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REVIEW

Early Institutionalization: Neurobiological Consequences and Genetic Modifiers

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Abstract Children raised in the profound deprivation associated with institutionalization are at elevated risk for negative outcomes across a host of social and cognitive domains. This risk appears to be mitigated by early foster care or adoption into a family setting. Although pervasive developmental problems have been noted in a substantial proportion of previously institutionalized children, marked variation exists in the nature and severity of these deficits. Increasing evidence suggests that institutional deprivation impacts the developing brain, potentially underlying the wide range of outcomes with which it is associated. In the current review we examine the neural consequences of institutionalization and genetic factors associated with differences in outcome in an effort to characterize the consequences of early deprivation at a neurobiological level. Although the effects of institutional deprivation have been studied for more than 50 years much remains unanswered regarding the pathways through which institutionalization impacts child development. Through a more complete and nuanced assessment of the neural correlates of exposure and recovery as well as a better understanding of the individual factors involved we will be better able to delineate the impact of early adversity in the setting of severe social deprivation.

Keywords BEIP · Institutionalization · Romania · Developmental psychopathology · Child development · Neurodevelopment · Genetics · Gene by environment interaction

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Introduction

Around the world a staggering number of children are orphaned or abandoned, many of who live in institutional settings (Nelson 2007). Institutional rearing constitutes an extreme form of social deprivation where caregiver-to-child ratios are low and individual attention to the child is limited. In addition, institutional rearing is associated with other forms of deprivation. Basic necessities such as food and clothing are inadequate or uniform and regimented, play experiences are infrequent and often outside of a social context. There is limited, if any, individual attention to the social, emotional or even physical needs of the child. Across country settings, institutionalization is associated with developmental delays, disorders across physical, cognitive, and social domains as well as alterations in neural function and physiology, however, these delays are variable, likely related to variability in institutional environments across country settings (Miller et al. 1995; Miller et al. 2008; Miller and Hendrie 2000). Children raised in institutions are more likely than their family-raised peers to have decreased physical size and head circumference (Benoit et al. 1996); deficits in cognitive function (O'Connor et al. 2000) and in language production and comprehension

(Albers et al. 1997). In addition, children have a higher incidence of disorders of attention and hyperactivity; (Kreppner et al. 2001), sensory integration, and exhibit a quaisi-autism like syndrome (Rutter et al. 1999). Elucidating how this form of environmental deprivation results in developmental deviations is important both for the health of children raised in these environments and may inform our understanding of typical and atypical child development.

Observing the degree to which extreme environments influence behavior, social and cognitive ability, and neural function provides evidence regarding the amount of variation in developmental trajectories that can be attributed to the environment in which children are raised. Genetic and gene-environment interactions influencing developmental outcomes in this setting also provides important information about individual variability in outcomes in children placed in improved care giving environments. Finally, the presence of sensitive periods for cognitive and social-emotional development can be identified by observing the effect that age of removal has on development. Although it is clear that the brain develops across childhood and that some areas appear "adult-like" earlier than others, there is little concrete evidence for sensitive periods in middle childhood or for complex cognitive and emotional functions.

Bucharest Early Intervention Project (BEIP)

Multiple studies have treated adoption out of institutions as a natural experiment, observing the putative effect of adoption into families on cognitive, physical, and emotional development. Problems with causality in these studies are unavoidable because selection effects and adoption effects are confounded (e.g. healthier children are chosen for adoption out of institutions). Apparent developmental differences may, in fact reflect extant differences in children selected for adoption compared to those children who were not adopted. Even if this is not true for all the cognitive, physical, and emotional differences observed between institutionally raised and adopted children, it is impossible to tell which aspects of development are most mutable and which are not. The Bucharest Early Intervention Project (BEIP) was designed to address the challenges faced in naturalistic studies. The BEIP, started in Romania in 2001 by Drs. Charles Nelson, Charles Zeanah and Nathan Fox is the first randomized control trial (RCT) of foster care compared to continued institutional care. Although this experimental design is superior for investigating the causation, it has the potential to represent an ethical hazard, e.g., some children are randomly assigned to care as usual, a kind of care known to be associated with severe negative outcomes. In the current study not all children could be accommodated in researcher-created foster care. Given that some children were not going to be accommodated, it could be argued that the most ethical manner of assigning foster care is through random assignment. These and other ethical issues associated with the BEIP study, including a policy of non-interference with the normal plan of care of either group and assurance that no child removed from the institution could be returned to the institution have been extensively discussed in publications from the BEIP group (Nelson et al. 2007; Zeanah, et al. 2003a; Smyke et al. 2009).

In this review we focus on findings from the BEIP study because of its unique RCT design. When relevant, we will provide information from other studies of adoption out of institutionalization that extend and expand findings from the BEIP study. Although the effects of institutionalization on child development have been discussed extensively (see Kreppner et al. 2007; MacLean 2003; Rutter et al. 2004; Pollak et al. 2010; Rutter and Sonuga-Barke 2010), we focus primarily on two new areas of investigation in the current review. First, we review evidence concerning the effect of institutionalization on neural and cognitive development, and second, we review the interaction between genetic predisposition and exposure to the institutional environment.

Sensitive Periods During sensitive periods of neurodevelopment, expected environmental inputs are necessary to guide neural differentiation and pruning (Cyander and Frost 1999), and children raised in institutions confront social and environmental circumstances that deviate markedly from expected environments. Thus, a number of the expected environmental conditions necessary for proper neurodevelopment may either be absent or inadequate in institutional settings. Indeed, increasing evidence finds marked detrimental effects of institutional deprivation on brain development (Chugani et al. 2001; Eluvathingal et al. 2006; Marshall and Fox 2004). It has therefore been suggested that the lasting effects of severe early deprivation on neurodevelopment are responsible for the wide range of physical and mental health problems that are associated with institutionalization (Rutter and Sonuga-Barke 2010). Genetic variability may result in both quantitative and qualitative differences in the way in which lack of an expectable environment affects development.

BEIP Sample Description Prior to the intervention, 136 institutionalized children (average age 22 months; range 6–30 months) and 72 age-matched controls from the community were assessed for cognitive, social, emotional, and neural development (Zeanah et al. 2003a, b). This assessment, which occurred prior to randomization, was termed the *baseline assessment*. The community group, was comprised of children living with their biological families

in the greater Bucharest area and were described as the never-institutionalized group (NIG). Most of these comparison children had been born at the same maternity hospitals as the institutionalized children. Following the baseline assessment children were randomly assigned either to remain in the institution, called care as usual (CAU) or to high-quality foster care (FC). All three groups where then assessed at 30 months, 42 months, and 54 months, 8 years of age for a range of physical, cognitive, social, neurophysiological, emotional and behavioral outcomes. Finally, a 12-year follow up assessment is currently underway. Because children were placed into foster care at different ages, the effects of duration of institutionalization and age at removal could be independently observed. Although children were randomized at the outset of the study, over the 8+ years these children have been followed, many children did not remain in their original living situations. A number of children, particularly within the CAU group were reunited with their biological families, adopted, or transferred into a government-run foster care program. Thus while many analyzes from the BEIP study conducted an intent-to-treat analysis, the actual differences in the amount of time a child spent in institutional care between the FC and CAU groups decreased significantly by the 8 year assessment. Consequently, changes in care giving environment may have positively influenced outcomes. This inherent aspect of the intent to treat analysis is one reason that differences between the FC and CAU groups may differ across time. In some analyses comparison is done between participants who were never institutionalized group (NIG) and children with any history of institutionalization, who are referred to the ever institutionalized group (EIG).

General Neural Function in Children Exposed to Institutionalization

In the BEIP study electroencephalogram (EEG) was used to record electrical activity at the scalp at 30 months, 42 months, and 54 months of age when children were viewing benign visual stimuli. EEG was decomposed into frequency bands and compared across subjects. Event related potentials (ERP), variation in neural activity time locked to a stimulus display, were averaged across trial types and compared across subjects. EEG was recorded from 16 electrodes distributed over the head labeled using the 10–20 system. These electrodes were sewn in to a Lycra Electro-Cap (Electro-Cap International Inc., Eaton, OH).

Electrical activity recorded at the scalp is decomposed into component frequencies, reduced into frequency ranges (e.g. 7–12 hz) and labeled (e.g. alpha) for ease of analysis. Typical maturation across development as well as atypical developmental patterns, including various types of psychopathology, have previously been associated with patterns of EEG activity including greater contribution of specific frequency bands (Bell 2002; Bell and Wolfe 2007). The three frequency bands most relevant for the current discussion are beta (13–20 hz), alpha (7–12 hz), and theta (4–6 hz). As children age alpha and beta frequencies increasingly contribute to the EEG signal while theta decreases (Marshall et al. 2002). There are many possible explanations for this observation. One possible explanation, is that the structural integrity of white matter tracts is responsible for modulations of alpha frequency, as white matter integrity increases linearly across development, so do alpha contributions to EEG signal. Increased alpha and beta frequency contributions coupled with decreased theta contributions have been associated with increased attention in patient populations (Barry et al. 2003). At baseline, group differences between EIG and NIG children emerged such that the EIG had increased theta and decreased alpha and beta frequencies relative to the NIG group (Marshall and Fox 2004). This was interpreted in light of the developmental patterns in EEG as a potential shift in towards a ‘less mature’ EEG profile. At 42 months of age, after randomization to foster care, EEG was re-acquired and group differences between the CAU group and FC group were tested. Children in the FC group had been in foster care for between 11 to 36 months. In this follow up examination group differences were non-significant, however, a negative association between age at placement in foster care (in months) and relative power in the alpha frequency band was observed. It appeared possible that foster care was having an effect on EEG frequency power in the direction of making children exposed to foster care appear more like typically developing children but that the intervention effects were not strong, potentially because the intervention had not lasted long enough (Marshall et al. 2008). In the most recent follow up at 8 years of age EEG was again acquired. Children in the FC group had now been in their foster care families for between 5.5 to 7.5 years. Again, an effect of age at placement emerged for the alpha frequency band. In addition, children who were placed into foster care when they were younger than 2 years compared to their NIG peers had indistinguishable contributions from the alpha frequency band to the EEG signal, evidencing a typical pattern of EEG activity. Children who had been placed after they were 2 years of age had alpha power contributions that were indistinguishable from children in the CAUG group (Vanderwert et al. 2010). These findings generated two important conclusions. First, there appears to be a sensitive period for the development of neural structures underlying increased alpha power in the EEG signal, with amelioration of the

environment prior to 2 years of age being critical for remediation. Second, although this developmental 'catch up' was made possible by placement into foster care before the age of two, it required years of exposure to foster care to emerge. Although the BEIP group has not yet published data using other neuroimaging techniques, such as MRI, findings related to these global changes in EEG power have emerged in other samples.

In one of these previous studies Eluvanthingal and colleagues used magnetic resonance diffusion tensor imaging (DTI) to examine 7 adolescents adopted from Romania to Canada and 7 adolescents born and raised in Canada (Eluvathingal et al. 2006). DTI assesses the degree to which water molecules in the brain diffuse in a specific orientation. In fluid-filled spaces, such as ventricles, diffusion is unrestricted and isotropic. In tissue with a highly linear structure, such as a white matter fiber bundle, diffusion has a restricted orientation, is anisotropic, and commonly expressed as fractional anisotropy (FA) (for review, Chanraud et al. 2010). Eluvanthingal reported non-significant but pervasive lower FA across all white mater tracts in previously institutionalized compared to never institutionalized adolescents. Because FA is a measure of the degree to which a tract follows a uniform orientation and can be thought of as a measure of the integrity of a white matter tract, the finding that children exposed to institutionalization had pervasively lower FA values indicates a general compromise of white matter tract integrity. It is likely that this kind of microstructural compromise of white matter could be accompanied by impairment in processing speed and generalized damping of neural function, potentially like the EEG changes described above. In a second investigation from the English and Romanian Adoptees study (ERA), grey and white matter volumes were measured using structural MRI. This technique does not specifically address white matter microstructural integrity in the way DTI does, but it does allow the observation of the amount of grey and white matter in the brain. In this study significant widespread volume deficits in white and grey matter were observed for previously institutionalized compared with never institutionalized adoptees (Mehta et al. 2009).

Some have argued that the structural integrity of white matter tracts is responsible for modulations of alpha frequency across typically developed adults (Valdés-Hernández et al. 2010). Patients with mild cognitive impairment, who evidence a decline in structural connectivity as measured by DTI also exhibit EEG profiles that are nearly identical to those observed in previously institutionalized children (Claudio Babiloni et al. 2006; Rossini et al. 2006; Wolf et al. 2003). It may be that in the case of children exposed to institutional environments, the low power of electrical activity found in EEG is attributable to decreases in white matter. It could be that individuals placed into foster care after 2 years of age missed an important sensitive period for typical neural development, perhaps related to white matter density and structural connectivity. However, only when development is permitted to proceed in an expectable environment for several years in the context of foster care do typical patterns of EEG frequency power emerge.

Specific Cognitive and Neural Function: IQ

The effects of institutionalization on cognitive functioning have been well-documented. This research began following observations that previously institutionalized children had IQ deficits relative to never-institutionalized children. More than 50 years ago, Dennis and Najarian (1957) described significantly lower IQ scores for 49 Lebanese children living in a foundling home (or orphanage) as compared to a community sample. More recently, researchers have examined the impact of severe, early deprivation on children's IQ in a variety of contexts (Nelson et al. 2007; Rutter and Sonuga-Barke 2010; van den Dries et al. 2010). In a meta-analytic review, (Van Ijzendoorn, Bakermans-Kranenburg, & Juffer 2007) found that children reared in orphanages had consistently lower IQ scores across 75 studies when compared to their peers reared in foster families. The BEIP has made a unique contribution to this growing body of literature by examining the effects of continued institutional care on cognitive development, up to age 8, using a comparison group of children raised in within-country foster care (Smyke et al. 2009; Nelson et al. 2007; Fox et al. 2010b).

The first report of children's cognitive development in the BEIP at baseline revealed significant delays and deficits in the ever-institutionalized sample as a whole (Smyke et al. 2002). Children were assessed using the Bayley Scales of Infant Development (Bayley 1993) and the institutionalized group had a mean Mental Development Index (MDI) of 66, whereas children in the community group had a mean MDI of 102. Follow-up assessments of children's cognitive development were subsequently conducted when the children were 30, 42, and 54 months of age (Nelson et al. 2007) using the Bayley at the earlier two ages and the Wechsler Preschool Primary Scale of Intelligence (WPPSI-R; Wechsler 2000) at the third time point. Results showed that children removed from the institution and placed into foster care displayed higher scores compared to those children randomized to the CAU group at each of the follow up assessments. In addition, the timing of placement into foster care showed an important impact on scores at 42 and 54 months. Specifically, the earlier a child within the FC group was removed from the institution, the higher their score at 42 months, whereas at 54 months, children placed before 24 months of age had the highest scores.

Recently, children were reassessed at 8 years of age using the Wechsler Intelligence Scale for Children (WISC-IV; Wechsler 2003). The WISC yields scores in four domains of functioning, as well as a full-scale IQ score. An examination of these scores across groups revealed both similarities and differences to findings from the earlier assessments. Specifically, children in the FC group scored significantly higher on the verbal subscale of the WISC than did children in the CAU group and marginally higher on full scale IQ. The age at which children in the FC group were placed into foster care was related to processing speed scores on the WISC, such that children who were placed into foster care before 26 months of age had higher scores (Fox et al. 2010a, b). Therefore, the strong intervention and timing effects found at earlier ages were only partially maintained at age 8.

The pattern of results from the BEIP is somewhat consistent with those reported by Rutter and colleagues in the ERA study, an examination of institutionalized Romanian children adopted into British homes before 42 months of age and followed to 11 years of age (Rutter et al. 1998; Rutter et al. 2010). Using a comparison group of children born and adopted within the UK before 6 months of age, they found that Romanian adopted children were significantly impaired in their cognitive development at the time of entry into the UK. When examined during a follow-up at age 4, they reported significant gains for those Romanian children who were adopted before the age of 6 months, whereas those children adopted after 6 months were still delayed in their cognitive development (Rutter et al. 1998). By age 6, children adopted before 6 months of age no longer differed from the community group in their cognitive scores, and children from both of these groups had scores that were significantly higher than those of children adopted after 6 months of age. Similar results were found at age 11; however, only children in the late adopted group experienced significant increases in their cognitive scores between the 6- and 11-year assessments, potentially indicating a significant and late-occurring period of catch-up for these children (Beckett et al. 2006).

Specific Cognitive and Neural Function: Face and Emotion Processing

In addition to the general changes in EEG frequency documented among children in the BEIP, specific changes in cognitive and social function have been observed in children exposed to institutionalization. Kreppner and colleagues compared seven areas of function behaviorally among previously-institutionalized adopted children and adopted children *not* exposed to institutionalization (Kreppner et al. 2007). Institutionalization was associated with deficits in general cognitive function, a quasi-autistic syndrome, and disinhibited attachment. The quasi-autistic syndrome was identified using parent interview and included behaviors such as avoiding eye-to-eye gaze, difficulties forming selective friendships, deficits in empathy and emotional reciprocity (Rutter et al. 1999; Kreppner et al. 2007). Disinhibited attachment involved indiscriminately friendly behaviors, including displays of attachment-like behaviors with unfamiliar adults or willingness to leave with unfamiliar adults (Rutter et al. 1999; Rutter et al. 2007a). This cluster of problems reflects deficits in social-cognitive functioning. To identify the neural mediators of these deficits, ERP response to social stimuli were assessed in the BEIP sample.

ERP Studies of Face Perception (Familiarity) In these studies the neural response to presentation of two faces was assessed: a familiar caregiver and a gender-matched stranger. This experimental paradigm has been used to assess the development facial perception and expertise in infants and young children in a variety of studies (Gauthier and Nelson 2001). There are specific ERP components that are sensitive to face familiarity, including a middle-latency negative-going component (Nc), usually larger for familiar faces and a late positive slow wave (PSW), sometimes larger for unfamiliar faces (de Haan and Nelson 1997). There are several ERP components that appear to be responsive to face perception regardless of familiarity. These include the n170, a negative ERP component that occurs in adults at approximately 170 milliseconds (ms) and in infants or young children between 90 and 250 ms that is selectively responsive (larger) to faces. In addition to the n170 the following ERP components were extracted from the data: p250, a positive-going ERP component between ms 150–400 ms; the Nc, a negative-going component 325–650; and the positive slow wave (PSW) a late positive-going component 900–1500 ms. In an initial study, when children were between 7 and 32 months of age (Parker and Nelson 2005a) participants were shown familiar and unfamiliar faces while ERP response to these faces were recorded. In this study, the EIG group had reduced amplitudes in their ERP response for the n170, Nc, and PSW but increased amplitude in the p250 relative to the NIG. This differential response in neural function indicates a potential difference in face processing between these two groups. In addition, although both the NIG and EIG showed differential neural processing for familiar (caregiver) and unfamiliar faces for the Nc component, consistent with previous literature, only the NIG showed this same differentiation for the PSW component. The PSW is thought to be associated with encoding novel faces. This differential response in neural function indicates a difference in face, memory or novelty processing between these two groups, regardless of the cognitive source of this

difference, it is in the latest component, indicating that it is not initial perception, but later re-processing of the face stimuli, that differs for children raised in institutions and those raised in families. This finding, while suggestive of differences in encoding-related reprocessing for EIG as compared to NIG children could be a function of differences in caregiver familiarity. The caregivers in the EIG group would have been less familiar to the children who viewed them than for NIG children who viewed their parent's faces. Nonetheless, the children in the EIG group were very familiar with their caregiver's face and the relative difference between this familiarity and a stranger is likely preserved in both groups.

ERP Studies of Face Perception (Emotion) A second set of analyses further investigated social cognition by exposing infants to pictures of all unfamiliar women making happy, angry, sad, and fearful facial expressions (Parker and Nelson 2005b). ERPs were recorded and decomposed into the components as described above. In this analysis, EIG and NIG children differed in the n170 and p250 component response to emotional expressions. Children in the EIG group had larger amplitudes in the n170 and p250 response when viewing fearful faces whereas NIG children had larger amplitudes in these same components when viewing sad faces. Therefore, in this baseline study, earlier ERP components differentiated emotion perception among EIG and NIG children whereas later components differentiated facial perception processing.

These same experimental paradigms were administered at 42 months following randomization to foster care (Moulson et al. 2009). At 42 months of age CAU and FC groups did not differ in the amplitude or latency of their ERP responses to familiar/unfamiliar faces or happy, angry, sad, and fearful facial expressions. To examine whether duration of foster care was associated with changes in these ERP components, children placed early (before 24.5 months of age) and late (after 24.5 months of age) were compared. This analysis did not reveal differences in either perception of familiar and unfamiliar faces or perception of emotions across study groups. The finding that emotion expressions did not elicit different neural processing in any of the three groups is surprising given the obvious difference in social cognitive processing observed in previously-institutionalized children, particularly those placed into families at later ages (Rutter et al. 1999; Johnson et al. 2010).

Multiple aspects of social cognition are disrupted as a result of institutionalization, therefore neural correlates of social functioning will likely also be different as a result of institutionalization. This hypothesis is supported by two small studies which observed decreased glucose metabolism in the orbital frontal cortex and decreased FA values in the uncinate fasciculus, the primary connection between the orbital frontal cortex and subcortical limbic structures (Chugani et al. 2001; Eluvathingal et al. 2006). The orbital frontal cortex is broadly implicated in social cognition. When damage occurs to this area of the brain patients exhibit uninhibitied and socially inappropriate behavior in multiple areas of functioning. Connections between the orbital frontal cortex and subcortical areas such as the amygdala appear responsible for emotion perception and elicitation. In addition, amygdala development is impacted by exposure to early adverse environments both in humans and in animal models (see (Tottenham and Sheridan 2009) for review). Two studies of children exposed to institutionalization have observed associations between amygdala volume and age at adoption out of the institutional environment (Tottenham et al. 2010); (Mehta et al. 2009). These findings further argue for the importance of examining developmental differences in subcortical structures as potential explanations for differences in behavior observed among children exposed to institutionalization. Neural functions underlying social cognition in this population warrant further exploration. Although some aspects of social cognitive function appear to be intact in previously institutionalized children, such as basic emotion perception, other aspects are compromised (e.g. indiscriminate friendliness, increased incidence of autism-type behavior, disruptions of attachment) (Bos et al. 2010; Zeanah et al. 2005). It may be that institutionalization related differences in the volume and connectivity of neural structures known to be associated with social behavior cause observed differences in social behavior in institutionalized groups. However, the specific association between these behaviors and neural function is difficult to assess without functional neuroimaging studies.

Specific Cognitive and Neural Function: Mental Health

Although children reared in institutional settings evidence profound deviations from typically developing children across a number of cognitive, linguistic, and psychosocial domains, elevated psychiatric morbidity among previously institutionalized children is particularly striking (Gunnar et al. 2007; Kreppner et al. 2001; Rutter et al. 2001; Stevens, et al. 2008). The prevalence of attention-deficit/hyperactivity disorder (ADHD) is so marked among such children (Rutter et al. 2001; Stevens et al. 2008) that some have suggested these symptoms represent a core feature of an institutional deprivation syndrome (Kreppner et al. 2001). Findings from the BEIP confirm the substantial burden of inattention and hyperactivity among children reared in institutional settings.

Psychiatric disorders were first assessed in BEIP participants at the 54-month assessment using a structured

diagnostic interview for young children, the Preschool Age Psychiatric Assessment (PAPA) (Egger et al. 1999, 2006). This instrument collects information from a caregiver about the presence, frequency, and duration of psychiatric symptoms and generates DSM-IV diagnoses (American Psychiatric Association 1994). Biological or foster care mothers completed the assessment for non-institutionalized children. An institutional caregiver provided information for children living in institutional settings. Caregivers who worked with the child regularly and knew the child well were selected to complete the interview. If the child had a favorite caregiver, agreed upon by staff consensus, the favorite caregiver completed the assessment.

Psychiatric Disorders (ADHD) The prevalence of ADHD among children who had ever been institutionalized in the BEIP was 20.7%, whereas the prevalence of ADHD among children raised in the community was just 3.4% (Zeanah et al. 2009). Elsewhere in Europe and the United States the prevalence of ADHD is between 3–7% (Lavigne et al. 2009). Children who had been reared in institutions were more than 7 times as likely to have ADHD by age 54 months than children who had never been institutionalized. The foster care intervention did not have ameliorative effects on ADHD. The prevalence of ADHD among children who received the foster care intervention (18.6%) was not significantly different from the prevalence among children who remained in institutional care (23.1%). Similarly, no significant difference in the mean number of ADHD symptoms in the FC versus CAU group was observed. Across all groups boys had higher levels of ADHD symptoms than girls consistent with findings from community and epidemiologic studies (Fergusson et al. 1993; Willoughby et al. 2000). This pattern was evident both in children who had been institutionalized and those reared in the community.

Research among previously institutionalized children revealed that the duration of institutional deprivation had a marked influence on their risk for developing ADHD (Kreppner et al. 2001; Stevens et al. 2008). Specifically, the prevalence of ADHD was higher among children who remained in institutional care in Romania for greater than 6 months than among children who were adopted within the United Kingdom (UK); in contrast, no difference in the prevalence of ADHD was found between children who remained in institutional care for less than 6 months and those adopted within the UK (Stevens et al. 2008). In the BEIP, however, no association was found between age at placement into institutional care, age at foster care placement, or duration of time spent in an institution and risk for ADHD or the number of ADHD symptoms (Zeanah et al. 2009). The absence of an effect of duration of deprivation on ADHD in the BEIP is likely attributable to the fact that the vast majority of institutionalized children in the study spent greater than 6 months in institutional care.

Although the deleterious effects of institutionalization on risk for ADHD and other psychiatric disorders are clearly documented, the mechanisms that underlie these associations remain poorly understood. Deviations in typical brain development among previously institutionalized children are likely to explain the elevated rate of ADHD in these children. Although intuitive, evidence to support this claim has previously been lacking. Children reared in institutions in the BEIP evidenced abnormalities in brain activity, assessed using EEG, relative to children raised in the community at entry into the study (Marshall and Fox 2004). As described in detail above, compared to community controls, children who had ever been institutionalized had higher relative power in low-frequency bands (theta) and lower relative power in high-frequency bands (alpha) (Marshall and Fox 2004). A similar pattern of brain activity also has been found among children with ADHD (Barry et al. 2003; Barry et al. 2009; Clarke et al. 2001; Mann et al. 1992; Matsuura et al. 1993). The BEIP thus presented a unique opportunity to evaluate whether elevations in ADHD symptoms among previously institutionalized children were attributable to atypical patterns of brain development associated with institutional deprivation.

Consistent with this hypothesis, elevations in theta relative power and decrements in alpha relative power significantly mediated the association between institutionalization and symptoms of ADHD at 54 months (McLaughlin et al. 2010). Specifically, children who had ever been institutionalized had greater theta relative power in frontal, temporal, and occipital areas and decreased alpha relative power in frontal and occipital regions as compared to community control children at entry into the study. Theta and alpha relative power, in turn, were associated with ADHD symptoms at 54 months; these associations were stronger for hyperactivity and impulsivity than for inattention. Mediation analyses revealed that approximately 20% of the association between institutionalization and ADHD symptomatology was explained by these atypical patterns of brain activity (McLaughlin et al. 2010). Importantly, the pattern of elevated low-frequency EEG power and decreased high-frequency power indicative of a delay in cortical development uniquely predicted ADHD; EEG relative power was largely unrelated to depression, anxiety, or oppositional defiant disorder.

These findings suggest the presence of a neurodevelopmental mechanism linking institutional rearing with hyperactivity and impulsivity, two core features of ADHD. Specifically, differences in electrical brain activity among children raised in institutions relative to community controls explained, in part, differences in the prevalence of ADHD symptoms between these groups at 54 months.

Some have argued that the pattern of elevated low-frequency theta brain activity and decreased high-frequency activity typical of children with ADHD, that we observed among children in the BEIP, reflects a developmental *delay* in cortical maturation that results in greater relative theta activity (Barry et al. 2003; Kinsbourne 1973; Matsuura et al. 1993). Longitudinal findings documenting delays in cortical maturation among children with ADHD relative to children without the disorder support the developmental delay theory (Shaw et al. 2007). BEIP findings extend this work by documenting a similar pattern of brain activity in institutionalized children suggestive of a delay in cortical maturation and providing evidence that this pattern of brain activity represents a neurodevelopmental pathway that explains the association between institutionalization and ADHD. These findings have important implications for understanding the effect of early experience on neurodevelopment. In particular, they suggest that aspects of neural functioning measured by the EEG, potentially reflecting cortical maturation, are sensitive to social and environmental context and may be delayed or stunted in deprived environments, eventually manifesting as psychopathology.

Other Psychiatric Disorders High rates of other psychiatric disorders, in addition to ADHD, have been documented among previously institutionalized children (Gunnar et al. 2007; Hoksbergen et al. 2003; Rutter and ERA Study Team 1998; Rutter et al. 2001). Consistent with these studies, substantial elevations in the prevalence of psychiatric disorders were observed among institutionalized children in the BEIP. More than half (53.2%) of children reared in institutional settings had developed a psychiatric disorder by age 54 months, whereas less than one-quarter (22%) of never-institutionalized children met criteria for a disorder (Zeanah et al. 2009). Compared to NIG children, children in the EIG were approximately five times as likely to meet criteria for an externalizing disorder (6.8% versus 27%, respectively) and three times as likely to meet criteria for an internalizing disorder (13.6% versus 34%, respectively).

Among the group of children exposed to institutional rearing, lower rates of some, but not all, psychiatric disorders were found among children who received the foster care intervention compared to children in the CAU group. Children in the FC group had lower rates of internalizing disorders (22%) than children in the CAU group (44.2%). In contrast, the prevalence of externalizing disorders was equivalent in the FC group (25.4%) and CAU group (28.8%) (Zeanah et al. 2009). Notable gender differences in the effects of the foster care intervention on psychiatric morbidity were found. Specifically, the ameliorative effects of the intervention were evident only among girls. Girls who received the foster care intervention had lower levels of overall psychiatric symptomatology, internalizing symptoms, and externalizing symptoms than girls in the CAU group, whereas no intervention effects were found on psychiatric symptoms of any kind among boys. No association was observed between any of the psychiatric outcomes and duration of institutional care, age at placement into an institution, or age at foster care placement.

Sensitive Periods and Age at Placement

Many of the findings discussed in this paper appear to be sensitive to age at placement. Broadly, such findings argue for the existence of sensitive periods whereby certain neural circuits can only develop typically if an expectable environment is available to a child during the correct periods of development. Sensitive or critical periods exist across species in the sensory motor cortex (Morishita and Hensch 2008; Fox et al. 2010). The concept that specific experiences, even grossly aberrant caretaking environments such as institutionalization, might exert their greatest impact during specific time periods seems likely. What the literature to date does not appear to converge on is the time-window after which placement in foster care or an adoptive home can 'normalize' neural development.

Several findings from the ERA study point to the importance of placement into a typical caretaking environment before 6 months of age (Mehta et al. 2009; Kreppner et al. 2007; O'Connor et al. 2000). In another study, neural correlates of institutionalization were normalized if children were placed before 15 months of age (Tottenham et al. 2010). Finally, in the BEIP study, many aspects of neural function and some aspects of cognitive and emotional function were normalized in longitudinal follow up if children were placed before 2 years of age (Nelson et al. 2007; Vanderwert et al. 2010). Notable exceptions included IQ at age 8, externalizing disorders, which were equally prevalent for children placed before or after 24 months of age, and internalizing disorders, which seemed responsive to foster care intervention regardless of the age at which children were placed. In these analyses placement between 0–18 months of age was indistinguishable from placement between 18–24 months of age (Nelson et al. 2007). Many of these studies also found linear associations with age at placement where earlier placement resulted in more positive outcomes than later placement.

This difference between the ERA and BEIP studies can be accounted for in several ways. First, the ERA study included children who were adopted before the age of 6 months, while no child in the BEIP was placed into foster care before the age the age of 6 months. Therefore, a direct comparison of the timing results from the two studies is not

possible. Second, unlike children in the BEIP, institutionalized children in the ERA were adopted in a new country where the cultural and economic context may have uniquely impacted their development. Third, there was no existing government foster care system at the time when the BEIP began, but one was later established when the sample was approximately 54 months of age. As a consequence, many of the children experienced multiple changes in their placement across the course of the study. These care-giving changes likely impacted their cognitive development (Fox et al. 2010a, b) and may impact other domains as well. Finally, in the BEIP study children were randomized to foster care intervention, minimizing selection biases. Therefore, the BEIP may constitute a better estimation of the actual effect of foster care intervention in the general population. It is likely that sensitive periods for exposure to institutionalization exist. However, given the widely divergent trajectories for the development of different areas of cortex (Giedd et al. 1996), sensitive periods are likely to differ by cognitive function and neural circuit. Future work in this areas should aim at better delineating sensitive periods for specific areas of cortex and areas of cognitive and emotional functioning.

Genetic Influences on Early Deprivation

We now turn our attention to the impact of gene-environment interactions on cognitive, social and mental health outcomes following early institutionalization. As we have reviewed above, studies consistently demonstrate that early, severe social deprivation due to institutional rearing is a risk factor for a range of negative outcomes across social, emotional, and neurobiological domains (O'Conner et al. 2000; O'Connor and Rutter 2000; Rutter et al. 2007b; Zeanah et al. 2009). Nevertheless across studies, even in children with similar degrees of exposure, there remains marked variation in both impairment and in individual recovery (Kreppner et al. 2007). Genetic variation may be one mechanism that accounts for this variation in outcome and recovery.

Gene by Environment Interactions Common variations in the DNA sequence of genes, called polymorphisms, may interact with exposure to institutional deprivation to impact an individual's risk for developing psychopathology later in life (Kaufman et al. 2004, 2006; Binder et al. 2008). Gene-environment interactions have been demonstrated in psychiatric and medical health outcomes in adults and children, including children exposed to extreme adversity due to abuse and neglect (Humphries et al. 2001; Caspi et al. 2003; Kaufman et al. 2004, 2006). However, few studies have explored gene-environment interactions prospectively or with objective measures of adversity; most have relied on retrospective reports (Uher and McGuffin 2008). Preclinical animal models of early adversity have consistently demonstrated that gene-environment interactions influence a range of biological and behavioral outcomes (Stevens et al. 2009). Given the limitations of retrospective reports of early adversity, prospective studies of children with a history of institutionalization offer a unique opportunity for the study of gene-environment interactions in humans and have the potential to offer significant insight into the wide variability in outcome in these children.

Genetic Variation in Serotonin Re-Uptake (Serotonin transporter gene, 5HTT) One of the most studied polymorphisms in behavioral genetics is the serotonin transporter length polymorphism in the 5′ untranslated region (UTR) of the gene (5httlpr) (Caspi et al. 2003; Risch et al. 2009; Caspi et al. 2010). The serotonin transporter is a key regulator of serotonin levels in the brain and this polymorphism has putative functional significance where the short (s) allele is associated with decreased transcription relative to the long (l) allele (Lesch et al. 1996). This polymorphism has been found to moderate the influence of early adverse life experiences on the development of anxiety and depression as well as influence the neural systems related to threat perception and amygdala reactivity irrespective of early adversity (Caspi et al. 2003; Pezawas et al. 2005; Gunthert et al. 2007; Pérez-Edgar et al. 2010). Although multiple studies have demonstrated gene-environment interactions with the 5httlpr and environmental adversity in predicting anxiety and depression, significant debate continues (Caspi et al. 2003; Kendler et al. 2005; Kaufman et al. 2006; Kilpatrick et al. 2007; Uher and McGuffin 2008; Grabe et al. 2009; Risch et al. 2009; Xie et al. 2009; Caspi et al. 2010; Rutter 2010).

In the English and Romanian Adoptees (ERA) study the amount of time spent in institutional care was significantly related to emotional problems at both 11 and 15 years of age. For Romanian children adopted before 6 months of age no statistically significant differences in emotional problems were found compared to the with-in the United Kingdom adopted control children. To understand differential recovery in these children Kumsta and colleagues explored the influence of the 5httlpr on emotional problems at 11 and 15 years of age (Kumsta et al. 2010). They additionally explored whether genotype moderated the impact of stressful life events that occurred during adolescence on the change in emotional symptoms between the 11- and 15-year assessments. A significant main effect of genotype and a significant gene-environment interaction on emotional problems at both 11 and 15 years of age was detected. Children adopted after 6 months of age that were s allele carriers had significantly greater emotional problems

than other groups (children adopted before 6 months with either genotype and community controls). Further, a four way interaction was detected when exploring intervening life events in adolescence. For community children, intervening life events did not predict differences in emotional problems between assessments. However in children exposed to institutionalization, a high number of intervening stressful life events combined with the presence of at least one copy of the s allele predicted increased emotional problems from one assessment to the next. Children with exposure to institutionalization who carried two copies of the l allele (l/l) had decreased symptomology from one assessment point to the next regardless of intervening stressful life events. However, the lowest level of symptoms was found in children with two copies of the s allele (s/s) children who had a low number of intervening life events indicating a putative protective effect of the s/s genotype when children are in supportive environments. Similar findings have been reported in primate studies (Barr et al. 2004).

Genetic Variation in Dopamine Re-Uptake and Receptors (DAT/DRD4) As we reviewed above significant improvement in some domains is seen when children are placed into foster care or home environments. One domain that appears to be particularly resistant to recovery across studies of institutionalized children (Stevens et al. 2008; Zeanah et al. 2009) is inattention, hyperactivity and impulsivity. This constellation of symptoms, associated with ADHD, is part of the more general category of externalizing disorders. The Dopamine Transporter (DAT) is the target of stimulant medications and has been associated with ADHD diagnosis. Dopamine is a modulatory neurotransmitter known to be critical to aspects of neural and cognitive function, specifically those aspects of cognition associated with the prefrontal cortex, striatum, and associated subcortical and brain stem structures. DAT regulates dopamine availability in the striatum, an early developed subcortical structure, and has little influence in the prefrontal cortex, a cortical area with a developmental trajectory which is not complete until young adulthood. Located within the 3′ untranslated region (3′UTR) of the DAT gene is a 40 base pair variable number tandem repeat (VNTR) and putative functional differences exist between the 9 and 10 alleles (Michelhaugh et al. 2001), although in vivo studies examining the influence of genotype on DAT binding have been somewhat inconsistent (Heinz et al. 2000; Jacobsen et al. 2000; Martinez et al. 2001). This polymorphism has been associated with inhibitory capacity and most consistently with ADHD (Bellgrove et al. 2005, 2008; Stevens et al. 2009). Meta-analyses have demonstrated the association of ADHD and the DAT VNTR allele and another polymorphism located in another gene involved in dopamine regulation, the Dopamine D4 (DRD4) receptor VNTR. DRD4 is expressed in both the basal ganglia and prefrontal cortex and the 7 allele of the VNTR is a putative risk factor for ADHD. Stevens et al. examined whether the DAT transporter was associated with symptoms of ADHD the ERA study (Stevens et al. 2008). In this study a haplotype of the DAT gene containing the 10 allele was significantly associated with symptoms of ADHD at both age 11 and 15, but not at age 6. The impact of genotype was seen specifically in those children with a high exposure to institutionalization and the vulnerable haplotype. In this sample the DRD4 7 allele VNTR was not associated with symptoms of ADHD, although this genotype has previously been associated with ADHD in children without a history of institutionalization (Grady et al. 2003).

Genetic Variation in Dopamine Re-Uptake (COMT) Catechol-O-Methyltransferase (COMT) is densely expressed in the hippocampus and the prefrontal cortex and functions as the main regulator of dopamine and other catecholamine degradation in the prefrontal cortex (Karoum et al. 1994; Gogos et al. 1998). COMT's expression pattern is complex and differs during development with the highest levels of the enzyme found early in life and decreasing with age (Guldberg and Marsden 1975). Located within the COMT gene are multiple polymorphic sites that impact its expression and function including the val 158 met amino acid substitution in exon four. The met variant has a four fold decreased enzyme activity and has been found to result in differential levels of dopamine and other catecholamines in the prefrontal cortex (Lotta et al. 1995; Lachman et al. 1996). This polymorphism has been associated with a range of psychological outcomes including depression and other mood disorders(O'hara et al. 1998; Rotondo et al. 2002; Funke et al. 2005; Massat et al. 2005; McClay et al. 2006; Burdick et al. 2007). In the BEIP we demonstrated that the rate of depressive symptoms was significantly lower among children with at least one copy of the met allele, even after adjusting for group, and sex. Further, a significant interaction between COMT genotype and group (FC vs CAU) was revealed where an 108% lower risk for depressive symptoms was found in the CAU in individuals with the met/met genotype, and a 60% lower risk of depressive symptoms in heterozygotes (val/met) compared to individuals with the val/val genotype (Drury et al. 2010). This finding, in the setting of a randomized controlled trial of alterations of early care giving environments, provides further support for the hypothesis that both inherent genetic predisposition and environmental conditions influence the development of affective symptoms, even in very young children.

Reactive Attachment Disorder as an Example of G x E Although gene-environment studies can point to putative

risk and resilience factors, an alternative approach is to use genetic studies to assist in the identification of the underlying neural systems in psychological disorders where limited biological knowledge currently exists. One example of this approach is the exploration of genes in Reactive Attachment Disorder (RAD). Extremes of early caregiving adversity, such as neglect and institutional care have been associated with the development of disturbances of attachment behaviors and relationships, including the development of RAD (Zeanah and Smyke 2009). Indiscriminate/Disinhibited RAD, is characterized by disturbed and developmentally inappropriate social behavior, lack of expected reticence around unfamiliar adults, and social boundary violations including overly friendly and intrusive behavior with relative strangers. In previously institutionalized children who are adopted into adequate caregiving settings, clinical signs of Indiscriminate/Disinhibited RAD remain years post-adoption in some children (Hodges and Tizard 1989; Chisholm 1998; Rutter et al. 2007a). Early adverse caregiving experiences are necessary but not sufficient etiological factors for the development of RAD as not all children who experience institutionalization develop RAD and recovery is variable with improved caregiving (O'Connor and Rutter 2000; Boris et al. 2004; Zeanah et al. 2004; Zeanah et al. 2005; Lyons-Ruth et al. 2009). Genetic studies of RAD may provide insight into both the individual variation and the underlying neurobiology.

No previous studies have examined genetic vulnerability to RAD. As little is know about the biological basis of RAD we decided to explore genes associated with selective social attachment behavior. We looked specifically at genes regulating the mesolimbic dopamine circuit due to its putative role in the formation of selective social attachments, pair bonding, maternal attachment behaviors, and approach/avoidance response to socially relevant stimuli in animal models (Aragona et al. 2003; Insel and Fernald 2004; Young and Wang 2004; Berton et al. 2006). Increasing evidence implicates this same circuit in human social affiliative behaviors and maternal attachment (Swain et al. 2007; Strathearn et al. 2009; Rilling et al. 2002). Two genes known to influence dopaminergic signaling in this circuit are the DAT and Brain Derived Neurotrophic Factor (BDNF).

In addition to its role in dopamine regulation in the striatum, DAT is responsible for dopamine regulation in the Nucleus Accumbens (NAc), and the Ventral Tegmental Area (VTA) associated subcortical and brain stem structures (Garris and Wightman 1994; Ciliax et al. 1995).The dopaminergic neurons in the VTA are a major source of brain derived neurotrophic factor (BDNF) in this region and BDNF signaling potentiates dopamine release in the NAc, thereby regulating NAc output signals (Guillin et al. 2001). BDNF expression from the VTA neurons is required for the acquisition of salience of a threatening stimuli and influences activity dependent neuronal plasticity related to salience of threat (Berton et al. 2006). Located with in the BDNF gene is a functional polymorphism, val 66 met, where the less common met allele is associated with decreased release of BDNF (Egan et al. 2003). Because the met 66 allele of BDNF and the 10 allele of DAT are both associated with disrupted mesolimbic dopamine signaling, we hypothesized that if this circuit were related to RAD we would detect associations with these variants and RAD. RAD diagnosis was determined using both the PAPA (described above) and the Disturbances of Attachment Interview (DAI). Both categorical diagnosis of RAD from the PAPA and symptoms of RAD from the DAI were significantly higher in individuals with the 10/10 genotype of the DAT and met carriers of the BDNF polymorphism in children with any history of institutional care. In only the CAUG, the combined risk genotypes (10/10 DAT genotype and met carrier of the BDNF allele) accounted for 32% of the variance of RAD symptoms. This association between the combined genotypes was specific to RAD and was not seen with externalizing disorders (ADHD/ODD) or disorganized attachment providing support for a complex model of attachment disorders and classifications which includes neurobiological, environmental, and relational components (S. Drury, *personal communication)*.

These findings, if replicated, both add to the increasing number of studies demonstrating gene-environment interactions in the setting of early social deprivation and describe a novel neurobiological model of RAD involving aberrant regulation of dopamine signaling in mesolimbic dopamine circuit. Perhaps the greatest, and as yet untapped, benefit of gene-environment studies in behavior and neuroscience is that these studies can provide insight into the mechanism by which environmental exposures get "under the skin" to cause mental illness.

Conclusion and Future Directions

In this review we describe the effect of early institutionalization on neural and cognitive processing in children ages 30 months to adolescence. There is conclusive evidence across studies that institutionalization results in global differences in cognitive and neural function and that, in some cases, foster care or adoptive interventions ameliorate this deficit. We reviewed the impact of early deprivation of this kind on both global (i.e. EEG frequencies) and specific (i.e. ERP components, ADHD symptomology) neural and cognitive function. Finally we review recent literature on the association between genetic differences and variation in both the initial impact and putative recovery from institu-

tional rearing. The fact that institutional exposure early in development has profound effects on global measures of cognitive and socio-emotional development has been known for more than 50 years. Consistent with this knowledge, we report that global differences in neural function are also associated with institutionalization. However, recent investigations into the effect of institutionalization have attempted to capture the variance in outcome by measuring more specific aspects of cognition and associated neural function. Neural circuits are highly specialized and have different developmental trajectories. Investigations into more specific measurements of neural function, such as the ERP response to emotion processing have revealed heterogeneity in the effect of institutionalization on cognitive and neural outcomes. In this review we described the case of neural response to expressions of emotions which, in our study were unaffected by institutionalization. In contrast, ADHD symptomology and associated neural correlates are associated with institutionalization and appear unchanged by exposure to improved care giving environments.

Finally we reviewed reasons for within exposure-group heterogeneity reporting on evidence for both sensitive periods for placement out of institutional settings and variation in genetic polymorphisms which moderate the effect of exposures. Already, examining genetic variation has lead to a better understanding of groups exposed to institutionalization, as in the case of allelic variation in DAT moderating the effect of institutionalization on ADHD symptom expression. However it has also provided new evidence for the biological basis for behaviourally defined disorders like RAD.

There are myriad unanswered questions regarding the impact of early experience on neural, cognitive, and emotional function, and the work reviewed here provides interesting points of entry into this investigation. Future work should attempt cross disciplinary collaboration, particularly in the area of gene-environment interaction and neural development. Already moderating effects of genetic polymorphisms as in the case of ADHD or RAD suggest novel hypotheses about the neural correlates of exposure to institutionalization and the biological bases of these disorders. Future investigations may further refine the impact of institutional care on specific neural circuits given known within group heterogeneity in genotype. Importantly, identifying how to better address and treat the negative consequences of institutionalization is paramount. While the information attained by these investigations is unique in human studies, these findings are relevant not only public health policy and clinical practice but also offer unique insights into developmental neuroscience and genetics.

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