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Using cross-species comparisons and a neurobiological framework to understand early social deprivation effects on behavioral development

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Abstract

Building upon the transactional model of brain development, we explore the impact of early maternal deprivation on neural development and plasticity in three neural systems: hyperactivity/impulsivity, executive function, and hypothalamic–pituitary–adrenal axis functioning across rodent, nonhuman primate, and human studies. Recognizing the complexity of early maternal–infant interactions, we limit our cross-species comparisons to data from rodent models of artificial rearing, nonhuman primate studies of peer rearing, and the relations between these two experimental approaches and human studies of children exposed to the early severe psychosocial deprivation associated with institutional care. In addition to discussing the strengths and limitations of these paradigms, we present the current state of research on the neurobiological impact of early maternal deprivation and the evidence of sensitive periods, noting methodological challenges. Integrating data across preclinical animal models and human studies, we speculate about the underlying biological mechanisms; the differential impact of deprivation due to temporal factors including onset, offset, and duration of the exposure; and the possibility and consequences of reopening of sensitive periods during adolescence.

The relevance of the early caregiving environment for child development is well established. Recently there has been a concerted effort to define the mechanisms by which this critical early dyadic interaction shapes the developing brain. Consistent with the fundamental principles of developmental psychopathology, the rapid advancement of neuroimaging and genetic technologies coupled with enhanced research linking cognitive neurodevelopment, developmental psychopathology, and molecular biology represents a unique opportunity for greater mechanistic understanding.

This manuscript utilizes a neural systems approach and focuses specifically on data synthesized from human studies of children exposed to institutional rearing with that from animal models postulated to be most reflective of an institutional setting, specifically artificial rearing (AR) of rat pups and peer rearing (PR) in nonhuman primates (NHP). Consistent with the National Institute of Mental Health Research Domain Criteria (RDoC) project (Cuthbert & Kozak, 2013), this article focuses on neural pathways that span traditional psychological diagnoses. We selected three pathways that are consistently impacted across studies of early deprivation and measurable in animal model systems: hyperactivity/impulsivity (H/I), executive function (EF), and the hypothalamic–pituitary–adrenal (HPA) axis. These are, by no means, the only neural systems impacted by early maternal deprivation. Other systems, such as the immune system, as well as broader cross-domain constructs, such as resilience, merit investigation, but they are beyond the scope of this article.

The term *early life adversity* can conceptually encompass many different experiences, including sexual abuse, physical abuse, witnessing violence, exposure to natural disasters, poverty, and neglect. Whether these different forms of early adversity vary in their impact on neurodevelopment and neural plasticity, and the implications of single versus repeated/cumulative exposure, has yet to be disentangled (Cicchetti, Rogosch, Gunnar, & Toth, 2010; McLaughlin, Sheridan, & Nelson, 2013). Critical distilling of data is needed when drawing parallels between animal and human studies of early adversity due to known limitations of preclinical animal models of early adversity (e.g., rodent and NHP) and the range of existing experimental paradigms (e.g., maternal separation and stress induction). Consolidating translational research and emphasizing the dynamic and reciprocal interplay between levels of analyses, within a developmental context, is invaluable as we seek to apply the core principles of developmental psychopathology to advance the understanding and treatment of early psychopathology (Cicchetti & Toth, 2009).

First, we define the basic concepts of critical and sensitive periods, discuss the evidence of sleeper effects, and consider the importance of differential susceptibility. Second, we review the methodology, strengths, and limitations of the selected animal models. Third, we discuss the current data

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regarding neural plasticity and the existence of sensitive periods in relation to H/I, EF, and HPA axis. Fourth, we discuss the challenges related to defining sensitive periods and the implications of these neurobiological models for treatment and prognosis.

Maternal Deprivation and Neural Development

The caregiver–child relationship is the strongest, most enduring social relationship in mammalian species with established relevance to a range of psychopathology (Kraemer, 1992; Mirescu, Peters, & Gould, 2004). Early caregiving powerfully sculpts the developing neural systems, particularly those pathways underlying H/I, EF, and the HPA axis. It is therefore not surprising that extreme deviations from the expected caregiving experiences influence a range of behavioral, psychological, and neurobiological outcomes (Zeanah et al., 2001).

Neural plasticity, the reorganization of the central nervous system to permit adaptation to the changing environment, results in alteration in brain structure, function, and connectivity. These alterations occur as a result of synaptogenesis (formation of synapses between neurons), myelination (production of myelin sheath around axons, which increases impulse propagation speed), and pruning (reduction of neurons and synapses to leave more efficient connections). Both the actual rate of development and the specific time periods most critical for normative function vary across the central nervous system. Prenatal and throughout the first years of life represent the time periods associated with the greatest production of neuronal cells and synapses. This rapid early proliferation is followed by experience-dependent selective decreases in both the number of cells through apoptosis and the number of axonal and dendritic connections through pruning. At the same time that rapid neurodevelopment is occurring, the maternal–child relationship also appears to be highly influential for a myriad of developmental outcomes indicating the widespread neurobiological impact of early caregiving. Rodent models of maternal deprivation (described in detail below) demonstrate *decreased* neuronal apoptosis, some of which is reversed with increased artificial tactile stimulation, suggesting that early maternal caregiving influences not only synaptic formation and pruning but also the actual number of neurons (Chatterjee et al., 2007).

The first years of life lay the foundation for cognitive, social, and emotional competencies (Humphreys, Zeanah, & Scheeringa, 2014). Current research examining the association between maternal care and the underlying molecular processes controlling neural plasticity is expected to complement the existing behavioral and psychological studies. Understanding not only the biobehavioral impact of exposure to adverse early caregiving but also the ability of enhanced caregiving to repair or reverse the negative consequences, at the cellular and molecular levels, has an extensive public health and policy implication. This multilevel approach, combining genetics, neuroscience, social context, and developmental trajectories, is consistent with the field of development psychopathology and integral to an enhanced understanding of individual patterns of adaptation (Cicchetti & Toth, 2009).

Critical periods versus sensitive periods

Critical and sensitive periods likely moderate the impact of maternal deprivation on child development. "Critical periods" are defined as developmental periods when the organization and formation of a particular neural system requires definitive input. The opening and closing of critical periods is expected to be rapid and well defined. Absence of the needed exposure or experience during a critical period is expected to result in the failure of a particular phenomenon or skill to develop. Even if the needed exposure occurs at a later time point, full recovery may not be feasible (Bavelier, Levi, Li, Dan, & Hensch, 2010; Fox, Almas, Degnan, Nelson, & Zeanah, 2011; Hensch, 2004, 2005; Nelson et al., 2007). Critical periods have been most clearly demonstrated in the visual system with monocular deprivation (Wiesel & Hubel, 1965). Hensch has described time-sensitive activity-dependent development in the primary visual cortex, and work by his group and others is now beginning to define the molecular processes controlling the opening and closing of critical periods (Hensch, 2004, 2005). This research suggests that, although critical periods were once thought static, opportunities and approaches to reopen critical periods may exist (Bavelier et al., 2010; Hensch & Bilimoria, 2012).

In contrast, "sensitive periods" refer to developmental periods during which there is heightened potential for neural (re)organization in response to environmental input. Sensitive periods, by definition, have more gradual opening and closing than critical periods. Distinct from critical periods, once a sensitive period is closed, plasticity is still possible; however, the responsivity of that neural system to environmental changes is dramatically reduced. Exposure to environmental stimuli during a sensitive period is expected to result in greater phenotypic changes than exposure outside of the sensitive period. The ability to define, as well as detect, sensitive periods, in addition to the impact on specific neural pathways, varies across development and neural system (Nelson et al., 2007). For the sake of clarity, this review uses the term "sensitive periods" to refer to plasticity windows.

Once closed, it was previously thought sensitive periods could not be reopened (Hensch, 2004). However, data now suggests that developmental plasticity "windows," as well as environmental manipulations, such as aerobic exercise and environmental enrichment, may reopen or recalibrate neural pathways (Kraemer, 1992; Nithianantharajah & Hannan, 2006; Wang, Feng, Liu, Liu, & Cang, 2013). Puberty, a developmental time point where both substantial environmental changes are expected and significant neural remodeling occurs (Guo et al., 2013; Quevedo, Johnson, Loman, Lafavor, & Gunnar, 2012; Sisk & Zehr, 2005), may represent a developmental switch point with implications for sensitive periods. Pharmacologic manipulations may also influence the duration and pliability of sensitive periods by influencing the structural restraints of neurons, as well

as the balance between inhibitory and excitatory inputs, even in circuits thought to be fully developed (Bavelier et al., 2010; Hensch & Bilimoria, 2012; Sale, Berardi, Spolidoro, Baroncelli, & Maffei, 2010). While reopening sensitive periods at first glance may appear beneficial, it is not without risk. Unpredicted developmental discontinuities and outcomes are possible with the reorganization of previously closed neural systems, particularly in neurocognitive domains where higher order processes are often dependent upon earlier developing less complex neural systems (Bavelier et al., 2010; Hensch & Bilimoria, 2012; Pascual-Leone, Amedi, Fregni, & Merabet, 2005).

Sleeper effects

The impact of maternal deprivation on all child outcomes may not be immediately apparent, and in some cases the detrimental effects may only be detected at later developmental time points, a phenomena termed *sleeper effects* (Humphreys, Lee, et al., 2014; Zeanah, Gunnar, McCall, Kreppner, & Fox, 2011). Sleeper effects imply that although the impact on the neural system occurred earlier in development, the ability to detect the consequence(s) of an earlier "hit" may not readily be discernable. As a child ages, the increased complexity of the underlying neurobiological pathways needed for higher order behavioral and cognitive tasks may accentuate deficits that were less apparent in more simplistic testing paradigms or tasks (Zeanah et al., 2011). The implication is that behavioral or neurological outcomes measured at early stages of development may overlook deficits that only become apparent in later years.

The concept of sleeper effects has long been recognized in psychology where the impact of a highly influential experience (such as early psychosocial deprivation) resulted in increasing, rather than decreasing, symptomology over time. In some cases, the development of serious psychological symptoms only appeared well after the initial exposure (Finkelhor & Baron, 1986; Finkelhor & Berliner, 1995; Kraemer, 1992; Trickett & Putnam, 1998). The recent partnership among neuroscience, genetics, and developmental psychopathology is expected to uncover the neurobiological and molecular pathways underlying this well-recognized clinical phenomenon.

The prefrontal cortex (PFC), given its protracted development, may be especially prone to sleeper effects. Evidence related to maternal deprivation and accelerated development of the amygdala–PFC connections has been found. Specifically connectivity within previously institutionalized (PI) young children exhibited a more advanced pattern of *negative* amygdala–medial PFC (mPFC) coupling that resembled the connectivity found in healthy older adolescents (Gee et al., 2013). Typically developing age-matched comparison children, however, demonstrated a less developmentally advanced *positive* amygdala–mPFC coupling. This accelerated development of amygdala–mPFC connectivity is a neurobiological mechanism that may explain the increasing risk for internalizing and externalizing disorders found as PI children enter adolescence and adulthood (Tieman, van der Ende, & Verhulst, 2005; Tottenham, 2012; van der Vegt, van der Ende, Ferdinand, Verhulst, & Tiemeier, 2009; Verhulst, Althaus, & Versluis-den Bieman, 1990).

An additional sleeper effect may also exist in relation to maternal deprivation and decision making. PI males initially demonstrated a risk-averse pattern of behavior in early childhood; however, as adolescents they demonstrated excessive risk-taking behaviors (Humphreys, Lee, et al., 2014). These findings suggest that elevated impulsivity and risk taking in adolescent PI individuals may be the result of earlier differences in the connections between the limbic system and the PFC. These altered circuits may contribute to risk aversion in younger males, but in older youth, as a result of developmental changes in the connectivity between the limbic system and the PFC, lead to excessive risk taking. The association between observable phenotypes and functional impairment may further differ as a result of compensatory neural pathways. As such, identification and strengthening of compensatory pathways may represent novel future intervention approaches. As we seek to further define both the mechanisms leading to impairment and novel pathways for recovery enhanced exploration of genetic and epigenetic contributions is needed (Champagne et al., 2006).

Differential susceptibility

Although early institutionalization has consistently been associated with H/I, EF deficits, and altered HPA axis functioning, individual differences among children exist. Differential susceptibility theory, the theory that some individuals are highly susceptible to the environment while the majority of individuals demonstrate significantly less responsiveness, may explain some of these individual differences (Belsky & Pluess, 2009). According to differential susceptibility theory, highly susceptible individuals not only fare the worst in negative environments but also are the most *responsive* to positive environments. In the case of early caregiving, differential susceptibility would propose that the subset of children who experienced the most negative outcomes when in institutional settings would also be the same children who, when placed into a positive environment (e.g., placement in foster care) would preferentially benefit. Nonsusceptible individuals would be expected to experience *less variation in outcomes*, even with the dramatic change in their environments.

Genetic differential susceptibility, in which individual genetic variation drives the degree of sensitivity, may have particular utility for defining sensitive periods and neurobiological mechanisms and has been demonstrated in relation to early experiences. (Bakermans-Kranenburg & van IJzendoorn, 2007; Belsky, Bakermans-Kranenburg, & van IJzendoorn, 2007; Belsky & Pluess, 2009; Bradley & Corwyn, 2008; Ellis, Boyce, Belsky, Bakermans-Kranenburg, & van IJzendoorn, 2011; Jonas et al., 2013; McLaughlin et al., 2010; Mileva-Seitz et al., 2011). In studies of institutional children, genetic differential susceptibility has been found in relation to the serotonin transporter linked polymorphic region gene (*5-HTTLPR*; a gene that codes for the serotonin

transporter, which plays a key role in serotonin reuptake) and externalizing behavior (Brett, Humphreys, et al., 2014), and both *5-HTTLPR* and brain-derived neurotrophic factor (BDNF; a protein involved in the maintenance, growth, and differentiation of neurons) with indiscriminant social behavior (Drury et al., 2012). In this second study, both the individual genes and the cumulative genotype predicted differential susceptibility; however, the effect associated with the *5-HTTLPR* genotype occurred earlier in development than the effect associated with BDNF. One interpretation is that the changes related to BDNF required a longer period of time to develop. An alternative hypothesis is that the serotonergic pathway linked to *5-HTTLPR* had an earlier sensitive period. Either or both of these hypotheses are feasible and need to be empirically tested.

Evidence of differential susceptibility is suggested in other studies of children exposed to early institutional care, that is, catechol-*O*-methyltransferase (*COMT*; involved in the degradation of several catecholamines, including dopamine [DA]) and depression; Drury et al., 2010), *5-HTTLPR* and attention-deficit/hyperactivity disorder (ADHD; Kumsta et al., 2010), and *5-HTTLPR* and attachment disorganization (Bakermans-Kranenburg, Dobrova-krol, & van IJzendoorn, 2011). In rhesus monkeys, differential susceptibility may also exist in relation to the interaction between recombinant human *5-HTTLPR* (*rh5-HTTLPR*) and PR compared to maternal rearing and later alcohol consumption (Barr, Newman, Lindell, et al., 2004). In this study, PR NHP with the short allele demonstrated significantly greater alcohol consumption, while NHP with the same genotype, when reared with their mothers, consumed significantly less alcohol. In AR rodent models, genetic differential susceptibility has been found in relation to DA receptor D2 expression levels and the amount of tactile stimulation and maternal care (Lovic et al., 2013). Future studies are needed that directly test whether subpopulations of individuals exist who differ in their susceptibility to changes in the caregiving context as a result of intrinsic genetic variation. This approach would be expected to decrease the risk of overlooking *individual* differences in studies exploring larger *group* differences. Genetic associations can also potentially indicate what neural systems are affected (Brett, Sheridan, et al., 2014; Drury et al., 2012). Epigenetic effects may compound or decrease the impact of underlying genetic variation, as well as influence sensitive periods, adding yet another intriguing level of complexity (Levenson & Sweatt, 2006; Putignano et al., 2007).

Translational Models of Maternal Deprivation

Consistent with the current direction of the field of developmental psychopathology, progress in defining sensitive periods will require increased interface between genetics and neuroscience and the integration of data from human studies and preclinical animal models (Cicchetti & Toth, 2009). As a starting point for this integration, we define the two model systems (i.e., AR in rodents and PR in NHP) that we postulate are most reflective of early institutional rearing. We fully acknowledge that the experience and environmental demands for animals reared in isolation are substantially different from animals in their normal rearing environments and from the rearing environments experienced by children. Although parallels can be drawn with animal models, the human caregiving context can never fully be reflected in animal studies.

AR of rat pups

There are multiple rodent models of maternal care involving both variations in the amount of maternal separation and variations in the developmental timing of the separation. Some models utilize pup removal, while others remove the dam; others trigger maternal distress and subsequent pup neglect through the provision of limited bedding and/or food, or exposure to intruder odors. Distinct from these models, the "pup-in-a-cup" paradigm of AR (Burton, Lovic, & Fleming, 2006; Gonzalez, Lovic, Ward, Wainwright, & Fleming, 2001; Hall, 1975) involves complete early maternal deprivation. We suggest that the lack of individualized attention, regimented approach to rearing, and the extremely low sensory and environmental complexity intrinsic to the AR model is most reflective of institutional care.

In the AR paradigm, pups are removed from dams on postnatal day (PND) 2. A cheek cannula is surgically inserted in the pup's cheek for feeding, and pups are placed in a cup within a warm water bath to assist in temperature regulation. This AR regimen allows for a range of manipulations including temperature, food type/amount, and diurnal schedule. The most studied variation is the amount of tactile general body and anogenital swabbing stimulations the pup receives by "stroking" the pup with a paintbrush. These swabbing stimulations replace the maternal licking critical for the normal development of endocrine and physiologic function, including the induction of defecation and urination (Burton et al., 2006; Gonzalez et al., 2001; Levy, Melo, Galef, Madden, & Fleming, 2003; Lovic & Fleming, 2004; Melo et al., 2006). Manipulations in the amount of anogenital and overall body somatosensory stimulation have been found to moderate the effect of maternal deprivation (Gonzalez et al., 2001; Lovic & Fleming, 2004; Novakov & Fleming, 2005). In the AR model, once animals have reached PND 18, they are "weaned" off the feeding cannula at the same time that their control siblings are weaned off the mother, and animals are placed into cages in pairs until adulthood. In studies of AR, maternally reared animals are compared to two groups of AR animals: those receiving minimal anogenital stimulation (two swabbings a day), and those receiving maximal stimulation (two anogenital and six daily bouts of body stroking distributed throughout the daylight hours).

The altered behavioral and psychological patterns associated with early maternal deprivation likely reflect altered neural development and dysregulation in neurotransmitter systems. In the AR model, there is substantial evidence that dopaminergic pathways, implicated in reward, stimulus sa-

lience, emotion regulation, and EF, are particularly impacted (Surmeier, 2007; Volkow, Wang, Fowler, Tomasi, & Telang, 2011). Elevations of baseline DA in the nucleus accumbens and alterations in DA output, DA receptors, and DA-mediated behaviors, such as increased locomotion and impulsivity, have been found in AR animals when compared to maternally reared animals (Lovic, Fleming, & Fletcher, 2006; Lovic, Keen, Fletcher, & Fleming, 2011).

Alterations in these dopaminergic pathways may also have implications for subsequent generations. Alfonso, King, Novakov, Burton, and Fleming (2011) compared extracellular DA in the nucleus accumbens of virgin and postpartum animals raised in the AR paradigm to maternally reared (MR) animals. DA levels were measured before (baseline), during, and after pup presentation, a highly salient stimulus for mothers. Postpartum MR animals had higher baseline DA levels and greater DA response to pup presentation than virgin (or nonprimed) MR animals. Among AR animals, no differences were found between virgin and postpartum animals in response to pup presentation. Further, baseline DA levels in both virgin and postpartum AR animals were elevated compared to MR virgin animals. Thus, AR appears to decrease the signal to background levels of DA normally expected with the presentation of offspring, a finding that may have broader implications for parenting behaviors in subsequent generations. Preweaning tactile stimulation partially reversed these effects (Afonso et al., 2011).

Despite the advantages of rodent studies, limitations exist. Although rat pups may be removed from the dam and fed by cannulation at any time during the postnatal period, once removed, pups cannot be returned to the dam prior to weaning because they have difficulty attaching to the nipple (A. S. Fleming, unpublished data). The developmental stage at birth in rodents is substantially earlier than primates and more related to third-trimester human development. Such deprivation in the AR model likely reflects both prenatal and postnatal exposures when compared to human studies. A further limitation of the AR model is that the pups are completely isolated, not just from the dam, but from conspecifics and almost all forms of environmental stimuli. While this complete deprivation may reflect the earliest periods of institutional care, where children are individually isolated in cribs with poor environmental stimulation and regimented caregiving, it is less representative of the care of toddlers and older children, where groups of same-age children are placed together and environmental stimulation is minimal, but not absent. Consistent with this, Melo et al. (2006) found that some of the deficits in behavior and physiology in the AR model are ameliorated by raising pups in cups with a same-sex conspecific.

The limited ability to perform in vivo neuroimaging and examine intact neural structure in living rodents is another limitation. While magnetic resonance imaging (MRI) studies of rodents have recently been described (Denic et al., 2011), these studies require anesthesia and high field strength magnets (4.7–11.7 Tesla), increasing image artifacts and analytic difficulty (Denic et al., 2011). No neuroimaging studies of AR rodents have been reported to date.

Although limitations exist, the rodent model does offer significant advantages. The predominant benefit of rodent models is the ability to directly examine neuronal structure, deviations from normal neuronal development, and molecular changes at multiple developmental time points in genetically homogenous animals (Akbari, Chatterjee, Levy, & Fleming, 2007; Chatterjee et al., 2007; Gonzalez & Fleming, 2002). For example, Chatterjee et al. (2007) demonstrated reduced expression of several neural proteins (including proteins involved in cell adhesion, synaptogenesis, axon elongation, and astrocyte integrity) and enhanced expression of others (*Neu-N*) in brain regions involved in attention, impulsivity, and social behavior. Furthermore, this study showed that some of these expression changes were not present in maximally tactile stimulated AR animals, suggesting reversal of altered gene expression patterns (Chatterjee et al., 2007).

Two as of yet unexplored areas of research currently only feasible in rodent models are the examination of different genetic strains or knockout models (Makinodan, Rosen, Ito, & Corfas, 2012) and the newly developed "CLARITY" technique (Chung et al., 2013). Replication of the association between specific genetic variants and outcomes in human studies within rodent animals, and the subsequent neurobiological characterization as a result of genetic differences, is an appropriate next step. The CLARITY technique removes the lipid layer within the brain while maintaining the three-dimensional structure, thus creating a "clear" brain. While not yet applied to AR models, this technique offers even greater potential for enhanced understanding of the impact of differences in early caregiving on the developing central nervous system.

PR of NHP

The NHP maternal deprivation studies first initiated by Harlow and colleagues in the 1950s were motivated by "strange" and devastating types of behavior observed among institutionalized orphans across Western Europe and Great Britain following World War II (Bowlby, 1951; Spitz, 1945, 1946). A myriad of effects of maternal deprivation have since been reported in NHP, including alterations in temperature regulation, immune function, social interactions, impulsivity, and cognitive function (Kraemer, 1992; Kraemer et al., 2004). If maternal and social isolation extends beyond 6–9 months of age, the majority of these effects persist into adulthood (Harlow, Harlow, & Suomi, 1971; Kraemer, 1992; Suomi & Ripp, 1983).

Similar to the rodent model, this review will present data specific to the PR NHP model. In this model, as with the AR model, animals are initially hand-fed in an incubator and isolated from peers. Subsequently, they are transferred to an individual cage containing an inanimate, cloth-covered "surrogate" with a fixed feeding bottle (Barr, Newman, Shannon, et al., 2004; Harlow, Dodsworth, & Harlow, 1965). After this initial

month, animals are housed with a small number of other PR animals of approximately the same age (Barr, Newman, Shannon, et al., 2004; Barrett et al., 2009; Shannon, Champoux, & Suomi, 1998). As such, PR NHP can interact socially with peers, but lack adult caregivers (Barr, Newman, Shannon, et al., 2004). Variations on this paradigm include nursery reared, where the NHP is hand reared and not provided with an inanimate surrogate (Capitanio, Mendoza, Mason, & Maninger, 2005), surrogate PR, where the NHP retains access to the inanimate surrogate even after introduction to the peer setting (Roma, Ruggiero, Schwandt, Higley, & Suomi, 2006), or group housing models that include exposure to both adults and juveniles following the isolated rearing period (Barr, Newman, Shannon, et al., 2004; Barrett et al., 2009).

A unifying theme across studies is that PR and MR NHP demonstrate neurobiological differences. However, the magnitude and direction of these differences may vary over development and in response to changing environmental circumstances (Clarke, Kraemer, & Kupfer, 1998; Higley, Haseert, Suomi, & Linnoila, 1991; Higley, Suomi, & Linnoila, 1991, 1992; Kraemer, 1997). For example, juvenile PR NHP housed in stable social groups generally maintain lower baseline levels of cerebrospinal fluid NE and the DA metabolite homovanillic acid, compared to MR NHP housed in stable social groups (Kraemer & Clarke, 1996). When challenged, through either social challenges or drugs activating NE and DA systems, the behavioral response of PR NHP is significantly greater than that of MR NHP (Kraemer, Ebert, Lake, & McKinney, 1984; Kraemer et al., 2004). Juvenile PR NHP housed in stable social groups have lower baseline levels of adrenocorticotrophic hormone and cortisol levels but flatter HPA axis responses to psychosocial stressors, such as separation from cage mates, when compared to MR NHP (Clarke, 1993). This heightened behavioral response to stressors in PR NHP, flattened HPA axis response, and hypersensitivity to drugs activating NE and DA pathways, suggests alterations in the underlying neural pathways as a consequence of PR.

In typically reared NHP, regulation and levels of serotonin, NE, and DA levels appear to be highly correlated during development (Agren, Mefford, Rudorfer, Linnoila, & Potter, 1986; Higley et al., 1992; Kraemer, Ebert, Schmidt, & McKinney, 1989). Specifically, in maternally reared NHP, there is substantial correlations among NE, homovanillic acid, and the serotonin metabolite 5-hydroxyindoleacetic acid levels measured from 2 months after birth to preadolescence (Kraemer et al., 1989). Further, in maternally reared NHP, measures of NE and/or DA system activity covary with social behavior and development during stressors such as maternal and peer separations (Higley, Haseert, et al., 1991; Kraemer et al., 1989; Kraemer, Ebert, Schmidt, & McKinney, 1991). In peer-reared primates, the correlation and synchrony of these neurotransmitter systems fail to develop properly, suggesting that the integration of these pathways is influenced by early caregiving (Kraemer et al., 1989, 1991).

As with the AR rodent studies, the use of NHP models is somewhat limited by the differential cross-species continuity in the timing of gestation, birth, and postnatal maturation. Although the brains of both humans and NHP follow a cubic trend of growth, NHP mature more rapidly than humans. Rhesus monkeys experience the most rapid brain growth between birth and 4 months of age, and achieve maximal total brain volume and sexual maturity around 3–4 years of age (Malkova, Heuer, & Saunders, 2006). Although this rapid postnatal development facilitates longitudinal and transgenerational studies of this species, the temporal misalignment in neurodevelopment compared to humans is an important consideration when drawing cross-species comparisons.

The limited ability to manipulate the NHP genome and reduced access to neuronal tissue, both due to the high cost for large sample sizes and heightened ethical concerns, are notable challenges to NHP studies compared to rodent models. Although evolutionarily far closer to human studies, NHP models are unable to capture the entire spectrum of human developmental capabilities, including higher order processing. While MRI studies of NHP have become feasible in the last decade (Andersena et al., 2002; Malkova et al., 2006; Sundstrom et al., 2004), the practicalities of data acquisition in these studies remains complex. Imaging studies of PR NHP have not yet been reported.

Despite these limitations, NHP studies have several advantages over rodent models. PR in NHP may be more reflective of the psychosocial deprivation experienced by humans in institutional care, particularly in terms of the availability of interaction with peers. However, it is important to note that peer interaction in the NHP model is introduced at a much later developmental stage than is found in the human institutional setting (i.e., NHP are placed with peers at the human equivalent of around 2 years, whereas institutionalized children are frequently exposed to peers earlier). In addition, the increased similarity between NHP and humans (as opposed to rodents) across neurocognitive capabilities (particularly EF), peer interactions, social structure, and phylogenic relation are important advantages of NHP models. Although gene knockouts are not feasible in NHP models, the greater evolutionary link with humans is another advantage because there is at least one specific genetic variant with relevance to responsivity to early caregiving (i.e., *5-HTTLPR* in the promoter region of *SLC6A4*) found only in some NHP species and humans (Suomi, 2011). This genetic variant is not endogenously found in rodents, though there are polymorphisms in other regions of the *SLC6A4* gene (Belay et al., 2011). The abilities to randomize placement in maternally deprived environments, to freely manipulate the temporal aspects of the caregiving context, and to study the impact early deprivation in multiple generations (in a time period shorter than would be possible in humans) are obvious benefits of NHP models over human studies.

Institutional/orphanage care for humans

Over 8,000,000 children are estimated to reside in institutional settings worldwide (Bos, Fox, Zeanah, & Nelson,

2009). While large variations in institutional care exist (Zeanah et al., 2003; Zeanah, Smyke, Koga, Carlson, & the Bucharest Early Intervention Project Core Group, 2005), several features are common to institutional care, including a highly regimented schedule, rotating caregivers, and limited individualized attention, human interaction, and play. Although malnutrition (Schanberg, Evoniuk, & Kuhn, 1984; Sonuga-Barke et al., 2008) and prenatal factors (Mychasiuk, Ilnytskyy, Kovalchuk, Kolb, & Gibb, 2011; Pluess & Belsky, 2011; Theall, McKasson, Mabile, Dunaway, & Drury, 2013; Weinstock, 2008) contribute to negative outcomes, deviations from the expected caregiving environment likely confer independent risk. Efforts focused on defining sensitive periods, both in response to initial deprivation and following placement in adoptive or foster care settings, are needed.

Numerous studies, both longitudinal and cross-sectional, of PI children exist (Chisolm & Chisholm, 1998; Gunnar & van Dulmen, 2007; Jacobs, Miller, & Tirella, 2010; Juffer & van IJzendoorn, 2005; Kreppner, O'Connor, Rutter, & the English and Romanian Adoptees Study Team, 2001; Tottenham et al., 2010; van den Dries, Juffer, van IJzendoorn, & Bakermans-Kranenburg, 2010). In addition to studies of children who were exposed to early institutional care and subsequently adopted internationally, several studies examined young children still residing in institutional care (Bakermans-Kranenburg et al., 2011). The majority of studies are longitudinal in nature, capturing the growth and development of these children after removal from institutional care and placement into adoptive homes (Chisolm & Chisholm, 1998; Fisher, Ames, Chisholm, & Savoie, 1997; Kreppner et al., 2001; Le Mare, Audet, & Kurytnik, 2007; O'Connor, Marvin, Rutter, Olrick, & Brittner, 2003; Rutter et al., 2007; Teilmann, Pedersen, Skakkebæk, & Jensen, 2006). One challenge across these studies is the absence of prenatal data and highly limited information about experiences prior to placement in the institution. Given these limitations, it is not surprising that heterogeneity is found among institutionalized children.

Most of the existing longitudinal studies of internationally adopted children demonstrated wide variation in both the duration of institutional exposure and the level or amount of physical, social, emotional, and cognitive recovery. Differences in ethnic background, language, culture, and nutrition when adopted out of their country of origin add additional complexity. Even with these differences, there is consistent evidence that the recovery of children is moderated by both the duration of institutional care and the amount of time in adoptive care. Collective data from these studies suggest that earlier placement is substantially better. Specifically, in the Romanian Adoption Project, children adopted before 4 months of age (Chisolm & Chisholm, 1998; Fisher et al., 1997), and in the English and Romanian Adoptee (ERA), children adopted before 6 months of age (Kreppner et al., 2001; O'Connor et al., 2003; Rutter et al., 2007), were largely comparable to never-institutionalized children. In both studies, children who were adopted later were significantly more likely to have negative lasting cross-domain difficulties. Other studies where children were placed into foster care later in development, such as the Bucharest Early Intervention Project (BEIP; mean age of placement = 22 months), found significant impairment across most outcomes. Together these findings suggest that the greatest potential for recovery following institutional care requires stable adoptive or foster care placement during the first 2 years of life and ideally prior to 6 months of age.

The BEIP is unique among studies of examining the impact of early institutional care on child development. Briefly, 187 children residing in one of six institution orphanages in Bucharest, Romania, were screened, and 51 children were initially excluded for medical reasons (i.e., genetic syndromes, fetal alcohol syndrome, or microcephaly). The 136 remaining children (age 6–22 months at baseline assessment), all of whom spent at least half their life in the institution, comprised an ever institutionalized group. Following baseline assessment, ever institutionalized group children were randomly assigned either to care as usual (care as usual group) or to placement into a newly created high-quality foster care network. A group of comparison children, who were never institutionalized (never institutionalized group; n = 87), were recruited from the same maternity hospitals. Although age at placement was relatively late in the BEIP compared to many other studies of institutionalized children, the BEIP has two substantial advantages: foster care placement was within the same country (Romania) and placement into foster care was randomized. The randomized, within-country design offers unique scientific advantages relative to the determination of sensitive periods (Zeanah et al., 2003).

Although the randomized design and continuity of placement in the same country are substantial strengths to the BEIP study, limitations exist. Specific limitations include the absence of prenatal data, unknown variation in maternal care prior to abandonment, inability to evaluate socioeconomic status of foster families versus institutional care, and the relatively late timing of the initial intervention (e.g., average age of placement in foster care of 22 months). One further limitation in the BEIP study is the significant amount of placement changes that occurred after randomization, particularly in the care as usual group.

The study of institutionalized children, such as those in the BEIP, raises ethical issues (Miller, 2009; Millum & Emanuel, 2007; Zeanah, Fox, & Nelson, 2012; Zeanah et al., 2006). Given the extensive findings across studies of PI children that exposure to institutional care has severe negative impacts on child development, additional randomized control trials are unlikely. As such, careful integration of data from previous human studies with rodent and NHP models, where more precise environmental and biological manipulations are feasible, is needed. This integration is likely the most efficacious approach to enhancing the care, treatment, and long-term behavioral, cognitive, and psychological outcomes of these highly vulnerable children.

Cross-Species Comparisons of the Neural Systems Impacted by Maternal Deprivation

H/I

H/I symptoms are among the most common clinical findings in children with a history of early institutional care. They are so prevalent that they are included in the hypothesized deprivation specific pattern (Smith, Need, Cirulli, Chiba-Falek, & Attix, 2013; Torgersen, Flaatten, Engelsen, & Gramstad, 2012; Vintan, Palade, Cristea, Benga, & Muresanu, 2012). Within the RDoC matrix, H/I is found within the cognitive domain and can be measured via paradigms testing response selection, inhibition, and choice suppression (http://www.nimh.nih.gov/research-priorities/rdoc/rdocconstructs.shtml#response_selection). While arguably having subtle clinical inferences, the terms "hyperactivity" and "overactivity" are semantically interchangeable. We utilize hyperactivity to be both consistent and for easier comparison with "hyperlocomotion" in rodent models and impulsive behavior in NHP. Impulsivity refers to rapid decision making, premature actions, and decreased tolerance of delayed gratification. The construct of impulsivity has relevance to several psychological disorders (Dalley, Everitt, & Robbins, 2011), and although the symptoms assessed in H/I are most often associated with ADHD, there is significant overlap with other disorders, including oppositional defiant disorder, conduct disorder, and substance abuse. The ventral frontal–striatal circuits, DA, and NE are primarily implicated in H/I. It is intriguing that these areas, particularly dopaminergic systems, are found to be altered in both animal and human studies of early maternal deprivation (Afonso et al., 2011; Brake, Zhang, Diorio, Meaney, & Gratton, 2004; Hall, Willkinson, & Robbins, 1999; Kraemer et al., 2004; Lovic et al., 2006).

In this article, we conceptualize H/I symptoms in terms of their underlying altered neural pathways and suggest that the H/I found in PI children may neurobiologically differ from ADHD found in typically developing children. Data consistent with different neurobiological underpinnings include the absence of the expected higher prevalence of ADHD symptoms in males compared to females in institutionalized children (Gershon, 2002; i.e., no evidence of gender differences in H/I among PI children) as well as the lack of an association between ADHD and EF deficits in PI children, an association commonly found in typically developing ADHD children (Kumsta et al., 2010; Stevens et al., 2008, 2009).

Rodent studies. Hyperlocomotion measured via the open field test is a common and developmentally persistent behavioral response to AR (Burton et al., 2006; Gonzalez et al., 2001; Lovic & Fleming, 2004; Lupien, McEwen, & Heim, 2009; Novakov & Fleming, 2005). Additional somatosensory, licking-like stimulation to AR rats appears to partially reverse some of these hyperlocomotive effects (Burton et al., 2006; Gonzalez et al., 2001; Levy et al., 2003; Lovic & Fleming, 2004; Lovic et al., 2011; Novakov & Fleming, 2005). In rodent models, impulsivity is subdivided into impulsive action and impulsive choice that can be distinguished both behaviorally and neuroanatomically (Dalley et al., 2011; Lovic et al., 2011). AR rodents who experienced minimal stimulation demonstrate higher rates of impulsive action than do maximally stimulated AR and MR rodents. However, male minimally stimulated AR rodents demonstrate lower impulsive choice than do either maximally stimulated or maternally reared males. These findings suggest that enhanced maternal care (e.g., increased tactile stimulation) can reverse the effect of AR on impulsive action. The combination of increased impulsive action with decreased impulsive choice is consistent with results in other rodent studies that demonstrated elevated DA tone (Fletcher, Rizos, Noble, & Higgings, 2011).

Neurobiological data from the AR model provides some insight into the underlying molecular mechanism linking increased H/I and early maternal deprivation. Hyperlocomotion is primarily associated with changes in DA inputs to the cortex, although alterations in additional pathways may also exist (Lovic et al., 2013). Amphetamine administration resulted in *increased* locomotor activity in AR rats compared to maternally reared rats. Further, co-injection of the alpha-adrenergic receptor antagonist blocked the amphetamine-induced increase in locomotor activity and resulted in normalization of AR rodent activity. These results suggest that while DA neurotransmission is involved, changes in alpha-adrenergic NE receptors may further mediate the association between maternal deprivation and increased locomotor behavior (Levine, 2002; Lovic et al., 2006). In response to amphetamine, but not to methylphenidate, AR minimally stimulated animals demonstrated an increased locomotor response compared to maximally stimulated animals and maternal-reared control animals. As methylphenidate acts to block the reuptake of DA, while amphetamine triggers the release of presynaptic DA, these results suggest that AR increases DA synthesis/release, rather than reuptake. Alterations in NE may provide a compensatory pathway when animals are given methylphenidate (Lovic et al., 2006). Sex differences in the neurobiological consequence of maternal deprivation are also suggested by these results. However, whether these sex differences are related to the known differences in the amount of maternal care given to male and female pups in maternally reared animals, which are not mimicked in AR paradigms, has yet to be fully evaluated (Lovic et al., 2011).

Consistent with the pharmacologic studies, gene expression data also suggest that alterations in striatal DA receptors, as well as intermediate early genes, contribute to the hyperlocomotion phenotype (Lovic et al., 2013). A recent paper by Makinodan et al. (2012) provides data implicating altered myelination and a gene, v-erb-a erythroblastic leukemia viral oncogene homolog 3 (*Erbb3*), in the pathogenesis of decreased PFC myelination and subsequent neurocognitive outcomes. These studies indicate that the DA pathways and alterations in PFC function and myelination are associated with the persistent behavioral outcomes following AR. Ap-

plying the translational principles of developmental psychopathology to this data, potential next steps could include examination of genetic associations with these genes in studies of PI children.

Although not testable in the current cohorts of PI children due to the lack of information about prenatal exposure, the interaction between prenatal stress exposure and subsequent AR has been reported in rodent models. While increased stroking of the AR pups normally results in decreased pup locomotor activity, pups exposed to prenatal stress prior to AR rearing did not benefit from increased anogenital stimulation following birth, indicating that prenatal exposures further moderate the impact of early maternal deprivation (Burton et al., 2006). The potential transgenerational effect has also been suggested in multigenerational rodent studies where AR dams demonstrated hyperactivity and persistent distractibility, and were more inattentive to their pups compared to MR dams (Gonzalez et al., 2001). The impact of AR on maternal behavior has substantial clinical implications for intervention approaches for children with a history of early institutional care as they themselves become parents.

Other studies report the association between early social isolation and increased activity and impulsivity in rodent models (Cusack, Swahari, Henley, Ramsey, & Deshmukh, 2013; Teffer & Semendeferi, 2012). However, due to the differences in the timing of isolation (i.e., some studies begin social isolation at PND 21, weaning) and/or duration of separation (i.e., daily maternal separation compared to complete deprivation), these findings are beyond the scope of this manuscript. Studies that compare the neurobiological impact of separation beginning at birth versus social isolation beginning at weaning are needed.

NHP studies. An early study by Harlow et al. (1965) indicated that NHP models of isolative rearing or PR, with almost complete deprivation of maternal presence, resulted in elevated levels of aggression and impulse control deficits, including impulsive violence and aggressive play during peer interactions (Higley et al., 1996; Higley, Linnoila, & Suomi, 1994; Huang & Lo, 1998; Kraemer & Clarke, 1996; Kraemer, Schmidt, & Ebert, 1997). In NHP that are maternally deprived, aggression is less predictable, more frequent, more severe, longer in duration, and directed toward more improbable objects, compared to that observed in MR NHP (Kraemer & Clarke, 1996). Maternally deprived NHP show functional deficits in areas of the PFC associated with impulse control and impulsive aggression (Heinz et al., 1998; Higley et al., 1996). In normative settings, the maternal responses to infant aggression are thought to be critical experiential input for the development of inhibitory control (Maestripieri, 2009; Suomi, 1982), likely via serotonergic pathways (Heinz et al., 1998; Higley et al., 1996; Kraemer et al., 1997).

After 3 years of normal social life, PR NHP persistently showed decreased locomotion and initiation of sitting together (a social affiliation behavior), as well as increased stereotypical behaviors compared with MR NHP (Feng et al., 2011; Harlow et al., 1971). Similar to AR rodent models, PR female NHP, when they become mothers, display deficits in maternal behavior. Additional examination, in human, NHP, and rodent modes, of sex differences is clearly warranted.

Human studies. Since the 1940s, hyperactivity and impulsivity have been reported in children with a history of early institutional care (Goldfarb, 1943). Developmental continuity and persistence of hyperactivity are consistently reported in studies of PI children (Barnett, Heron, Goldman, Jones, & Xu, 2009; Kreppner et al., 2001; Roy, Rutter, & Pickles, 2004; Zeanah et al., 2011). Recent research from the BEIP indicates that among children removed from institutions, amount of time spent in foster care was inversely related to ADHD symptoms ($r = -.41$; Tibu, Humphreys, Fox, Nelson, & Zeanah, 2014), suggesting that there may be some remediation of ADHD deficits with high-quality caregiving. Neurobiological data suggest that these symptoms are related to altered frontal striatal and ventral tegmental circuitry, areas implicated in idiopathic ADHD as well (McLaughlin et al., 2010). Increased fronto-striatal connectivity was associated with elevated externalizing behavior problems in a study of 15 PI children at 10 years of age (Behen et al., 2009). Evidence of the role of DA neural systems in hyperactivity has been found in the BEIP. Specifically, while there was no main effect of DA transporter 1 (*DAT1*) genotype on hyperactivity, genotype significantly predicted *change* in hyperactivity across early development. Individuals with the *10/10 DAT1* genotype were found to have a significantly increased slope in hyperactivity relative to other genotypes over time ($p = .003$; Humphreys, Zeanah, Nelson, Fox, & Drury, 2014). These results demonstrate a marginal elevated risk for hyperactivity symptoms at 54 months of age in individuals, regardless of intervention group status.

The association between hyperactivity and the *10/10* genotype is consistent with previous studies that reported increased risk of ADHD symptoms and diagnosis in association with the *10* allele (for a review, see Gizer, Ficks, & Waldman, 2009), including studies of children with a history of institutional care (Stevens et al., 2008, 2009). Taken together, rodent, NHP, and human studies indicate that H/I following early maternal deprivation is associated with alterations in DA, serotonin, and NE transmission, as well as structural and functional changes in the ventral striatal and frontostriatal circuits. The differential response of AR rodents to amphetamine and methylphenidate suggests that children with a history of early institutionalization and symptoms of H/I may differentially respond to these medications. The implications of these rodent studies for pharmacologic treatment approaches addressing H/I in PI children represents an intriguing area of future research.

Sensitive periods. The strongest evidence for the existence of a sensitive period for any of the three neural systems presented in this review exists in relation to H/I. Within the ERA study, a clear dose response relation between H/I and

duration of institutional care has been demonstrated. In this study, children removed from institutional care before 6 months of age had no increased risk for H/I when compared to community-controlled children (Stevens et al., 2008). While not directly testable within the BEIP, because the earliest age at placement was after 6 months, the findings that ADHD symptoms were particularly resistant to the foster care intervention are consistent with the existence of an early sensitive period (Zeanah et al., 2009). Similar resistance of ADHD symptoms to recovery following later adoption was also found in the International Adoption Project (Gunnar & van Dulmen, 2007). The ability to mitigate the hyperlocomotive phenotype in AR rats with increased tactile stimulation following birth is also consistent with the presence of a very early sensitive period given the developmental timing differences in gestation. Studies in the AR rodent model that begin with minimal stimulation and subsequently incorporate maximal stimulation at varying later developmental time points could refine this sensitive period further.

An additional peripubertal sensitive period is suggested by several longitudinal studies. First, Kumsta et al. (2010) noted the while children with the short allele of *5-HTTLPR* overall had increased symptoms of ADHD when examined at ages 6, 11, and 15, those children with the short allele, but no stressful life events between age 11 and 15, placed into adoptive homes had decreased symptoms. These results suggest that at earlier time points the short allele conferred increased risk, but between 11 and 15 years of age, these children appeared to preferentially benefit from the improved caregiving found in adoptive stable homes. Second, although sex differences, across multiple studies of PI children, in H/I were not demonstrated during preschool and middle childhood, the expected higher prevalence in males was demonstrated in the ERA study at ages 11 and 15 (Kumsta et al., 2010; Zeanah et al., 2009). Preliminary examination of teacher-reported symptoms using the Health Behavior Questionnaire in the BEIP study at age 8 failed to find sex differences in inattention and H/I (unpublished data). It is interesting that, in a study of children ages 8 to 11 years old ($N = 68$ PI children), Wiik et al. (2011) utilized the parent and child Health Behavior Questionnaire report, and the expected higher rates of symptoms in males was found. However, the mean age of children in this study was not reported. At 13 years of age, females who experienced a mean of 20.7 months of institutional care appeared to have a remission of H/I symptoms. Males from this same study, with a similar length of exposure to institutional care, did not demonstrate significant remission of symptoms at age 13 years (Zeanah et al., 2011). Taken together, these findings suggest that between the ages of 8 and 11, a sex-specific sensitive period may occur. Longitudinal studies, incorporating measures of pubertal development, through adolescence are needed.

EF

Work from rodent, NHP, and human studies indicates that maternal deprivation is associated with significant EF deficits. EF is a set of higher order cognitive skills that includes inhibitory control, planning, set shifting, working memory, and problem solving. In the RDoC matrix, EF falls under the cognitive domain, but it is subdivided into several constructs. Similar to H/I, deficits in components of EF cut across psychiatric diagnostic categories and involve multiple neural pathways; however, a majority of EF is integrated through the PFC (Cicchetti & Rogosch, 2012).

In youth, for the most part, EF improves with age, likely due to the protracted maturational process of the PFC (Huizinga, Dolan, & van der Molen, 2006). Among noninstitutionalized children, EF is linked to a number of outcomes, including psychopathology and academic achievement (e.g., Pennington & Ozonoff, 1996; St. Clair-Thompson, & Gathercole, 2006). Given the association among early deprivation, psychopathology, academic functioning, and functional impairment (MacLean, 2003; Zeanah et al., 2009), identifying developmental windows when interventions would have enhanced efficacy to improve EF represents an important target for improving long-term outcomes.

Rodent studies. The attentional domain of EF appears to be particularly impaired in AR rodents. Lovic and Fleming (2004) compared female rats who were AR and MR with two attentional tasks: attentional set-shifting and prepulse inhibition. These tasks selectively assess complex and automatic attentional processes, respectively. Attentional set-shifting requires both learning and reversal learning, and is measured via association learning of specific odors or textures with a reward. Prepulse inhibition measures the automatic inhibitory mechanisms of attention. While MR and AR rats did not differ in learning simple stimulus–reward associations, minimally stimulated AR rats needed significantly more trials than MR rats in reversal learning tasks. Maximally stimulated AR rats did not differ in shifting and reversal learning compared to MR rats, indicating that the impact of AR can be mitigated, to some extent, by maternal replacement behaviors.

Minimally stimulated AR female rats also demonstrated reduced levels of prepulse inhibition, a measure of automatic attentional inhibitory processes, compared to MR rats (Burton et al., 2006; Lovic & Fleming, 2004). In the second study, rearing conditions did not predict differences in spatial working memory, a task expected to load onto broader EF. Recent studies in male rats have reported that the effect of AR effect on prepulse inhibition is moderated by genetic variation in the serotonin transporter gene (Belay et al., 2011), suggesting a sex-dependent effect of AR on prepulse inhibition and that the relative amount of maternal-like stimulation can improve performance on some attentional measures. Variation in the amount of tactile stimulation has also been found to impact social learning, including the ability to learn general and olfactory characteristics of a conspecific (Levy et al., 2003; Melo et al., 2006). The previously discussed alterations of DA systems following maternal deprivation represent one likely mechanism related to EF and attentional deficits (Afonso et al., 2011; Hall et al., 1999; Lovic & Fleming, 2004).

Attentional set-shifting has been linked to the mPFC using lesion studies in rats (Parr, Winslow, & Davis, 2002). At the cellular level, juvenile AR rodents (compared to MR rodents) have increased numbers of neurons and astroglial cells, but reduced expression of neural proteins involved in synaptic and neuronal plasticity (Chatterjee et al., 2007), a state characterized as "reduced cortex functionality." Increased tactile stimulation appeared to partially mitigate these cellular effects, as maximally stimulated AR animals demonstrated apoptotic cell death and expression levels of neural proteins that were intermediate to, and significantly different, from both the MR and the minimally stimulated AR animals. Though the PFC was primarily examined, several other brain regions, including the nucleus accumbens, an area associated with learning, memory, and reward, and implicated in a range of psychological disorders (e.g., depression and substance abuse), demonstrated similar altered expression patterns. These findings suggest that the alterations in the molecular mechanisms controlling neural plasticity, apoptosis, the connections from the PFC, and the efficiency of neural transmission likely contribute to EF deficits in AR animals.

NHP studies. Volumetric measures in rhesus monkeys indicated that PR NHP had significantly *larger* dorsomedial PFC and dorsal anterior cingulate cortex volume compared to MR NHP, although total volumes were not significantly different (Spinelli et al., 2009). This increased volume is consistent with the decreased apoptosis found in the AR rodent models. In humans, the dorsomedial PFC volume is linked to attention and broader EF (Hornak et al., 2004), though it is unclear whether increased volume would be associated with better or worse function.

The NHP model provides insight into the involved molecular pathways as well. PR NHP demonstrated deficits in attention orientating when compared to MR NHP (Champoux et al., 2002). This effect was moderated by the serotonin transporter gene, such that PR NHP with the *rh5HTTLPR* short/long genotype (as opposed to long/long genotype) demonstrated lower orientation scores (indicating worse attention). Genotype did not impact orientation performance within the MR NHP. Consistent with the rodent data, changes in DA and NE systems following maternal deprivation are likely involved (Ichise et al., 2006); however, there may be greater evidence for a role of serotinin systems in NHP studies. Evolutionary differences in cortex development between these two model systems (rodent and NHP) may explain these differences (Robbins, 2000). Refinement of these mechanistic pathways, potentially though the examination of the modifying effects of genetic and epigenetic variation, are important future research directions.

Human studies. Studies of EF in preschool-age children exposed to early institutional rearing have mixed results. In one sample of preschool-age children, those with a history of PI did not significantly differ from typically reared children (Merz & McCall, 2011). However, another study examined EF in internationally adopted children age 4–5 years and found that EF deficits were present in a substantial proportion of the sample, with 11% of the children scoring in the clinically significant EF impairment range (Jacobs et al., 2010). In a third sample of preschool-age children, adopted at a mean age of 24 months (range 16–36 months) and tested 1 year after adoption, PI youth had significantly lower EF scores than the non-adopted comparison group, even after controlling for group differences in full-scale IQ (Hostinar, Stellern, Schaefer, Carlson, & Gunnar, 2012). While duration of institutional care was associated with lower IQ, a different pattern emerged for EF. Specifically, after controlling for IQ, duration of institutional care itself was not associated with EF; however, other measures of the preadoptive environment were associated with EF. After accounting for the effect of IQ, both higher quality and more time with family prior to placement in institutional care were associated with higher EF scores. No direct sex or sex by early care group interactions in EF were found.

Findings from the BEIP indicate that institutionalization is associated with reduced EF at age 8 years as measured via the Cambridge Neuropsychological Test Automated Battery (Bos et al., 2009). The effect of high-quality foster care did not appear to remediate EF abilities, though the relatively late age of placement into foster care (average of 22 months) limits the ability to detect potential advantages conferred by earlier placement. Within the ERA study, children adopted before the age of 6 months did not differ from UK adoptees on the Stroop task, a measure of response inhibition (Colvert et al., 2008). However, children adopted after 6 months of age performed significantly worse on the Stroop task than did the comparison group. It appears that both continued deprivation after 6 months of age and longer total duration of institutional care predict poorer EF abilities, particularly when children are tested after preschool age. Another recent study, of 138 children ages 6–15 years (47 PI) found longer duration of institutional care associated with worse performance on an associative learning task (Humphreys, Lee, et al., 2014). This study also found that sex moderated the association, because PI males failed to demonstrate learning across the course of the task, whereas PI females and comparison children all improved in performance with experience. Sex differences have also been reported in the AR rodent model; however, few studies are performed concurrently in both sexes.

In another study, EF was measured in 61 children (31 PI children, adopted at a mean age of 31 months (range = 4–77 months) using the Intra-Extra Dimensional Set Shift, Stockings of Cambridge, and Spatial Working Memory tests from the Cambridge Neuropsychological Test Automated Battery (Bauer, Hanson, Pierson, Davidson, & Pollak, 2009). In each of these tasks, there was a significant effect of group, such that PI youth had significantly lower EF than comparison youths but no differences on attentional tasks. In this study, length of institutionalization was not examined. Deficits in EF was also reported for children 5–8 years old adopted from Russia whose adopted parents reported that PI children, on average, had significantly more global EF difficulties than the

mean of typically developing children (Merz & McCall, 2011). Children adopted before the age of 18 months did not differ from the typically reared population mean, while those adopted later demonstrated significantly larger deficits in EF (Merz & McCall, 2011).

Few research studies have examined the neural correlates of these EF deficits in humans. PI children from the BEIP had smaller cortical gray matter volume than did never institutionalized children (Sheridan et al., 2012). This study found that children placed in foster care did not have significantly different cortical white matter volumes compared to never institutionalized children, whereas children who were randomized to remain in institutional care had significantly smaller cortical white matter volumes. The EF deficits found among institutionalized children from the BEIP may be partially mediated via relative alpha power measured with electroencephalogram (McLaughlin et al., 2010; Sheridan et al., 2012). In one study, differences in cerebellar volume were found between PI children and comparison children as well as a significant association between superior–posterior lobe volume and Stockings of Cambridge task performance, suggesting a link between these two findings although formal mediation was not tested (Bauer et al., 2009). In a small sample ($N = 10$) of children adopted from Romania at a mean age of 38 months (range = 16–90 months), Chugani et al. (2001) found below-average EF performance on measures of sustained attention, impulse control, and cognitive efficiency. Using positron emission tomography in this same sample, differences in glucose utilization in several brain regions associated with EF, including within the PFC, were also found in PI children, although, again, direct mediation was not tested. Although volumetric, electroencephalogram, and glucose metabolic rate differences have been found between PI and comparison children, more research is needed to formally link these neuroanatomical difference to EF deficits.

Sensitive periods. Extrapolation from data across all studies suggests an early sensitive period for EF occurring before 6 months of age. The timing of this would be consistent with the ability of the AR maximal stimulation model to rescue some measures of EF deficits. Similar evidence of sensitive periods in other outcomes is reported in the NHP literature (Kraemer et al., 2004; Nelson et al., 2002; O'Connor & Cameron, 2006; Sabatini et al., 2007); however, EF deficits have not directly been assessed to date. Human studies suggest that children adopted at very young ages (i.e., 6 months) may not demonstrate later deficits in EF, though 18 months was also indicated as a potential cutoff age (Merz & McCall, 2011). Maternal care prior to institutionalization may also have a moderating effect (Hostinar et al., 2012).

A challenge when defining sensitive periods in EF is the multicomponent nature of EF. For example, inhibitory control, a facet of EF, develops earlier than other processes (e.g., set shifting; Jurado & Rosselli, 2007). As such, different sensitive periods may exist for the individual circuits subserving components of EF, and disentangling these likely requires analyses focused on specific components of EF (i.e., working memory, attention, spatial orientation, and updating) more in line with an RDoC neural systems based approach.

Sleeper effects. Both the PFC and EF appear to undergo a protracted developmental course. This, coupled with the considerable evidence that the brain develops functionally from the bottom up, suggests that deficits in EF following maternal deprivation may be highly susceptible to sleeper effects. An early study on EF in a typical population found that "adult-level" performance on three EF tasks (Wisconsin card sort task, tower of Hanoi, and matching familiar figures task) varied significantly, reaching maturity at significantly different time points across development: age 6 years, 10 years, and in adolescence, respectively (Welsh, Pennington, & Groissier, 1991). The differential developmental trajectory of EF function suggests that environmental remediation following maternal deprivation before 6 months of age could result in typical development/performance on EF domains. The minimal evidence of EF deficits in the preschool studies contrasted with clear evidence of EF deficits in older children, when combined with the data from the rodent and NHP studies, suggests the existence of sleeper effects in EF. Recent work on amygdala–mPFC connectivity in children with and without a history of institutionalization indicated shifts in the developmental tempo of functional connectivity and potential acceleration in the development of "adultlike" connectivity in PI children (Gee et al., 2013). Thus, even though PFC development is protracted, and therefore somewhat buffered from the impact of early maternal deprivation, the impact of deprivation on earlier developing structures such as the amygdala and hippocampus may alter the connectivity between these structures and the PFC, thereby effecting EF.

HPA axis

The HPA axis is a major system that mediates the neuroendocrine response to stress and includes a complex set of circuitry among the hypothalamus, pituitary, and adrenal glands (Wismer Fries, Shirtcliff, Pollak, & Fries, 2008). In this system, glucocorticoids (i.e., corticosterone in rodents, and cortisol in NHP and humans) are released from the adrenal cortex during stressful conditions (Gold & Chrousos, 2002; Heim, Plotsky, & Nemeroff, 2004). The HPA axis plays an important role launching appropriate physiological responses to manage acute stressors throughout the life span. Within the RDoC matrix, the HPA axis is incorporated into the arousal and regulatory systems (http://www.nimh.nih.gov/research-priorities/rdoc/rdoc-constructs.shtml#arousal_regulatory). Similar to EF and impulsivity, alteration in the functioning and reactivity of the HPA axis is found across psychological disorders.

A growing body of literature indicates that maternal care, maternal deprivation, and therapeutic interventions targeting the dyadic relationship all impact the regulation of and function of the HPA axis (Cicchetti, Rogosch, Toth, & Sturge-

Apple, 2011; Fisher, Gunnar, Dozier, Bruce, & Pears, 2006; Gunnar & Quevedo, 2007a; Sanchez, 2006). However, experimental paradigms expected to activate the HPA axis, including the strange situation procedure (Ainsworth, Blehar, Waters, & Wall, 1978), may not reliably produce a cortisol response in very young children, especially in children with organized attachment (Bernard & Dozier, 2010). As such, given that the HPA axis plays a central role in child developmental trajectories, diurnal variations in cortisol or the cortisol awakening response (CAR) may be more appropriate for identifying sensitive periods in young children with a history of institutional care (Meaney et al., 1996). Alternatively, exploration of molecular changes in the genetic mechanisms controlling the HPA axis, in lieu of or in conjunction with cortisol, may have particular utility early in development. One example is changes in messenger RNA mRNA expression levels of *FKBP5*, a key regulator of the HPA axis ultrashort negative feedback loop (Binder, 2009; Jaaskelainen, Makkonen, & Palvimo, 2011; Vermeer, Hendriks-Stegeman, van der Berg, van Buul-Offers, & Jansen, 2003). Preliminary findings indicate that alterations in the regulation of *FKBP5* mRNA are found in children exposed to early institutional care (Brett, Binder, et al., 2014).

Studies of the impact of early life adversity on HPA axis activity in young children ought to consider the stress hyporesponsive period (SHRP). The SHRP refers to a time period early in life when baseline plasma glucocorticoid levels are lower than normal and increase only minimally with stress exposure (Levine, 1994; Lupien et al., 2009), yet the central components of the HPA axis, including the pituitary and the hypothalamus, remain reactive (Dent, Smith, & Levine, 2000; Smith, Kim, van Oers, & Levine, 1997). The SHRP is associated with the rapid regression of the HPA axis after birth and may have evolved to protect the rapidly developing brain from the impact of elevated glucocorticoids (Levine, 1994). In rodents, the SHRP is maintained primarily by maternal care; however, even during the SHRP, maternal separation is a potent inducer of the stress response.

Evidence of a SHRP has also been found in human studies (Gunnar & Quevedo, 2007b). At birth, glucocorticoid levels increase sharply in response to various stressors, such as a physical examination or a heel lance. However, over the course of the first year, the HPA axis becomes less sensitive to stressors (Lupien et al., 2009). This hyporesponsivity during the first year may reflect the fact that the HPA axis comes under strong social regulation and parental buffering during this time period (Gunnar & Quevedo, 2007a, 2007b; Hostinar & Gunnar, 2013; Hostinar, Sullivan, & Gunnar, 2013). Evidence suggests that the SHRP in humans is found during the first 3–5 years of life (Gunnar & Quevedo, 2007b).

Rodent studies. Both altered HPA function and altered behavioral stress reactivity have been found in AR rodent studies (Sanchez, 2006; Sanchez, Ladd, & Plotsky, 2001). AR males have been found to have corticosterone elevations after restraint stress, while this same effect is not seen in AR females (Belay et al., 2011). In females, there is evidence that exposure to prenatal stress further modifies the association between AR and HPA reactivity (Burton et al., 2007). In general, altered patterns of HPA activity persist in rodent models throughout the life course. However, environmental enrichment (Francis, Diorio, Plotsky, & Meaney, 2002; Iwata, Kikusui, Takeuchi, & Mori, 2007) and manipulation of the amount of early somatosensory stimulation may ameliorate some of these lasting effects (Brake et al., 2004; Caldji, Diorio, & Meaney, 2003; Caldji et al., 1998; Cameron, Fish, & Meaney, 2008; Champagne et al., 2008; Champagne, Francis, Mar, & Meaney, 2003; Francis & Meaney, 1999; Zhang & Meaney, 2010).

The amount of tactile stimulation (i.e., licking) provided by the mother, as well as the relative amount of tactile stimulation provided to AR pups, moderates HPA axis activity (Francis & Meaney, 1999; Gonzalez et al., 2001; Levine, Huchton, Wiener, & Rosenfeld, 1991; Levy et al., 2003; Liu et al., 1997; Lovic & Fleming, 2004; Novakov & Fleming, 2005; Schanberg & Field, 2003; Ward, Xing, Carnide, Slivchak, & Wainwright, 2004). Higher levels of licking are associated with increased levels of glucocorticoid mRNA expression in the hippocampus, a key component of the negative feedback system of the HPA axis (Liu et al., 1997; Merz & McCall, 2010). Presumably rat pups that are licked more would be expected to have a more "adaptive" stress responses, recovering faster after stress exposure, although contradictory findings have been reported (Belay et al., 2011).

NHP studies. In NHP studies, HPA axis activity has been shown to be affected by early social rearing experience (Champoux, Coe, Schanberg, Kuhn, & Suomi, 1989; Coplan et al., 1996; Coplan, Rosenblum, & Gorman, 1995; Hill, McCormack, & Mason; Mason, 1979; Meyer, Novak, Bowman, & Harlow, 1975; Sackett, Bowman, Meyer, Tripp, & Grady, 1973). PR NHP demonstrate altered HPA axis function (Parr et al., 2002; Sanchez, 2006; Winslow, 2005), characterized by elevated plasma diurnal cortisol (Barrett et al., 2009) and substantial delays in peak cortisol response to stress (Feng et al., 2011). HPA axis disruptions have been observed in 2-year-old PR NHP, a developmental phase equivalent to late childhood (prepuberty) in humans (Barrett et al., 2009). Even when the PR NHP are returned to normative social environments, altered HPA function remains (Feng et al., 2011). The persistent hypocortisol state may be the result of the downregulation of the negative feedback system after an initial hypercortisol state (Feng et al., 2011). Longitudinal studies, however, are needed to elucidate developmental effects, patterns of dysregulation, and the impact of interventions on HPA axis function.

Genetic variation, particularly in genes influencing serotonergic tone, may further influence the association between early caregiving and HPA axis function. NHP carriers of the short allele of the serotonin (*rh5-HTTLPR*) gene exposed to PR show altered stress-induced HPA axis responses compared to maternally reared short allele carriers and long allele

homozygotes (Barr, Newman, Lindell, et al., 2004; Barr, Newman, Shannon, et al., 2004; Erickson et al., 2005; Shannon et al., 1998).

The persistent effects of PR on the functioning of the HPA axis in both NHP and human studies are congruent with the psychobiology of attachment theory (Kraemer, 1992). This theory hypothesizes that infant primates are born with several psychobiological systems, including the HPA axis, that require intimate interaction with an appropriate caregiver to mature and become effective self-regulating systems (Kraemer, 1992). Although substantially more research is needed to define the underlying mechanisms (see Plotsky & Meaney, 1993; Plotsky, Thrivikraman, & Meaney, 1993; Viau, Sharma, Plotsky, & Meaney, 1993), NHP findings related to the effect of PR on the HPA axis are consistent with those from rodent (Plotsky & Meaney, 1993) and human studies (Spangler, 1991), suggesting a powerful maternal influence on the organization of HPA axis.

Human studies. In humans, the HPA axis is highly responsive, matures throughout infancy and childhood, and is influenced by the caregiving relationship (Cicchetti et al., 2011; Dozier, Manni, et al., 2006; Gunnar, Morison, Chisholm, & Schuder, 2001). Studies have shown that children 2–3 years of age still residing in institutional care have blunted diurnal cortisol rhythm and low CAR (Carlson & Earls, 1997; Gunnar, Bruce, & Grotevant, 2000). Children 6–12 years of age who were removed from institutional care after 8 months of age had significantly *higher* cortisol levels over the course of the day than did both children adopted by 4 months of age and children raised in their biological families (Gunnar et al., 2001). These findings initially appear incongruent. However, these apparent discrepancies may suggest disruption in the normative developmental trajectory of the HPA axis, resulting in different patterns of HPA axis function depending on the age when cortisol levels are determined.

Early morning cortisol and decreases in diurnal cortisol were evaluated in a study of PI children, 7–11 years of age, living for at least 3 years with adoptive parents. In this study, duration of institutionalization did not predict cortisol levels. However, growth delay was associated with duration of institutional care, higher early morning cortisol, and a steeper cortisol decrease across the day (Kertes, Gunnar, Madsen, & Long, 2008). Similarly, in a study of Ukrainian institution-reared children 3–6 years of age, overall diurnal cortisol was associated with growth delay. PI children with temporary growth delay had higher overall diurnal cortisol, compared to both never institutionalized children and chronically stunted PI children. Although in this study duration of institutional care was not addressed, findings across studies suggest that growth and developmental stage are important considerations for future studies (Dobrova-Krol, van IJzendoorn, Bakermans-Kranenburg, Cyr, & Juffer, 2008).

Urine cortisol levels were measured in a study of PI children by Wismer-Fries et al. (2008). In this study, PI children (mean age 4.5 years) had prolonged elevations in cortisol following parent interaction, compared to same-age never institutionalized children (Wismer Fries et al., 2008). However, consistent with nonhuman animal research and other studies, basal cortisol levels did not differ. Additional analysis revealed that, within the PI group, children exposed to more *severe* neglect (based on parent report of their impressions of the institution in which their child had previously resided) exhibited the highest basal cortisol levels (Wismer Fries et al., 2008). These findings suggest that the qualitative aspects of caregiving, rather than simply exposure to institutionalization, may predict altered HPA axis regulation. In older children, cortisol reactivity, rather than basal measurement, may be a more sensitive indicator of exposure. Therapeutic repair of the attachment relationship has been found to normalize HPA axis function in high-risk toddlers, an approach that may have utility, particularly early in development, for post-institutionalized children (Bernard & Dozier, 2010; Cicchetti et al., 2011; Dozier, Manni, et al., 2006; Dozier, Peloso, et al., 2006; Fisher et al., 2006).

Sensitive periods. Evidence suggests an HPA axis sensitive period, or a developmental switch, exists between pre- and postpubertal periods. Hankin, Badanes, Abela, and Watamura (2010) described a pubertal developmental switch from cortisol hyporeactivity to hyperreactivity among at-risk, dysphoric youth. The pubertal stage likely influences HPA axis function, and the peripubertal transition may be a critical "reset" time period for HPA axis function. Quevedo et al. (2012) examined the relation between puberty and CAR in a group of adopted 12- to 13-year-old children exposed to variable amounts of early institutional care. Compared to typically reared children, PI children in the prepubertal or early pubertal phase had flatter CAR, whereas no significant difference in CAR was found for children in the mid- to late-pubertal phase. The apparent correction of the CAR in PI children may reflect "catch-up" maturation of this system during puberty (Quevedo et al., 2012). These findings parallel those of the altered maturational rate of amygdala–mPFC connectivity found in functional MRI studies of PI children (Gee et al., 2013).

One unexplored caveat is that alterations in the rate of development may or may not be beneficial. Rapid catch-up development has the potential to create sleeper effects if the neural substrate underlying a particular pathway is built differently as a consequence of altered developmental tempo. In the case of the HPA axis, abnormal regulation early in development in PI children, followed by more normative responses in adolescence, may reflect repair in the system. Alternatively, if the neurobiological processes underlying the HPA axis developed fundamentally different than that of typically reared individuals, the potential for elevated risk throughout the life course remains. Disentangling these hypotheses has significant clinical implications. If the peripubertal transition is a critical time period when repair of HPA functioning occurs, then targeted interventions focused on stress reactivity could substantially decrease future psy-

chopathology risk. Following this same logic, puberty also represents a time point with significant risk should negative psychosocial conditions persist. These developmental switch periods have significant implications for the pathophysiological understanding of how at-risk youth may be differentially susceptible to both psychopathology and psychotherapy across development.

Evidence of sensitive periods related to threat and self-comforting exist in the NHP model (Nelson et al., 2002; O'Connor & Cameron, 2006; Sabatini et al., 2007). NHP separated from their mother at 1 week and 1 month of life show markedly different behavioral responses to social threat stimulus (a "stare" from a human stranger) compared to NHP separated at 6 months of life (regular time period of weaning; Nelson et al., 2002; Sabatini et al., 2007). Specifically, NHP separated at 1 week of age showed little response to social threat and fewer social behaviors (e.g., did not seek social comfort), were not socially vigilant, and had increased self-comforting behaviors (e.g., thumb sucking). NHP separated at 1 month of age showed increased anxiety and hypervigilance to social cues and increased seeking of social comfort later in life (Nelson et al., 2002; O'Connor & Cameron, 2006; Sabatini et al., 2007). These behaviors were associated with altered amygdala expression of guanylate cyclase 1 α 3 (*rhGUCY1A3*) mRNA, an element of the nitric oxide signaling cascade specifically associated with the timing of early life social stress (Sabatini et al., 2007). Further, studies of sensitive periods in NHP are required, ideally with concurrent assessment of cortisol levels.

Overall, the relative inconsistencies in the existing HPA axis studies prevent clear conclusions about the role of sensitive periods in relation to the impact of early maternal deprivation. These inconsistencies are likely the result of cortisol measurement differences (diurnal, CAR, and acute), comparison across developmental time periods, and wide variation in the amount and intensity of deprivation experienced by children. Current findings from human studies suggest that longer duration of exposure to maternal deprivation is associated with higher risk of persistent deviations in HPA axis function. Evidence demonstrates that early institutionalized children experience altered HPA axis function; however, the SHRP, growth delay, changes to circadian rhythm, and potential reorganization of HPA axis during puberty are important covariates. If adolescence represents a sensitive period for HPA development, it is likely influenced by both past experiences and the current environment. Longitudinal studies, across pubertal development, incorporating HPA axis response to acute stress, as well as considerations of genetic and epigenetic regulators of the HPA axis, are important next steps.

Conclusions and Future Directions

Combining multiple levels of analysis, a transdisciplinary perspective, and translational research is key to the discipline of developmental psychopathology (Cicchetti & Toth, 2009). To better understand neural plasticity and sensitive periods in response to maternal deprivation, we have attempted to integrate data from preclinical models and human studies. Data across AR rodent studies, PR NHP studies, and human studies of PI children provide preliminary evidence of a sensitive period for H/I before 6 months of age, and potentially a somewhat broader sensitive period modified by the SHRP period for the HPA axis. In both neural systems, human studies hint at a peripubertal developmental switch point where neural plasticity may be heightened. As such, this time period may represent a reopening of particular sensitive periods and, if present, a time period when interventions could have enhanced effects.

Given that adolescence is associated with heightened psychopathology risk, regardless of early experiences, attention to this developmental period and the provision of an enhanced environmental and caregiving support during this time may be crucial for positive long-term outcomes in children with a history of early institutional care. Therapeutic interventions focused on the regulation of the stress response and impulsivity may be of benefit during adolescence, particularly if neural plasticity in these systems is elevated. Differential effects of various stimulant medications and alpha agonists in the AR rodent models suggest that differences exist in the neural pathways leading to H/I following early maternal deprivation compared to H/I in typically developing children. Further studies in the AR rodent model refining the differences in stimulant sensitivity and response coupled with careful trials comparing classes of stimulant and nonstimulant medications in postinstitutionalized children with H/I are predicted to enhance current treatment modalities.

While evidence in younger children suggests that early removal from institutional care can remediate EF deficits, more recent data suggests that sleeper effects may be present in this domain as well as overall cognitive function. For example, in the BEIP study, a sensitive period for foster care at 24 months of age was detected in IQ when the children were 54 months of age. Specifically, if a child was placed into foster care before 24 months of age, there was significant recovery in IQ at 54 months of age. Placement after 24 months of age did not result in significant improvement in IQ. However, when these same children were evaluated at 8 years of age, the putative sensitive period of 24 months was no longer present (Fox et al., 2011). Several interpretations of these findings are possible. The first interpretation is that the initial sensitive period was not present. A second interpretation is that although there was a sensitive period with an impact at 54 months of age on IQ, because of the complexity of the neural systems underlying IQ, the detectable impact of this sensitive period at later developmental points diminished. This would indicate that studies testing more refined aspects of IQ that reflect more precise neural pathways could potentially identify persistent sensitive period effects. A third alternative is that the effect of institutional care on IQ represents a sleeper effect. If this is correct, evidence of less intervention effects from foster care, as well as larger differences in IQ between typically

reared children, may unfortunately be discovered as these children age.

Treatment implications are obvious. Early attention, identification, and enhanced intervention for even small cognitive deficits are likely critical for the long-term outcomes in these children. Even if only minor differences are detected in the preschool time period, enhanced educational support should be provided to leverage the greater neural plasticity early in development because substantial data indicates the importance of earlier developing cognitive processes for higher order EF.

Much remains to be done to define sensitive periods in development. Molecular genetic studies of neural plasticity and direct integration of preclinical animal models with human studies are needed to advance the field. Basic research must be conceived within a conceptual framework that strives to inform future clinical applications (Cicchetti & Toth, 2009). Selection of the most appropriate animal models for studies examining the impact of maternal deprivation, coupled with a neural systems approach reflective of RDoC, have the greatest utility for reaching a more mechanistic understanding. H/I, EF, and HPA axis functioning are highly relevant domains across development and psychopathology. These domains are also associated with significant overall functional impairment and related to a wide range of negative health consequences and health risk behaviors. Achieving the best outcomes for children exposed to negative early experiences requires a comprehensive, systems-based approach. The integration of neuroscience, molecular genetics, and developmental psychology theory offers the greatest potential to improve outcomes for these vulnerable individuals.

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