Published in final edited form as:

Dev Sci. 2015 May ; 18(3): 484–494. doi:10.1111/desc.12223.

Institutional Care and Iron Deficiency Increase ADHD Symptomology and Lower IQ 2.5-5 Years Post-adoption

Jenalee R. Doom^{a,b}, Michael K. Georgieff^{a,b,c}, and Megan R. Gunnar^{a,b}

^aInstitute of Child Development, University of Minnesota

^bCenter for Neurobehavioral Development, University of Minnesota

^cDepartment of Pediatrics, University of Minnesota

Abstract

Increased ADHD symptomology and lower IQ have been reported in internationally adopted (IA) children compared to non-adopted peers (Hostinar et al., 2013; Kreppner, O'Connor, & Rutter, 2001). However, it is unclear whether these outcomes are due to institutional deprivation specifically or to co-occurring micronutrient deficiencies that disrupt brain development (Fuglestad et al., 2008). In this study, IA children were compared to children raised in their biological families to examine differences in ADHD symptomology and IQ 2.5-5 years post-adoption and to assess the contributions of iron deficiency (ID) and duration of deprivation to these cognitive outcomes. ADHD symptoms (parent- and experimenter-reported) and IQ were evaluated in 88 IA ($M = 62.1$ months, $SD = 2.4$) and 35 non-adopted children ($M = 61.4$ months, $SD = 1.6$). IA children were assessed 29-64 months post-adoption ($M = 41.9$ months, $SD = 10.2$). ID was assessed during the initial post-adoption medical visit in 69 children, and children were classified into 4 groups by iron status, ranging from normal to ID anemia (most severe). IA children had greater ADHD symptomology, $p < .01$, and lower IQ, $p = .001$, than non-adopted children. Within the IA group, children with more severe ID at adoption had greater ADHD symptomology, $r(69) = 0.40$, $p = .001$, and lower IQ, $r(68) = -0.28$, $p < .05$. Duration of institutional care was positively correlated with ADHD symptoms, $r(86) = .28$, $p < .01$, but not IQ, $r(85) = -.08$, $p = .52$. Longitudinal results indicate improvement in IQ from 12 months post-adoption to age 5 for children with greater ID severity at adoption and longer duration of institutional care but no improvement in ADHD symptoms. These results signify continuing effects of early deprivation and ID on ADHD symptoms and IQ years after adoption.

Introduction

Institutional deprivation during early life is related to disruptions in social, cognitive, and physiological development that often persist after removal from the depriving environment (Gunnar, Morison, Chisholm, & Schuder, 2001; Kreppner et al., 2007; Nelson et al., 2011; Rutter et al., 2004; Rutter, Sonuga-Barke, & Castle, 2010). Researchers are interested in children adopted from institutional (e.g., orphanage or hospital) care as they model the

effects of an early period of deprivation on development (Nelson et al., 2011). For instance, children in institutions frequently experience stimulus, social, and/or nutritional deprivation (Rutter, 1972). Animal models of deprivation demonstrate lasting effects on brain development and cognitive functioning. Rodents raised in deprived environments show differential brain morphology and function than rodents in enriched environments (e.g., Bennett, Diamond, Krech, & Rosenzweig, 1964; Diamond, Rosenzweig, Bennett, Lindner, & Lyon, 1972; Globus, Rosenzweig, Bennett, & Diamond, 1973). In addition, nonhuman primate models demonstrate cognitive deficits, impaired PFC circuitry, and altered chemoarchitecture of the striatum (Martin, Spicer, Lewis, Gluck, & Cork, 1991; Sánchez, Hearn, Do, Rilling, & Herndon, 1998; Sánchez, Ladd, & Plotsky, 2001).

Echoing the animal literature, deprivation produces pervasive effects on brain and cognitive functioning, with greater cognitive deficits related to longer periods of institutional deprivation in early life (Colvert et al., 2008; Pollak et al., 2010). For example, increased ADHD symptomology (e.g., attention, impulsivity, hyperactivity) and lower IQ have been reported in internationally adopted (IA) children compared to non-adopted peers (Hostinar et al., 2013; Kreppner, O'Connor, & Rutter, 2001; Pollak et al., 2010). Institutional care in early life is associated with reduced cortical gray matter volume (Sheridan, Fox, Zeanah, McLaughlin, & Nelson, 2012) and decreased glucose metabolism in multiple brain regions, including the infralimbic prefrontal cortex and the orbital frontal gyrus (Chugani et al., 2001). McLaughlin and colleagues (2013) reported that institutionalization is related to lower cortical thickness in prefrontal, parietal, and temporal brain regions, which was associated with increased ADHD symptoms.

It is currently unclear whether these outcomes are due to institutional deprivation specifically or to co-occurring micronutrient deficiencies that disrupt brain development (Fuglestad et al., 2008; Rutter, 1972; Sonuga-Barke, Schlotz, & Rutter, 2010; Sonuga-Barke et al., 2008). Previous studies have used weight-for-age or height-for-age as proxies for macronutrient status when assessing the effects of deprivation (e.g., Sonuga-Barke et al., 2008). This method is incomplete to assess overall nutrition status as it may be uncorrelated with micronutrient deficiencies, and it is not known whether macronutrient status reliably predicts developmental outcomes.

Specifically, iron deficiency (ID) in early childhood produces disruptions in neurodevelopment, cognition, and attention that are similar to those reported in children who have experienced early deprivation (Lozoff et al., 2006; Rutter et al., 2010). Samples of Eastern European adoptees suggest that ID affects approximately 25% of children at adoption (Fuglestad et al., 2013; Fuglestad, Lehmann, et al., 2008), so it is probable that some of the neurobehavioral effects of early deprivation are due to co-occurring ID. ID disrupts striatal-frontal dopaminergic connections and produce deficits in attention, general cognitive ability, and socioemotional development (Lozoff et al., 2006). ID in early life likely affects brain regions that are rapidly developing at the time of insufficiency as well as connections to areas with more prolonged development, such as the frontal lobe, which explains the diverse effects of ID (Georgieff, 2011). ID in infancy predicts attentional problems years later (Lozoff et al., 2000), and ID in childhood has been linked to both ADHD symptoms and diagnosis (for review, see Cortese, Angriman, Lecendreux, &

Konofal, 2012). Deficits in attention and behavior regulation may also impact performance on cognitive testing (Fuglestad et al., 2013; Lozoff et al., 1998). Thus, symptoms of ADHD following early ID may result in difficulty paying attention and managing cognitive resources during testing and in school settings, resulting in lower scores that do not represent the child's actual abilities. Indeed, Beckett and colleagues (2007) found that IA children's scholastic performance was mediated by inattention and hyperactivity in addition to IQ. After controlling for these factors, there was little difference between the performance of adopted and non-adopted children, indicating that IA children with symptoms of ADHD are at an even greater risk for poor school performance. As ID is associated with poorer attention, ID in addition to institutional care could put children at risk for poorer scholastic performance.

ID may result from a diet lacking in iron and/or psychosocial stress that interferes with nutrient absorption (Monk et al., 2013), which is why ID is especially common in IA children who have often experienced both poor nutrition and psychosocial stress. In IA children, ID is especially risky as it may persist or worsen after adoption especially in children experiencing rapid catch-up growth, and in spite of consumption of recommended levels of dietary iron (Fuglestad, Lehmann, et al., 2008). Alarming, the cognitive effects of early ID persist into adulthood even after prompt treatment (Lukowski et al., 2010). ID is known to operate in a severity and temporal hierarchy in which specific iron markers are related to different stages of deficiency (Cook, 1982). Low ferritin levels characterize the first stage of pre-anemic ID, and low iron saturation and elevated iron binding capacity (IBC) are associated with the second stage. In the third stage, red blood cells decrease in size, as indicated by low mean corpuscular volume (MCV) levels. These 3 stages are called "pre-anemic" ID, which is three times more prevalent than ID anemia (IDA). The final stage is IDA, which is characterized by abnormally low levels of hemoglobin concentration and hematocrit; this stage has well-researched negative effects on brain development (Lozoff et al., 2006; Lozoff et al., 2008). There is a small body of research in humans that suggests that pre-anemic ID also has negative implications for brain development (Lozoff et al., 2008). As a result, this study will examine whether pre-anemic and anemic ID in IA children still predicts cognitive functioning beyond the effect of institutional care duration.

In this study, IA children were compared to children raised in their biological families to determine if ADHD symptomology is present 2.5-5 years after adoption. The effects of iron deficiency (ID) and duration of deprivation on cognitive functioning in children between 58 and 71 months of age were examined to determine whether institutional care, nutrition, or both are responsible for deficits. A previous study in this group conducted 12 months post-adoption reported lower IQ compared to non-adopted peers (Hostinar et al., 2013), and a follow-up to that study reported that both greater ID severity and longer institutional care duration predicted lower IQ scores (Doom et al., 2014). In the current study, children who were adopted internationally were expected to have greater ADHD symptomology and lower IQ than children who were raised in their biological families. Children with longer institutional care duration were hypothesized to have greater difficulties than children with less time in an institution. Within the adopted group, children with more severe levels of ID at adoption were expected to have greater difficulties with ADHD symptoms and lower IQ at age 5 than those who were iron sufficient. ID was hypothesized to at least partially

mediate the impact of institutional care on ADHD and IQ, and ADHD symptoms were hypothesized to mediate the impact of both ID and duration of institutional care on IQ.

Methods

Participants

Participants included 88 IA ($M = 62.1$ months, $SD = 2.4$) and 35 non-adopted children ($M = 61.4$ months, $SD = 1.6$). More IA than non-adopted children were recruited to assess a wider range of pre-adoption experiences. IA children were adopted from 12 countries in Asia, Europe, Africa, and Latin America, and they spent between 0-34 months ($M = 12.4$, $SD = 11.2$) in an institution (e.g., orphanage or hospital) before arrival in the U.S. In the IA group, 39.5% of children spent at least 80% of their life in an institution prior to adoption, and 31.7% spent at least 80% of their life in foster care, which is typically associated with better outcomes than institutional care. Children from Russia, Eastern Europe, Nepal, and India were more likely to spend a majority of their lives in an institution ($M = 98.7\%$ of life in an institution) compared to Southeast Asia (47.9%), Latin America (30.3%), and Africa (28.7%), $F(1,86) = 16.6$, $p < .001$. IA children were assessed 29-64 months post-adoption ($M = 41.9$ months, $SD = 10.2$). Non-adopted participants were recruited from a university participant pool that included families who agreed to be contacted for research opportunities. The non-adopted children were white (86%), Asian (3%), and multiracial (11%). The average education level of non-adopted children's parents was a bachelor's degree and the average household income for these families was \$75,001-100,000. These demographic variables were similar to IA families whose average level of education was a bachelor's degree and average income was between \$100,001-125,000. Exclusion criteria included fetal alcohol syndrome concern or diagnosis, severe cognitive impairment, autism, or congenital abnormalities that affect neurodevelopment.

Procedure

Parents signed a HIPAA (Health Insurance Portability and Accountability Act) form allowing researchers to contact the child's physician to obtain information from the first medical visit after adoption (range 0-5 months post adoption; $M = 0.73$, $SD = 0.83$). Information on health status, including iron status and weight, were requested. All parents of IA children signed the HIPAA form and physicians supplied the requested information for all children. Weight-for-age z-scores were computed using World Health Organization guidelines, which are not specific to country of origin. Parents completed a phone interview with an adoption expert soon after adoption using information supplied by the adoption agency and gleaned by the parents who traveled to the child's birth country. The adoption expert then put together a timeline of the child's living arrangements from birth to adoption from which duration of institutional and foster care were abstracted. When the children were approximately five years old ($M = 62.1$ months) and thus between 29-64 months post-adoption ($M = 41.9$ months, $SD = 10.2$), they completed a session in which, among other tasks, IQ was assessed, and parents and experimenters filled out questionnaires on the child's behavior. Non-adopted children in this age range also participated in the assessment. To examine longitudinal patterns, IQ was assessed previously in a subset of post-institutionalized children as part of a separate study approximately 12 months post-adoption

using either the Stanford-Binet ($n = 4$) or the Mullen Scales of Early Learning. None of the non-adopted children were assessed in this assessment. Parents gave permission to link information across studies. A review of the procedure is included in Figure 1.

Iron Deficiency (ID)

We were able to obtain iron status data on 69 of the 88 IA children (78%). Although all parents gave permission to contact their pediatrician, only 69 children had reports that included information on iron status. There were no significant differences on any values between IA children with and without ID data. ID status was abstracted using available information on the following markers in serum samples: hemoglobin, transferrin saturation (TS), mean corpuscular volume (MCV), ferritin, and iron-binding capacity (IBC). The following values were defined as abnormal: hemoglobin concentration $< 110\text{g/L}$, TS $< 12\%$, MCV $< 74\text{ fl}$, ferritin $< 12\text{ }\mu\text{g/L}$, and IBC $> 538\text{ }\mu\text{g/dL}$ (Lozoff et al., 2008; Fuglestad et al., 2012). Children were classified by ID severity from least to most severe: normal (normal results for all iron variables), pre-anemic with 1 abnormal iron index (normal hemoglobin and 1 abnormal TS, MCV, ferritin, or IBC result), pre-anemic with 2 or more abnormal indices, and IDA (low hemoglobin levels). In the current study, 50 children had normal iron status, 7 were ID with 1 abnormal index, 5 were ID with 2 or more abnormal indices, and 7 children were IDA.

ADHD Symptomology

Parent-reported attention and impulsivity problems at the age 5 session were assessed using the MacArthur Health and Behavior Questionnaire (HBQ; Essex et al., 2002). The HBQ is a comprehensive questionnaire that measures parent perceptions of children's functioning, including the domains of mental and physical health, academic competence, and peer relations. Parents evaluate ADHD symptoms on 2 scales that measure inattention and impulsivity. Parents respond using a 3-point scale (0 = rarely applies, 1 = applies somewhat, and 2 = certainly applies). The HBQ has demonstrated high test-retest reliability, discriminant validity, and cross-informant agreement (Essex et al., 2002; Lemery-Chalfant et al., 2007). The overall ADHD scale shows strong internal consistency in this sample ($\alpha = 0.85$).

Parents reported ADHD symptoms at the 12-month post-adoption session using the Early Childhood Inventory-4 (Sprafkin and Gadow, 1996). One scale measures ADHD inattention symptoms (9 items), and a second scale measures ADHD hyperactivity and impulsivity symptoms (9 items). Categories show adequate internal consistency in this sample ($\alpha = .70$), test-retest reliability (Gadow & Sprafkin, 1997; Gadow et al., 2001), and criterion validity when compared with ADHD clinical diagnoses (Gadow & Sprafkin, 1997). The ECI-4 was highly correlated with the Teacher's Report Form and the Child Behavior Checklist (Sprafkin et al., 2002).

Following the 12-month post-adoption and age 5 sessions, trained research assistants rated ADHD symptoms by a survey of symptoms that occurred during the session. Three questions ask about attention to tasks, inhibitory control/impulsivity, and hyperactivity during the session. Behaviors are scored on a 5-point Likert scale: attention (1 = constantly

off-task, 5 = constantly attends), impulsivity (1 = consistently able to wait/resist temptation, 5 = consistently impulsive), and hyperactivity (1 = consistently hyperactive, 5 = consistently not hyperactive). Kappa ranged from 0.77 to 0.81 for these items.

In order to reduce the number of analyses, a multi-informant ADHD composite was created. The experimenter-reported attention and impulsivity questions were reverse-scored so that higher numbers would indicate greater difficulties. Then the two parent-reported scales and three experimenter-reported questions were standardized ($M = 0$, $SD = 1$), and the resulting scores were averaged to create a single ADHD composite with higher scores indicating more ADHD symptoms. Internal consistency for the composite was acceptable ($\alpha = .76$). A multi-informant ADHD composite was also created for the 12-month post-adoption session for longitudinal analyses. This composite utilized the two parent-reported scales from the ECI and the three experimenter-rated questions from session survey. These items were standardized, and the mean was used to create the 12-month post-adoption ADHD composite ($\alpha = .72$).

IQ

The Stanford-Binet Intelligence Scales (5th edition) Abbreviated IQ Battery was used by trained research assistants to test general intelligence for children in both groups at the age 5 session (Roid, 2003). This assessment included both verbal and nonverbal components and is suitable for children over 2 years of age. Scores for each scale were summed and then converted to an IQ score based on age using well-established norms ($M = 100$, $SD = 15$). The Stanford-Binet has been validated on large representative samples and is correlated with other cognitive measures, including the Wechsler Preschool and Primary Scales of Intelligence (Lichtenberger, 2005). One child in the IA group refused the verbal component and is excluded from IQ analyses.

For longitudinal analyses within the IA group, a clinical psychologist assessed IQ using the Mullen Scales of Early Learning at approximately 12 months post-adoption during a research visit (Mullen, 1995). The Mullen Scales assess fine motor, receptive language, visual reception, and expressive language skills. Scores on these subtests were summed and transformed to an age-scaled standardized score ($M = 100$, $SD = 15$). Large samples have been tested to validate the Mullen Scales, and Mullen-generated IQ scores are highly correlated with other measures of cognitive ability, including the Bayley Mental Development Index (Bradley-Johnson, 2001). When 12-month post-adoption testing commenced, 4 children were assessed for IQ using the Stanford-Binet Intelligence Scales, which is standardized on the same scale as the Mullen. All the other children were tested using the Mullen Scales.

Data Analytic Plan

The results are divided into three sections that 1) assess the effects of adoption status (IA vs. non-adopted) and gender on ADHD symptoms and IQ, 2) examine the impacts of ID and duration of institutional care on ADHD symptoms and IQ at age 5, and 3) assess the longitudinal impacts of ID and duration of institutional care on ADHD symptoms and IQ. First, ANOVAs were conducted to test for the main effects of adoption status (IA vs. non-

adopted) and sex as well as the adoption status by sex interaction on ADHD symptomology and IQ in the full group of IA children ($n = 88$). Second, correlational analyses were computed between the independent (ID and duration of institutionalization) and dependent variables (ADHD symptoms and IQ) of interest to determine if there were significant associations. If both ID and duration of institutionalization were correlated with ADHD symptoms or IQ, then a regression was conducted to analyze whether one or both variables had more predictive power within the IA group that had information on iron status ($n = 69$). MacKinnon's test of mediation was conducted to examine whether ID mediated the association between duration of institutionalization and ADHD, and a second mediation test was conducted to examine whether ADHD mediated the association between ID and IQ (Tofighi & MacKinnon, 2011). The same mediation analysis was then conducted to examine whether ADHD symptoms mediated the association between duration of institutional care and IQ. Finally, the effects of ID and duration of institutional care on IQ and ADHD symptoms over time were examined in a subset of IA children who had completed a session 12 months post-adoption and at age 5. Preliminary tests showed that this subset did not differ in IQ, ADHD symptoms, or ID status from the larger sample. Because only 2 children in the non-anemic group with 2+ abnormal indices completed both sessions, this group was combined with the non-anemic group with 1 abnormal index to yield a single pre-anemic group for the repeated measures analyses, leaving 3 groups in the iron severity index: normal iron, pre-anemic ID, and IDA. Groups were created by duration of institutional care, dividing into children who were in an institution for less than 12 months and those in an institution for 12 or more months. The first repeated measures ANOVA utilized IQ at 12 months post-adoption and at age 5 as dependent variables and iron severity group as the between-group variable ($n = 30$). The second repeated measures ANOVA was conducted with ADHD symptomology at 12 months post-adoption and at age 5 as dependent variables and iron severity group as the between-group variable ($n = 33$). A third repeated measures ANOVA with iron severity as the between-group variable utilized IQ at 12 months post-adoption and at age 5 as the dependent variable ($n = 39$). The fourth repeated measures ANOVA used duration of institutional care as the between-group variable and ADHD symptoms as the dependent variable ($n = 42$).

Results

An ANOVA demonstrated a main effect of adoption status on ADHD symptomology with IA children having more ADHD symptoms than children raised in their biological families at approximately age 5, $F(1, 119) = 8.35$, $p < .01$, $\eta^2 = 0.07$ (see Table 1). There was a main effect of sex on ADHD symptoms with boys ($M = 0.07$, $SE = 0.11$) having more symptoms than girls ($M = -0.24$, $SE = 0.09$), $F(1, 119) = 4.60$, $p < .05$, $\eta^2 = 0.04$. The interaction between adoption status and sex did not predict ADHD symptomology, $F(1, 119) = 0.98$, $p = 0.33$. IA children had lower IQ than their non-adopted peers, $F(1, 118) = 12.22$, $p = .001$, $\eta^2 = 0.09$ (see Table 1). There was no main effect of sex on IQ, $F(1, 118) = 0.35$, $p = .56$, and there was no interaction effect, $F(1, 118) = 1.34$, $p = .25$. Children who had spent longer periods in an institution had more severe ID at adoption, $r(67) = 0.43$, $p < .001$. Within the IA group, children with more severe ID at adoption had greater ADHD symptomology, $r(69) = 0.40$, $p = .001$ (Figure 2), and lower IQ, $r(68) = -0.28$, $p < .05$ (Figure 3). Duration of

institutional care was related to ADHD symptoms, $r(86) = .28$, $p < .01$, but not IQ, $r(85) = -.08$, $p = .49$. When entered into the same model, duration of institutionalization significantly predicted ADHD symptoms, $t(64) = 2.10$, $p < .05$, and despite the covariation between ID and duration of institutionalization, ID severity marginally added to the prediction of ADHD, $t(64) = 1.75$, $p = .09$. The effect of duration of institutionalization on ADHD symptoms was at least partially mediated by ID status as the 95% confidence interval for the mediation test did not include 0, [0.003, 0.019].

As IQ and ADHD were significantly correlated, $r(122) = -0.28$, $p < .01$, a mediation test was conducted to examine whether ADHD mediated the association between ID and IQ. This test was significant as the 95% confidence interval did not include 0, [-1.04, -0.16]. This result indicates that ID impacts IQ at least in part through its effect on ADHD symptoms. A mediation test was then conducted to test whether ADHD symptoms significantly mediated the relation between duration of institutional care and IQ. The 95% confidence interval did not include 0, [-0.21, -0.02], indicating that ADHD symptoms at least partially mediate the association between duration of institutional care and IQ. Weight-for-age ($M = -0.47$, $SD = 1.10$) was below the mean, and 10.5% of IA children had a weight-for-age z-score that was 2 or more standard deviations below the mean, consistent with macronutrient deprivation. Weight-for-age at adoption, a measure of macronutrient status, did not predict ADHD symptoms, $r(86) = -0.14$, $p = .21$, or IQ, $r(85) = 0.13$, $p = .23$, which suggests that these outcomes are not solely due to macronutrient deprivation.

The repeated measures ANOVA examining the impact of ID severity group on IQ over time yielded a significant group $\times$ time interaction, $F(3, 26) = 3.84$, $p < .05$ (Figure 4). A paired samples t-test revealed there was no difference in IQ scores between sessions for IA children with normal iron levels at adoption, $t(16) = .60$, $p = .56$. Non-anemic children scored significantly better on the IQ test 2.5-5 years after adoption, $t(8) = -2.45$, $p < .05$, and anemic children performed marginally better at the later session, $t(3) = -2.59$, $p = .08$. A repeated measures ANOVA testing the effect of ID severity on ADHD symptomology between the 12-month post-adoption and age 5 sessions showed no ID group $\times$ time interaction, $F(2, 30) = .69$, $p = .51$, indicating no significant improvement in ADHD symptoms by ID group. A repeated measures ANOVA examining the effect of institutional care on IQ yielded a significant group $\times$ time interaction, $F(1, 37) = 5.88$, $p < .05$ (Figure 5). A paired samples t-test revealed no difference in IQ scores over time for IA children with less than 12 months in an institution, $t(13) = 0.44$, $p = 0.66$. However, the IA children with 12 or more months in an institution demonstrated a significant increase in IQ over time, $t(24) = -3.60$, $p = .001$. A repeated measures ANOVA examining the effect of institutional care on ADHD symptoms between the 12 month post-adoption and age 5 session was not significant, indicating no change in ADHD symptoms by institutional care group, $F(1, 40) = 0.28$, $p = 0.60$.

Discussion

This study examined the relative impacts of duration of institutional care and ID on ADHD symptoms and IQ 29-64 months post-adoption. IA children had greater ADHD symptomology and lower IQ than non-adopted children at approximately 5 years of age.

Within the IA group, children with more severe ID at adoption had greater ADHD symptomology and lower IQ. Duration of institutional care was positively correlated with ADHD symptoms but not IQ. Both ID and duration of institutional care impact IQ at least in part through effects on ADHD symptoms. Longitudinal results indicate IQ recovery between 12 months post-adoption and age 5 for children with greater ID severity at adoption and longer institutional duration but no improvement in ADHD symptoms.

These results signify a continuing effect of early deprivation and ID on children years after adoption as IA children have greater ADHD symptomology and lower IQ than children living in similar families. Cognitive deficits related to both deprivation and ID have been documented in these children 12 months after adoption (Doom et al., in press), and this study demonstrates that deficits are still present 2.5-5 years post-adoption. Duration of deprivation is predictive of ADHD symptoms, and ID at adoption predicts greater ADHD symptoms (marginally beyond the effect of institutional duration) and lower IQ. These findings are consistent with the neurobiological and behavioral correlates of ID observed in the animal and human literature (Georgieff, 2011; Lozoff et al., 2006), which provides further evidence that cognitive outcomes are not fully explained by ID and that deprivation has a unique impact on behavior. Deprivation may impact neural circuitry that supports attention while ID may impact a combination of circuitry that supports general cognitive ability and attention, including the hippocampus and the frontal lobe. Duration of institutional care showed a more significant effect on ADHD symptoms than ID, so the stimulus and social deprivation experienced while in an institution may be particularly salient for the development of ADHD in later childhood and adolescence. As duration of deprivation and ID have independent effects, they should be understood as separate risk factors for neurodevelopment. Children with greater time spent in an institution were more likely to have ID, which at least partially accounts for increases in ADHD symptoms related to institutional care. Alarming, even children with less severe ID show deficits in attention and impulsivity years after adoption, which is important information for pediatricians who treat ID in IA children. Prevention and treatment should thus focus on prenatal and early postnatal iron supplementation as well as cognitive interventions that support brain development after early nutritional and institutional deprivation. In addition, those studying the impact of early deprivation on neurobehavioral development should consider assessing micronutrient deficiencies present during or shortly after the period of deprivation as part of their overall assessment.

Consistent with the animal and human literature on the effects of ID on the neural circuitry that scaffolds attention and behavioral regulation (Georgieff, 2011; Lozoff et al., 2006), ID had a significant impact on children's attention and regulation years after adoption. As ADHD symptoms mediated the association between ID and poorer cognitive outcomes, attention and behavior regulation may be key targets for clinicians trying to improve academic achievement following early ID. In IA children who have experienced institutional deprivation, a focus on ADHD symptoms and neural systems that govern attention and behavior regulation is especially important as ID and institutional care are both related to ADHD symptomology post-adoption. However, there is evidence for plasticity in general cognitive ability following early ID and deprivation. Longitudinal analyses demonstrate a lasting effect of early ID but indicate some recovery for IQ in children with more severe ID.

These results may suggest that for those pre-anemic and anemic children who showed higher IQ scores over time, ID did not occur during a sensitive period for IQ in which no recovery could be made. However, the group with normal iron levels remained stable, suggesting that recovery is greater for children with more severe ID, even though they have much poorer cognitive outcomes early in life. Likewise, plasticity in IQ was observed for children who spent greater than 12 months in an institution but not for children less than 12 months in an institution. This result also suggests the greatest recovery occurs for children with the poorest cognitive outcomes and the most time in a depriving environment. However, the same recovery was not observed for ADHD symptoms, raising the possibility that ID and institutional deprivation may have occurred during a sensitive period for neural circuitry that supports attention and behavior regulation. Finally, macronutrient status (weight-for-age) did not explain variance in ADHD symptoms or IQ, thus highlighting the importance of examining micronutrient status in future studies.

These findings may contribute to the study of ADHD in general. For example, more research is needed on the effects of prenatal and early post-natal ID on the development of ADHD during childhood. As early deprivation independently contributes to ADHD symptoms in this study, it will be vital to understand how other environments that involve social or stimulus deprivation (e.g., neglect or chronic poverty) affect neural circuitry that governs attention. As ADHD outcomes did not improve over time in the longitudinal analyses, it may be that an early insult to the brain that is not specific to a particular domain (e.g., nutritional or social) could impact brain development in a way that influences later development of inattention and hyperactivity. Meditational analyses also indicate that ADHD symptoms at least partially mediate the impact of deprivation and ID on IQ, so interventions following early ID and/or deprivation may target symptoms of inattention and hyperactivity to improve learning ability.

The study had limitations that must be considered. First, ID was not assessed at the follow-up assessment 2.5-5 years post-adoption so it is unclear whether changes in iron status since adoption affected cognitive outcomes. However, the rate of ID in children is low after age 3 on a typical western diet, and children at this age have a lower iron demand than in infancy and toddlerhood. The results in this study demonstrating lower IQ following ID are also consistent with research demonstrating that ID predicts poorer cognitive functioning and that early ID impacts cognition even after supplementation (Felt et al., 2006). Second, there were not enough children to be able to divide participants into distinct and well-characterized groups by specific iron marker deficiencies. Larger samples are needed to determine the stage at which ID affects cognition. Third, iron status was not assessed in non-adopted children. However, the rate of ID in children similar to our mostly white non-adopted sample is around 6% (Brotanek, Gosz, Weitzman, & Flores, 2007), which is much lower than the IA group. Fourth, the examination of ADHD symptoms is not standard and does not use a clinical diagnosis, but rather symptoms reported by parents and research assistants. Fifth, the use of different IQ assessments between the 12 month and 5 year sessions may explain some of the change between assessments. However, not all groups improved in IQ over time, so it is likely that change is partially due to increased cognitive capacity. Finally, other nutrient deficiencies (e.g., zinc, choline) may have been present but were not measured in the present study.

These results highlight the importance of examining both the duration of adverse/deprived care and micronutrient status when predicting child outcomes and designing individualized treatments to promote attention, behavior regulation, and cognitive development. Although our longitudinal analyses demonstrate plasticity in IQ post-adoption for children who experienced early ID and longer duration of institutional care, there was no such plasticity observed for attention and behavior regulation. Thus, interventions should focus on brain systems governing attention and regulation as these abilities partially mediate the effects of ID on IQ, and both IQ and ADHD symptoms predict poorer academic performance in IA children (Beckett et al., 2007). In addition, evidence that ID may increase risk for sleep disorders in children with ADHD suggests that the relations between ID, ADHD, and sleep should be further explored as they may be especially strong in IA children who have increased risk for both ID and ADHD (Cortese, Konofal, Bernardina, Mouren, & Lecendreux, 2009). Understanding the longitudinal effects of institutional deprivation and micronutrient status on brain development will facilitate a greater understanding of brain development in IA children.

Acknowledgments

We thank the participating families as well as the members of the International Adoption Project at the University of Minnesota. We also thank Alyssa Miller and Bao Moua for tirelessly collecting iron information from the children's clinics. This research was supported by Grants MH080905 and MH078105 (to Megan R. Gunnar), and, in part, by the Center for Neurobehavioral Development at the University of Minnesota. In addition, an NIMH training grant (T32MH015755, Dante Cicchetti, PI) supported Jenalee Doom.

References

- Beckett C, Maughan B, Rutter M, Castle J, Colvert E, Groothues C, Sonuga-Barke S. Scholastic attainment following severe early institutional deprivation: A study of children adopted from Romania. *Journal of Abnormal Child Psychology*. 2007; 35(6):1063–1073. doi: 10.1007/s10802-007-9155-y. [PubMed: 17643189]
- Bennett EL, Diamond MC, Krech D, Rosenzweig MR. Chemical and anatomical plasticity of brain. *Science*. 1964; 164:610–619. doi: 10.1126/science.146.3644.610. [PubMed: 14191699]
- Bradley-Johnson S. Cognitive assessment for the youngest children: A critical review of tests. *Journal of Psychoeducational Assessment*. 2001; 19(1):19–44. doi: 10.1177/073428290101900102.
- Brotanek JM, Gosz J, Weitzman M, Flores G. Iron deficiency in early childhood in the United States: Risk factors and racial/ethnic disparities. *Pediatrics*. 2007; 120(3):568–575. [PubMed: 17766530]
- Chugani HT, Behen ME, Muzik O, Juhasz C, Nagy F, Chugani DC. Local brain functional activity following early deprivation: A study of post-institutionalized Romanian orphans. *NeuroImage*. 2001; 14:1290–1301. doi:10.1006/nimg.2001.0917. [PubMed: 11707085]
- Colvert E, Rutter M, Kreppner J, Beckett C, Castle J, Groothues C, Sonuga-Barke E. Do theory of mind and executive function deficits underlie the adverse outcomes associated with profound early deprivation?: Findings from the English and Romanian adoptees study. *Journal of Abnormal Child Psychology*. 2008; 36:1057–1068. doi: 10.1007/s10802-008-9232-x. [PubMed: 18427975]
- Cook JD. Clinical evaluation of iron deficiency. *Seminars in Hematology*. 1982; 19:6–18. [PubMed: 6763340]
- Cortese S, Angriman M, Lecendreux M, Konofal E. Iron and attention deficit/hyperactivity disorder: what is the empirical evidence so far? A systematic review of the literature. *Expert Review of Neurotherapeutics*. 2012; 12(10):1227–1240. doi: 10.1586/ern.12.116. [PubMed: 23082739]
- Cortese S, Konofal E, Bernardina BD, Mouren MC, Lecendreux M. Sleep disturbances and serum ferritin levels in children with attention-deficit/hyperactivity disorder. *European Child & Adolescent Psychiatry*. 2009; 18:393–399. doi: 10.1007/s00787-009-0746-8. [PubMed: 19205783]

- Diamond MC, Rosenzweig MR, Bennett EL, Lindner B, Lyon L. Effects of environmental enrichment and impoverishment on rat cerebral cortex. *Journal of Neurobiology*. 1972; 3:47–64. doi: 10.1002/neu.480030105. [PubMed: 5028293]
- Doom JR, Gunnar MR, Georgieff MK, Kroupina MG, Frenn K, Fuglestad AJ, Carlson SM. Beyond stimulus deprivation: Iron deficiency and cognitive deficits in post-institutionalized children. *Child Development*. 2014 Advance online publication. doi: 10.1111/cdev.12231.
- Essex MJ, Boyce WT, Heim Goldstein L, Armstrong JM, Kraemer HC, Kupfer DJ. The MacArthur Assessment Battery Working Group. The confluence of mental, physical, social, and academic difficulties in middle childhood. II: Developing the MacArthur Health and Behavior Questionnaire. *Journal of the American Academy of Child and Adolescent Psychiatry*. 2002; 41:588–603. [PubMed: 12014792]
- Felt BT, Beard JL, Schallert T, Shao J, Aldridge JW, Connor JR, Lozoff B. Persistent neurochemical and behavioral abnormalities in adulthood despite early iron supplementation for perinatal iron deficiency anemia in rats. *Behavioural Brain Research*. 2006; 171:261–270. doi: 10.1016/j.bbr.2006.04.001. [PubMed: 16713640]
- Fuglestad AJ, Georgieff MK, Iverson SL, Miller BS, Petryk A, Johnson DE, Kroupina MG. Iron deficiency after arrival is associated with general cognitive and behavioral impairment in post-institutionalized children adopted from Eastern Europe. *Maternal and Child Health Journal*. 2013; 17:1080–1087. doi: 10.1007/s10995-012-1090-z. [PubMed: 22872286]
- Fuglestad AJ, Lehmann AE, Kroupina MG, Petryk A, Miller BS, Iverson SL, Georgieff MK. Iron deficiency in international adoptees from Eastern Europe. *Journal of Pediatrics*. 2008; 153:272–277. doi: 10.1016/j.jpeds.2008.02.048. [PubMed: 18534235]
- Fuglestad, A.; Rao, R.; Georgieff, MK. The role of nutrition in cognitive development. In: Nelson, CA.; Luciana, M., editors. *Handbook of developmental cognitive neuroscience*. 2nd. MIT Press; Cambridge, MA: 2008.
- Gadow, KD.; Sprafkin, J. *Early Childhood Inventory-4 Norms Manual*. Checkmate Plus; Stony Brook, NY: 1997.
- Gadow KD, Sprafkin J, Nolan EE. DSM-IV symptoms in community and clinic preschool children. *Journal of the American Academy of Child & Adolescent Psychiatry*. 2001; 40:1383–1392. doi: 10.1097/00004583-200112000-00008. [PubMed: 11765283]
- Georgieff MK. Long-term brain and behavioral consequences of early iron deficiency. *Nutrition Reviews*. 2011; 69:S43–8. doi: 10.1111/j.1753-4887.2011.00432.x. [PubMed: 22043882]
- Globus A, Rosenzweig MR, Bennett EL, Diamond MC. Effects of differential experience on dendritic spine counts in rat cerebral cortex. *Journal of Comparative and Physiological Psychology*. 1973; 82(2):175–181. doi: 10.1037/h0033910. [PubMed: 4571892]
- Gunnar MR, Morison SJ, Chisholm K, Schuder M. Salivary cortisol levels in children adopted from Romanian orphanages. *Development and Psychopathology*. 2001; 13:611–628. [PubMed: 11523851]
- Hostinar CE, Stellern SA, Schaefer C, Carlson SM, Gunnar MR. Associations between early life adversity and executive function in children adopted internationally from orphanages. *Proceedings of the National Academy of Sciences*. 2012; 109:17208–17212. doi: 10.1073/pnas.1121246109.
- Kreppner JM, O'Connor TG, Rutter M. Can inattention/overactivity be an institutional deprivation syndrome? *Journal of Abnormal Child Psychology*. 2001; 29(6):513–528. doi: 10.1023/A:1012229209190. [PubMed: 11761285]
- Kreppner JM, Rutter M, Beckett C, Castle J, Colvert E, Groothues C, Sonuga-Barke E. Normality and impairment following profound early institutional deprivation: A longitudinal examination through childhood. *Developmental Psychology*. 2007; 43:931–946. doi: 10.1037/0012-1649.43.4.931. [PubMed: 17605526]
- Lemery-Chalfant K, Schreiber JE, Schmidt NL, Van Hulle CA, Essex MJ, Goldsmith HH. Assessing internalizing, externalizing, and attention problems in young children: validation of the MacArthur HBQ. *Journal of the American Academy of Child and Adolescent Psychiatry*. 2007; 46:1315–1323. doi: 10.1097/chi.0b013e3180f616c6. [PubMed: 17885573]
- Lichtenberger EO. General measures of cognition for the preschool child. *Mental Retardation and Developmental Disabilities Research Reviews*. 2005; 11(3):197–208. [PubMed: 16161087]

- Liston C, Miller MM, Goldwater DS, Radley JJ, Rocher AB, Hof PR, McEwen BS. Stress-induced alterations in prefrontal cortical dendritic morphology predict selective impairments in perceptual attentional set-shifting. *Journal of Neuroscience*. 2006; 26:7870–7874. doi: 10.1523/JNEUROSCI.1184-06.2006. [PubMed: 16870732]
- Lozoff B, Klein NK, Nelson EC, McClish DK, Manuel M, Chacon ME. Behavior of infants with iron deficiency anemia. *Child Development*. 1998; 69:24–36. [PubMed: 9499554]
- Lozoff B, Beard J, Connor J, Felt B, Georgieff M, Schallert T. Long-lasting neural and behavioral effects of iron deficiency in infancy. *Nutrition Reviews*. 2006; 64:S34–S91. doi: 10.1301/nr.2006.may.S34-S43. [PubMed: 16770951]
- Lozoff B, Clark KM, Jing Y, Armony-Sivan R, Angelilli ML, Jacobson SW. Dose-response relationships between iron deficiency with or without anemia and infant social-emotional behavior. *Journal of Pediatrics*. 2008; 152:696–702. doi: 10.1016/j.jpeds.2007.09.048. [PubMed: 18410777]
- Lozoff B, Jimenez E, Hagen J, Mollen E, Wolf AW. Poorer behavioral and developmental outcome more than 10 years after treatment for iron deficiency in infancy. *Pediatrics*. 2000; 105:E51. [PubMed: 10742372]
- Lukowski AF, Koss M, Burden MJ, Jonides J, Nelson CA, Kaciroti N, Lozoff B. Iron deficiency in infancy and neurocognitive functioning at 19 years: evidence of long-term deficits in executive function and recognition memory. *Nutritional Neuroscience*. 2010; 13:54–70. doi: 10.1179/147683010X12611460763689. [PubMed: 20406573]
- Martin LJ, Spicer DM, Lewis MH, Gluck JP, Cork LC. Social deprivation of infant rhesus monkeys alters the chemoarchitecture of the brain: 1. Subcortical regions. *Journal of Neuroscience*. 1991; 11:3344–3358. [PubMed: 1682426]
- McLaughlin KA, Sheridan MA, Winter W, Fox NA, Zeanah CH, Nelson CA. Widespread reductions in cortical thickness following severe early-life deprivation: A neurodevelopmental pathway to Attention-Deficit/Hyperactivity Disorder. *Biological Psychiatry*. 2013 Available online 3 October 2013.
- Monk C, Georgieff MK, Osterholm EA. Research review: Maternal prenatal distress and poor nutrition – mutually influencing risk factors affecting infant neurocognitive development. *Journal of Child Psychology and Psychiatry*. 2013; 54:115–130. doi: 10.1111/jcpp.12000. [PubMed: 23039359]
- Mullen, EM. Mullen Scales of Early Learning. American Guidance Service, Inc.; Circle Pines, MN: 1995.
- Nelson, CA.; Bos, K.; Gunnar, MR.; Sonuga-Barke, EJ. The neurobiological toll of early human deprivation. In: McCall, R., editor. *Monographs of the Society for Research in Child Development*. Vol. 76. 2011. p. 127-146. Children without permanent parental care: Research, practice, and policy
- Pollak SD, Nelson CA, Schlaak M, Roeber B, Wewerka S, Wiik KL, Gunnar MR. Neurodevelopmental effects of early deprivation in post-institutionalized children. *Child Development*. 2010; 81:224–236. doi: 10.1111/j.1467-8624.2009.01391.x. [PubMed: 20331664]
- Roid, GH. Stanford-Binet Intelligence Scales. 5th. Riverside; Itasca, IL: 2003.
- Rutter, M. *Maternal deprivation reassessed*. Penguin; Harmondsworth, Middlesex: 1972.
- Rutter M, O'Connor TG, English and Romanian Adoptees (ERA) Study Team. Are There biological programming effects for psychological development? Findings from a study of Romanian adoptees. *Developmental Psychology*. 2004; 40:81–94. doi: 10.1037/0012-1649.40.1.81. [PubMed: 14700466]
- Rutter M, Sonuga-Barke EJS, Castle J. I. Investigating the impact of early institutional deprivation on development: Background and research strategy of the English and Romanian Adoptees (ERA) Study. *Monographs of the Society for Research in Child Development*. 2010; 75:1–20. doi: 10.1111/j.1540-5834.2010.00548.x. [PubMed: 20500631]
- Rutter M, Sonuga-Barke EJ, Beckett C, Castle J, Kreppner J, Kumsta R, Gunnar MR. Deprivation-specific psychological patterns: Effects of institutional deprivation. *Monographs of the Society for Research in Child Development*. 2010; 75:1–231. doi: 10.1111/j.1540-5834.2010.00548.x. [PubMed: 20500631]

- Sánchez MM, Hearn EF, Do D, Rilling JK, Herndon JG. Differential rearing affects corpus callosum size and cognitive function of rhesus monkeys. *Brain Research*. 1998; 812:38–49. doi: 10.1016/S0006-8993(98)00857-9. [PubMed: 9813233]
- Sánchez MM, Ladd CO, Plotsky PM. Early adverse experience as a developmental risk factor for later psychopathology: Evidence from rodent and primate models. *Development and Psychopathology*. 2001; 13:419–449. doi: 10.1017/S0954579401003029. [PubMed: 11523842]
- Sheridan MA, Fox NA, Zeanah CH, McLaughlin KA, Nelson CA. Variation in neuronal development as a result of exposure to institutionalization in early childhood. *Proceedings of the National Academy of Sciences*. 2012; 109:12927–12932.
- Sonuga-Barke EJS, Beckett C, Kreppner J, Castle J, Colvert E, Stevens S, Hawkins A, Rutter M. Is sub-nutrition necessary for a poor outcome following early institutional deprivation? *Developmental Medicine & Child Neurology*. 2008; 50:664–671. doi: 10.1111/j.1469-8749.2008.03065.x. [PubMed: 18754915]
- Sonuga-Barke EJS, Schlotz W, Rutter M. VII. Physical growth and maturation following early severe institutional deprivation: Do they mediate specific psychopathological effects? *Monographs of the Society for Research in Child Development*. 2010; 75:143–166. doi: 10.1111/j.1540-5834.2010.00554.x. [PubMed: 20500637]
- Sprafkin, J.; Gadow, KD. *Early Childhood Symptom Inventories*. Checkmate Plus; Stony Brook, NY: 1996.
- Sprafkin J, Volpe RJ, Gadow KD, Nolan EE, Kelly K. A DSM-IV–Referenced Screening Instrument for Preschool Children: The Early Childhood Inventory-4. *Journal of the American Academy of Child & Adolescent Psychiatry*. 2002; 41(5):604–612. doi: 10.1097/00004583-200205000-00018. [PubMed: 12014793]
- Tofighi D, MacKinnon DP. RMediation: An R package for mediation analysis confidence intervals. *Behavior Research Methods*. 2011; 43:692–700. doi: 10.3758/s13428-011-0076-x. [PubMed: 21487904]

Research Highlights

- The current study reports lower IQ and higher ADHD symptoms at age 5 for children adopted internationally compared to peers raised in their biological families.
- Both more severe iron deficiency at adoption and greater length of time spent in institutional care predicted more ADHD symptoms. However, only iron deficiency at adoption predicted lower IQ at age 5.
- Longitudinal results indicate improvement in IQ from 12 months post-adoption to age 5 for children with more severe iron deficiency at adoption and longer duration of institutional care but no improvement in ADHD symptoms.

Figure 1.

Review of the procedure from adoption to the age 5 assessment.

Figure 2.

ADHD scores at age 5 by iron group at adoption. Group means and standard errors for non-adopted children and IA children by iron status. The ADHD score is a multi-informant composite that averages z-scored ($M = 0$, $SD = 1$) results.

Figure 3.

IQ scores at age 5 by iron group at adoption. Group means and standard errors for non-adopted children and IA children by iron status. IQ was assessed using the Stanford-Binet Intelligence Scales (5th edition) and used standard scoring ($M = 100$, $SD = 15$).

Figure 4.

Association of ID at adoption with IQ. IQ was assessed in IA children 1 year post-adoption and again 2.5-5 years post-adoption. IQ was standard scored ($M = 100$, $SD = 15$), and longitudinal results are presented by iron severity group at adoption.

Figure 5.

Association of duration of institutional care with IQ. IQ was assessed in IA children 1 year post-adoption and again 2.5-5 years post-adoption. IQ was standard scored ($M = 100$, $SD = 15$), and longitudinal results are presented by duration of institutional care.

Table 1

ADHD and IQ Means and Standard Deviations by Iron Severity Group

	Non-adopted	IA: Normal Iron	IA: 1 abnormal index	IA: 2+ abnormal indices	IA: IDA
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
IQ	110.8 (15.1)	101.8 (12.3)	100.4 (15.1)	101.2 (11.1)	88.0 (11.2)
ADHD	-0.34 (0.63)	-0.03 (0.64)	0.20 (0.36)	0.67 (1.07)	0.79 (0.96)

Note: Non-adopted, IA children with normal iron, and IA children with ID anemia were compared. Z-scores are shown for the ADHD composite (M = 0, SD = 1) and the Stanford-Binet IQ scores were standardized (M = 100, SD = 15).