early adversity in influencing later development. The notion of epigenetic mechanisms that provide the biological scaffolding for the effects of early experience is consistent with this view, and that will likely be one prominent avenue for continued investigation, although options for assessing the epigenome in human development are currently very limited (Champagne & Curley, 2009). But even with the recent progress in this area, there is still a large gap between human and comparative work, and there remain many pieces of the puzzle that have yet to be put in place.

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