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Depression in Previously-Institutionalized Youth: Biological and Environmental Mechanisms of
Risk and Resilience

A dissertation submitted in partial satisfaction of the requirements of the degree Doctor of
Philosophy in Psychology

by

Bonnie Saramarie Goff

2016

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ABSTRACT OF THE DISSERTATION

Depression in Previously-Institutionalized Youth: Biological and Environmental Mechanisms of
Risk and Resilience

by

Bonnie Saramarie Goff

Doctor of Philosophy in Psychology

University of California, Los Angeles, 2016

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Previous institutionalization (PI) is a potent stressor for the human infant. Such early stress can have long-lasting effects on emotional development (e.g., depression) and associated neurobiology. However the mechanisms underlying how early-life adversity (EA) increase neurobiological risk for depression are not fully understood. In this dissertation, I use a multi-method program of research, including experimental tasks, questionnaires, functional magnetic resonance imaging (fMRI), and epigenetic measures, to examine the developmental course of depression related phenotypes, as well as potential epigenetic and neurobiological mechanisms of this association. I further examined a potential behavioral intervention that may ameliorate depressive outcomes following EA. Study 1 shows that the nucleus accumbens (NAcc), a limbic structure associated with reward learning and motivation demonstrates atypical functioning

following EA, specifically hypoactivity during the adolescent period, Study 2 shows that PI youth display blunted telomeres, DNA–protein complexes located at the end of chromosomes that protect from deterioration, which in concert with NAcc hypoactivity, predict depressive outcomes. Study 3 presents evidence suggesting that high levels of physical activity (PA) may predict decreases in depressive symptoms following EA. The results from the current study have important implications for understanding the associations between EA and both neural and genetic changes that may influence later depressive outcomes, and also provide a potential behavioral intervention by which these outcomes may be improved. Investigation of these associations in a developmental population is paramount, as early childhood may represent a critical period for the interaction between adversity, cellular aging, and neurodevelopment and thus highlights the significance of early intervention.

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For Andrew B, my daily reminder of what matters most in life.

TABLE OF CONTENTS

I.	Introduction.....	1
	Ventral Striatum – Nucleus Accumbens.....	3
	Telomeres.....	6
	Physical Activity as Treatment.....	7
	Overview of Studies.....	9
II.	Reduced Nucleus Accumbens Reactivity & Adolescent Emergent Depression Following Early-Life Adversity.....	12
	Introduction.....	13
	Methods.....	16
	Results.....	20
	Discussion.....	23
III.	Nucleus Accumbens Reactivity Mediates Relationship Between Human Chromosomal Modification and Future Early-Life Adversity Induced Depression.....	33
	Introduction.....	34
	Methods.....	38
	Results.....	44
	Discussion.....	47
IV.	Effects of Physical Activity on Depressive Symptoms in Children and Adolescence Following Institutional Care.....	66
	Introduction.....	67
	Methods.....	70
	Results.....	72
	Discussion.....	75
V.	General Discussion.....	82
	References.....	93

LIST OF FIGURES

<p>Figure 1.1. Depressive symptoms increase following early-life adversity. The PI group showed significantly higher depression scores (measured dimensionally) in adolescents when compared to children. In contrast, the comparison group did not show any age-related change in depression scores.....</p>	28
<p>Figure 1.2. Self-report mood. PI adolescents showed a unique combination of low positive affect and high negative affect.....</p>	29
<p>Figure 1.3. NAcc hypoactivation during adolescence following early-life adversity. Left panel shows anatomically defined NAcc regions selected for analysis. Right panel shows the normative developmental increase in NAcc activity from childhood to adolescence in the comparison group. In contrast, the PI group did not show any age-related change, resulting in a NAcc hypoactivity in adolescence.....</p>	30
<p>Figure 1.4. Negative association between depression scores and NAcc activation. Lower NAcc activation while viewing happy faces was inversely correlated with parent report of depression scores, controlling for age and PI group.....</p>	31
<p>Figure 2.1. Ages of participants at time 1 and time 2. Participants with 1 point had telomere data but no follow-up information on depression.....</p>	53
<p>Figure 2.2. Data collection timeline.....</p>	54
<p>Figure 2.3. Telomere length was blunted in PI youth. The PI group showed significantly shorter telomere length than the comparison group. The comparison group showed a normative age decline in telomere length (measured dimensionally) and no age related changes in telomere length were seen in the PI group.....</p>	55
<p>Figure 2.4. Parent-reported depression changes quadratically over time in PI youth. The black arrow marks age 12 years that post-hoc computation identified as the turning point, or moment when depression scores reached a developmental peak. The comparison group did not show any age-related change in depression scores.....</p>	56
<p>Figure 2.5. Telomere length was inversely correlated with parent report of depression scores, controlling for group type, sex, age, depression scores at time 1, and the difference in age between collection of depression and telomere data centered at 24 months.....</p>	57
<p>Figure 2.6. Left panel shows anatomically defined NAcc regions selected for analysis. Right panel shows that, for the PI group, mean NAcc activation significantly decreased from childhood to adolescence. PI adolescents exhibited significantly lower NAcc activation relative to the comparison adolescents.....</p>	58

Figure 2.7. Telomere length was positively correlated with NAcc activation while viewing happy faces, controlling for group type, sex, age, and the difference in age between collection of fMRI and telomere data.....	59
Figure 2.8. Lower NAcc activation while viewing happy faces was inversely correlated with parent report of depression scores two years later, controlling for group type, sex, age, and the difference in age between collection of fMRI and depression data.....	60
Figure 2.9. NAcc activation mediated the relationship between telomere length and depressive symptoms two years later.....	61
Supplemental Image 2.1. Anatomical averages for youngest (4-6 years old) and oldest participants (15-16 years old) overlaid on adult template.....	62
Figure 3.1. The PI group showed significantly greater depression scores than the comparison group at both time 1 and time 2. The pattern of results was the same in both PI children (ages 4-11 years) and adolescents (ages 12-17 years).....	79
Figure 3.2. Longitudinal changes in depression scores in PI youth when PA was Low, Average, and High. The pattern of results was the same in both PI children (ages 4-11 years) and adolescents (ages 12-17 years). There was no significant difference in depression scores at time 1 for PI participants regardless of level of PA. No changes were observed in the comparison group.....	80

LIST OF TABLES

Table 1.1. Demographic Information for Sample.....	32
Table 2.1. Demographic Information for Sample (with Telomere data).....	63
Table 2.2. Demographic Information for Sample (with NAcc data).....	64
Table 2.3. Demographic Information for Sample (with RCADS data).....	65
Table 3.1. Demographic Information for Sample.....	81

LIST OF APPENDICIES

Appendix A. PANAS-C.....88

Appendix B. RCADS-P.....89

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I. Introduction

Early-life adversity (EA) can be defined as exposure to adverse events or stressors during infancy and early childhood that have significant negative emotional and physical effects, exceeding an individual's ability to cope (Benjet, Borges, & Medina-Mora, 2010; Gunnar & Quevedo, 2007). These adverse exposures occur at every socioeconomic level, across ethnic and cultural lines, and at all levels of education. In the United States alone, more than 3,000,000 reports of early-life adversity involving more than 6,000,000 youth are reported each year (Child Welfare Information Gateway, 2013), and these numbers reflect only a fraction of domestic EA exposures. Of note, more than 33% of confirmed cases of maltreatment affect children under 4 years old, while 24% of cases are 4–7 years old, 18% of cases are 8–11 years old, and 16% of cases are 12–15 years old (NCANDS, 2012). These statistics suggest that EA is not uncommon, particularly amongst young children - an important distinction, as early childhood may represent a period of heightened vulnerability to the negative effects of stress (Gunnar & Quevedo, 2007) and differential psychological outcomes may be dependent upon the specific timing of exposure (Maercker, Michael, Fehm, Becker, & Margraf, 2004).

The scientific literature overwhelmingly demonstrates an association between EA and depression (Agid et al., 1999; Brown, Cohen, Johnson, & Smailes, 1999; Chapman et al., 2004; Heim & Nemeroff, 2001; McCauley et al., 1997; Mullen, Martin, Anderson, Romans, & Herbison, 1996). Though genetic factors have been shown to influence vulnerability for depression following EA (Francis, Caldji, Champagne, Plotsky, & Meaney, 1999), twin studies demonstrate that the effects of adverse environments play a substantial role in depressive outcomes beyond the influence of genetics (Kendler, Neale, Kessler, Heath, & Eaves, 1992; Romanov, Varjonen, Kaprio, & Koskenvuo, 2003). Clinical evidence highlights a dose-response relationship between EA and mental health in adulthood (Edwards, Holden, Felitti, & Anda,

2003), specifically with regard to the severity of EA and lifetime chronic depression (Chapman et al., 2004). For example, the risk of depression in persons with multiple EA experiences is four times that of a person not having experienced early-life trauma (Felitti et al., 1998). The results from these clinical studies support outcomes reported in epidemiological research. A 17-year longitudinal study examining more than 750 randomly selected children found that adolescents and young adults with a history of EA were three times more likely to become depressed compared with individuals without such a history (Brown et al., 1999). Thus, vulnerability for depression may increase linearly with both the quantity and severity of adverse experiences, suggesting a possible causal link between EA and depression (Kendler, Karkowski, & Prescott, 1999).

According to the DSM IV, depression is characterized by the presence of the majority of nine symptoms: depressed mood, loss of interest or pleasure, disturbed sleep or appetite, anxiety, low energy, feelings of guilt or low self-worth, poor concentration, and thoughts about death (American Psychiatric Association, 2000) – symptoms that typically emerge around the transition into adolescence (Andersen & Teicher, 2008; Costello et al., 2002; Paus, Keshavan, & Giedd, 2008; Zahn-Waxler, Shirtcliff, & Marceau, 2008). The dimensional approach of the RDoC matrix (Insel et al., 2010) suggests that the anhedonic aspects of depression (e.g. loss of pleasure), a central feature of depression (Chiu & Deldin, 2007; Loas & Boyer, 1996; Snaith, 1993), are consistent with dysfunction of the Positive Valence System which includes measures of behavioral and neural responsiveness to reward. Thus, alterations in the neural circuitry that supports reward processing may underlie the emergence of depression following EA.

Ventral Striatum — Nucleus Accumbens

Reward processing

Evidence for the role of atypical positive, or reward-related, processing in depression could implicate dysfunction in the responsiveness of mesolimbic dopamine circuits (Dunlop & Nemeroff, 2007). These neural circuits are most often associated with reward-related learning, which includes the valuation of pleasurable stimuli (Nestler & Carlezon, 2006). Mesolimbic dopamine circuits have been shown to be sensitive to stress (Cabib & Puglisi-Allegra, 1996; Pizzagalli, 2014) and alterations in their function may serve as a potential underlying neural mechanism of depression (Hardin, Schroth, Pine, & Ernst, 2007). The ventral striatum, a neural structure within the reward circuit, which includes the nucleus accumbens (NAcc) - a dopamine receptor-rich limbic structure associated with reward learning and motivation in response to pleasurable stimuli (Ikemoto & Panksepp, 1999), serves as a primary target of dopamine neuron projections (Haber, Fudge, & McFarland, 2000; Haber & Knutson, 2010; Robbins & Everitt, 1996; Sesack & Grace, 2010) and, as will be discussed in the following paragraph, reaches its developmental peak during adolescence. This peak in ventral striatum development coincides with the typical age of onset for depression following EA (Bos et al., 2011; Goff et al., 2013; Zeanah et al., 2009) and previous research has shown that dysfunction in this region is associated with depressive symptoms in this population (Goff et al., 2013; Mehta et al., 2010). Indeed, research provides evidence for the role of the ventral striatum in reward learning and motivation (Ikemoto & Panksepp, 1999; Knutson, Adams, Fong, & Hommer, 2001; O'Doherty et al., 2004; Pagnoni, Zink, Montague, & Berns, 2002; Tanaka et al., 2004), and dampened ventral striatal responsiveness to reward has been robustly associated with depression (Dunlop & Nemeroff, 2007; Elliott, Rubinsztein, Sahakian, & Dolan, 2002; Epstein et al., 2006; Lawrence et al., 2004; McCabe, Cowen, & Harmer, 2009; Monk et al., 2008; Pizzagalli et al., 2010; Steele, Kumar, & Ebmeier, 2007; Surguladze et al., 2004)

Functional development

Though much of the brain develops before birth and during early childhood (Giedd et al., 1996), ventral striatal function has been shown to develop in an inverted “U” shaped pattern such that the functional development of the striatum peaks in adolescence and then decreases into early adulthood (Ernst et al., 2005; Galvan et al., 2006; Geier & Luna, 2009; Urošević, Collins, Lim, Muetzel, & Luciana, 2012; Van Leijenhorst et al., 2010). This inverted “U” shaped pattern seen in the development of the striatum is paralleled by behavioral patterns of increased reward sensitivity during adolescence (Urošević et al., 2012). Importantly, depressive symptoms most commonly emerge during the adolescent period (Andersen & Teicher, 2008; Costello et al., 2002; Paus et al., 2008; Zahn-Waxler et al., 2008). As depression is being increasingly understood as arising from atypical maturational changes in the brain (Paus et al., 2008), adolescence may reflect one period during which neural regions implicated in depression are vulnerable to dysregulation as a consequence of their remodeling (Forbes & Dahl, 2005; Paus et al., 2008). Thus alterations in the development of the ventral striatum may provide one explanation for the emergence of depression in adolescence.

Atypical development following EA

The strong associations found between depression and atypical function in the ventral striatum (Bogdan, Nikolova, & Pizzagalli, 2013) do extend more specifically to the EA population. Rodents exposed to early adverse experiences have demonstrated dampened function of the mesolimbic dopamine reward-circuit (Hall et al., 1998; Jones, Hernandez, Kendall, Marsden, & Robbins, 1992; Powell et al., 2003), including hypoactivation of the ventral striatum (Fulford & Marsden, 1998; Jones et al., 1992), and reduced behavioral responsiveness to reward (Lapiz, Mateo, Parker, & Marsden, 2000). Corroborating studies in humans have found that

individuals with a history of EA displayed dampened behavioral responsiveness to reward and reduced activation in striatal structures (Dillon et al., 2009), and children who experienced EA in the form of caregiver deprivation exhibit hyporesponsivity in the ventral striatum in response to reward during adolescence (Mehta et al., 2010).

While the antecedents of depression are complex and not fully understood, there is increasing evidence to suggest that the association between EA and depression in later life may be mediated by stress-induced alterations to the ventral striatum. Evidence suggests that early life is a time of particular vulnerability, and the timing of adverse environmental experiences may be critical for depressive outcomes. Thus, in cases of atypical development of neural reward circuitry, imbalances in striatal function may result in psychopathological outcomes such as depression.

Telomeres

Identifying the neurobiological mechanisms underlying the relationship between EA and depression is critical to understanding this process at a systems level. However beyond these systems level mechanisms, emerging evidence suggests that telomere erosion, a chromosomal marker of biological aging, may provide additional insight into the relationship between EA and depression. Telomeres are DNA–protein complexes located at the end of chromosomes that protect the chromosome from deterioration. Telomere length shortening has been associated with normative aging; however stress exposure can hasten telomere shortening and lead to premature cell senescence (Tyrka et al., 2010). It has been hypothesized that this relationship is likely the result of increased cellular turnover resulting from stress related oxidative damage, which in turn accelerates the telomere attrition rate (Epel et al., 2004). Thus, telomere shortening may represent one mechanism by which EA results in biological alterations at the cellular level.

Indeed, several recent studies have provided support for an association between childhood EA. Adults who retrospectively recalled adverse events during childhood showed shorter telomere length as compared to adult controls (Kananen et al., 2010; Kiecolt-Glaser et al., 2011; O'Donovan et al., 2011; Surtees et al., 2011; Tyrka et al., 2010). In the first study to show effects of EA on telomere length in children, Drury et al. (2012) found that greater time spent in institutional care correlated with reduced telomere length in 6-10 year old girls. Similarly, a prospective longitudinal study of children tested at 5 years of age and again at age 10 found greater telomere shortening in children exposed to two or more forms of violence as compared with those children unexposed less exposed (Shalev et al., 2012).

Importantly, there is recent evidence suggesting that mood disorders are also associated with shorter telomere length. Specifically, research has shown that adults with depression demonstrate shorter telomere length than typical adults (for review see Ridout, Ridout, Price, Sen, & Tyrka, 2016) however this effect has not yet been examined in a developmental population.

Though still in the early stages of scientific exploration, recent evidence suggests that shortened telomere length is associated with EA and these cellular alterations have been shown in children as young as 6 years of age. Additionally, in adults, depression has been associated with shortened telomere length. Taken together, these findings suggest that the acceleration of the cellular aging process occurs with psychological distress and this may represent one mechanism by which EA is translated into increased risk for depression.

Physical Activity as Treatment

Further elucidation of the underlying genetic and neurobiological mechanisms of EA-induced depression may assist researchers in providing potential treatment options for this

population, thus continued research is necessary in this domain. To date, depression has commonly been treated with antidepressants, psychological therapies or a combination of both. While antidepressants have been shown to be an effective for the treatment for severe depression, the effects may be minimal or nonexistent, in those with mild or moderate symptoms (Fournier et al., 2010). Additionally antidepressants may induce numerous adverse side effects, often resulting in poor adherence (see Gartlehner et al., 2005 for review). While psychological treatments are generally free from side effects, evidence suggests that those with depression may not pursue psychological therapy due to low expectations of positive outcome or perceived stigma (Sirey et al., 2001). Furthermore, psychological treatments are generally not developmentally appropriate or sensitive for children (Weisz, Rudolph, Granger, & Sweeney, 1992), and children may lack the cognitive skills necessary for traditional therapies (e.g. Cognitive Behavioral Therapy) to be efficacious (Hammen, Rudolph, Weisz, Rao, & Burge, 1999; Kendall & Choudhury, 2003). Thus recent research has focused on alternative methods for ameliorating depressive phenotypes and has identified physical activity as a particularly promising approach. A great number of studies suggest that physical activity may reduce depressive symptoms in adult nonclinical and clinical populations (for review see Ströhle, 2009). Furthermore, a dose response relationship has been demonstrated such that those prescribed to a moderate to high level of exercise was an effective treatment for depression, while lower levels of exercise revealed no effect (Dunn, Trivedi, Kampert, Clark, & Chambliss, 2005; Singh et al., 2005).

The association between physical activity and depression in children and adolescents has not been well-characterized. Preliminary meta-analytic research has generally concluded that in both observational and intervention-based studies in youth the association between

physical activity and depression is evident, but research designs are often weak and effects are small (Biddle & Asare, 2011; Calfas & Taylor, 1994; Larun et al., 2006). Importantly, the effects of physical activity on depressive symptoms have yet to be examined longitudinally in a population of children, which is necessary to establish the causal role of physical activity's effects on depressive outcomes. Moreover, the effects of physical activity on EA induced depression have not yet been examined directly. However, there is promising research suggesting that the adverse effects of EA may be ameliorated by physical activity during development. For example, adolescents with a history of EA showed greater self-reported psychological wellbeing and lower rates of problem behaviors, such as substance abuse, when regularly engaged in physical activity (Field, Diego, & Sanders, 2001; Kirkcaldy, Shephard, & Siefen, 2002). Thus, exercise may serve as an important mechanism by which EA-induced depressive phenotypes may be ameliorated.

Given the robust association between EA exposure and depressive outcomes later in life, further delineating the neurobiological underpinnings, as well as characterizing epigenetic modifications, of depression following EA may provide insight into sources of deficits. Furthermore, physical activity may serve as a viable treatment option for youth-onset depression, one that may be beneficial in preventing, or even reversing, depressive outcomes following EA.

Overview of Studies

Study 1. This study examined the effects of EA in previously institutionalized (PI) children and adolescents and in a comparison to a group of youth without a history of EA. For this study, participants underwent fMRI during a face-processing task and parents completed questionnaires measuring depressive symptoms on a continuum. The findings showed that depressive symptoms were higher in PI adolescents than in children. Additionally, fMRI results

showed atypical NAcc function, where the PI group did not show a typical adolescent-related increase in NAcc reactivity to rewarding stimuli (happy faces). Consequently, the PI group showed NAcc hypoactivation during adolescence, and lower NAcc reactivity was correlated with higher depression scores. These findings have important implications for understanding how EA may influence adolescence-emergent depression via neural development, specifically those regions implicated in the processing of rewards.

Study 2. Study 2 aimed to gain insight into the mechanisms that underlie how negative early-life experiences alter psychobiological processes at a genetic level. This study expanded upon Study 1 by including a measure of telomere length, a marker of biological aging, and including a longitudinal assessment of depressive symptoms in a larger sample of PI and comparison children and adolescents. Longitudinal analyses revealed that depressive symptoms increased significantly from childhood to early adolescence, and remained high during the adolescent period in PI youth. Findings also demonstrated that PI youth have significantly shorter telomere length than the comparison group. Importantly, tests of mediation revealed that Nacc reactivity mediates the relationship between telomere length and future depression. The results from this study showed that the association between depressive symptoms could be prospectively predicted by telomere length and NAcc hypoactivity in a sample of PI youth. These findings have important implications for understanding the associations between EA and both neural and genetic changes that may influence later depressive outcomes. Investigation of these associations in a developmental population is paramount, as early childhood may represent a critical period for the interaction between stress, cellular aging, and neurodevelopment.

Study 3. Because EA has consistently been identified as a prominent risk factor for youth-onset of depressive phenotypes, we sought to examine possible non-pharmacological

interventions that may ameliorate depressive symptoms in this population. The current study examined the effects of physical activity on depressive outcomes in a subsample of children and adolescents from Study 1 & 2. Longitudinal parent-reported depression scores showed that depressive symptoms in PI youth were high and remained elevated two years later. Although at the group level no changes were seen in the developmental course of depressive symptoms, differences in physical activity levels modulated later depressive symptoms in both PI children and adolescents. Specifically, high levels of physical activity were associated with decreases in depressive symptoms two years later. Inversely, low levels of physical activity were associated with increases in depressive symptoms, and those with average level of physical activity demonstrated no change. These findings suggest a potential behavioral intervention in an at-risk developmental population that may be beneficial as early as the childhood period.

II. Reduced Nucleus Accumbens Reactivity & Adolescent Emergent Depression following
Early-life Adversity

Early-life adversity can be defined as exposure to adverse events or stressors during infancy and early childhood that have significant negative emotional and physical effects, exceeding an individual's ability to cope (Benjet et al., 2010; Gunnar & Quevedo, 2007). While biological responses to acute stress are considered to be an adaptive survival mechanism, high or chronic levels of stress may disturb normative brain development and negatively impact mental health (Anda et al., 2006; Lupien, McEwen, Gunnar, & Heim, 2009; Maniglio, 2009; Pirkola et al., 2005). Depression is a common outcome for those individuals with a history of EA (Heim and Nemeroff, 2001; McEwen, 2000), with the magnitude of childhood adversity predicting the severity of lifetime depression (Kessler, 1997). Although depression is a common outcome following EA, the onset of depression typically does not emerge until the adolescent period despite early environmental insults, and this relatively late onset of depression has been documented in both human and non-human animal models of EA (Andersen and Teicher, 2008; Costello et al., 2002; Paus et al., 2008; Rainecki, et al., 2012). EA effects have been found following both abuse (Anda et al., 2006; Maniglio, 2009; Rainecki, Cortés, Belnoue, & Sullivan, 2012) and maternal deprivation (Johnson, 2002; Loman & Gunnar, 2010), and the effects appear to endure into adulthood, suggesting that EA alters the development of brain systems involved in depression.

In both human studies and non-human animal models, depression has been associated with altered neural activity in the ventral striatum (Epstein et al., 2006; Eshel and Roiser, 2010; Monk et al., 2008.; Pizzagalli et al., 2010; Price and Drevets, 2010), which includes the nucleus accumbens (NAcc). The NAcc is a dopamine receptor-rich limbic structure associated with reward learning and motivation in response to pleasurable stimuli (Ikemoto and Panksepp, 1999) such as monetary gain (Knutson et al., 2001) and the visual presentation of happy faces for

humans (Monk et al., 2008). Developmentally, the NAcc response to pleasurable stimuli shows relatively late functional development, increasing significantly during the transition from childhood into adolescence, when it reaches a developmentally-normative peak in functional activity (Galvan et al., 2006; Ernst et al., 2005; van Leijenhorst et al., 2009; Geier et al., 2009; although see Bjork et al., 2004 for hypoactivity). We present findings to argue that deviation from this developmental trajectory coincides with the emergence of depressive behaviors in adolescence.

Adversity exposure has been associated with atypically low ventral striatum activity and depressive behaviors. For example, in a prospective examination of soldiers heading to combat, NAcc activity declined following stress exposure and was associated with clinical symptoms of depression (Admon et al., 2012). Similarly, Nikolova et al. (2012) has shown that low ventral striatum activity predicts an association between recent stressful events and low positive affect in a group of emergent adults, suggesting that the association between stress and depression may be mediated by stress-related changes in the NAcc. This NAcc mediated interpretation of human data has been supported in non-human animal work. Psychosocial stress indirectly, but strongly, impairs ventral striatum functioning via stress-sensitive dopamine innervation from midbrain sites (reviewed in Anisman and Matheson, 2005), and this decrease in striatal activity significantly decreases incentive motivation resulting in the anhedonic behaviors associated with depression (Leventopoulos, Russig, Feldon, Pryce, & Opacka-Juffry, 2009).

Similar effects of adversity on striatal function have been observed during development. In animal models, electrophysiological and lesion studies have demonstrated a sensitivity of dopaminergic pathways (Powell et al., 2003; Hall et al., 1998; Jones, Hernandez, Kendall, Marsden, & Robbins, 1992), including the NAcc (Fulford and Marsden, 1998; Jones et al.,

1992), and reduced responsiveness to reward (Lapiz et al., 2000) to early adverse experiences, such as social isolation. Similar effects of EA have been observed in humans. Dillon et al., (2009) found that participants with a history of early-life maltreatment displayed dampened behavioral responsiveness to reward and reduced activation in associated striatal structures, such as the NAcc. In a striking example of the enduring effects of EA, Mehta et al., (2009) examined children who had experienced maternal deprivation during infancy in the form of institutional care, but had then been adopted into stable families years prior to scanning. Previously institutionalized (PI) adolescents showed hyporesponsivity in the ventral striatum in response to reward, and unlike in typical adolescents, ventral striatum activity was not modulated by reward value. Collectively, these findings suggest that EA impacts the development of the ventral striatum, resulting in hyporeactivity, which adversely impacts reward and motivational processing.

In the current study we aim to further probe the association between EA, depression, and alterations in ventral striatum development. We measured brain development with functional magnetic resonance imaging (fMRI). Although fMRI does not have enough resolution to identify the NAcc with confidence, our analyses focused on an anatomically defined region consistent with the location of the NAcc. For brevity's sake, we refer to this region as the NAcc throughout the manuscript. We examined children and adolescents with and without a history of EA (institutional care in orphanages abroad) to examine developmental change in NAcc activity from childhood to adolescence. Additionally, we collected dimensional behavioral measures of depression to both chart its developmental course and to examine associations between NAcc activity and depression. Utilizing fMRI, we hypothesized that depression would increase

between childhood to adolescence in PI youth, and this behavioral change would be paralleled by a lack of developmentally normative increases in NAcc activity during adolescence.

Methods

Participants

A total of 76 individuals (42 PI and 34 comparison, never-institutionalized) participated in an fMRI study whose characteristics are described in Table 1. Seven participants were removed because of outlier values (> 3 SD from the mean). Therefore, our final sample of 69 participants included 39 children between the ages of 5 and 10 years-old (24 PI and 15 comparison) and 30 adolescents between the ages of 11 and 15 years-old (14 PI and 16 comparison). We chose this age cut off based on previous research showing that depression is most pronounced among early adolescents (Brooks-Gunn & Petersen, 1991; Petersen et al., 1993), showing a sharp increase after age 10 (Kessler and Magee, 1993; Angold and Rutter, 1992). PI youths were recruited via local international adoption agencies and family networks. The comparison group, comprised of non-adopted youths who had always lived with their families, was recruited via flyer advertisements within the surrounding community or from state birth records. Children in the comparison group were only included if they were psychiatrically healthy, which was confirmed via parent interview. The families of both the PI youths (\$85,001-\$100,000) and the comparison group (\$70,001-85,000) had a household income well above the median annual household income in the United States (\$58,172; US Census Bureau, 2010) similar to the high socioeconomic status that has been observed in another sample of Midwest families who have adopted internationally (Hellerstedt et al., 2008). The protocol was approved by the Institutional Review Board at the University of California, Los Angeles. Parents of participants provided informed consent.

MRI Task Paradigm

During the fMRI scan, participants completed two runs of an emotional faces task. The task consisted of a mixed design with one blocked variable (emotional valence: happy vs. fearful) and one event-related variable (emotion vs. neutral). During each run, participants viewed singly-presented faces that were either emotional or neutral. The order of runs was counterbalanced across participants, and the stimulus order within each run was randomized and fixed. To ensure that participants were paying attention, they were instructed to press a button with their index finger when they saw a neutral face. The faces were selected from the Karolinska Directed Emotional Faces database (Lundqvist, Flykt, & Ohman, 1998). The faces were presented in color at a visual angle of approximately 15 degrees. The probability of a neutral face was 50% on any given trial. Stimuli were jittered (variable inter-trial interval ranging from 3000-9000 msec) and randomized based on a genetic algorithm (Wager and Nichols, 2003) in order to allow for unique estimates of the hemodynamic response for each trial type. Each run contained 48 trials (24 neutral faces, 24 fearful or happy faces). Each face remained on the screen for 500 msec.

Procedure

Children and adolescents came to the laboratory for two sessions. In the first session, behavioral measures were collected and participants were acclimated to the scanner environment with an MRI replica. The emotional faces task was administered in the MRI scanner on the second visit, which occurred on a separate day.

fMRI Data Acquisition. Scanning was performed on a Siemens Trio 3.0 Tesla MRI scanner. A standard radiofrequency head coil was employed. For each participant, an initial 2D spin echo image (TR=4000ms, TE=40ms, matrix size 256x256, 4mm thick, 0mm gap) in the

oblique plane was acquired to allow configuration of slices obtained in the structural and functional scans. A whole-brain high-resolution, T1*weighted anatomical scan (MPRAGE; 192 X 192 in-plane resolution, 250 mm field of view [FOV]; 176 mm X 1 mm sagittal slices) was acquired for each participant for registration and localization of functional data to Talairach space (Talairach and Tournoux, 1988). The emotional faces task was presented on a computer screen through MR-compatible goggles. The task was completed during two functional scans. T2*weighted echoplanar images were collected at an oblique angle of approximately 30 degrees (130 volumes/run, TR=2000, TE=30ms, flip angle =90 degrees, matrix size 64x64, FOV=192, 34 slices, 4mm voxel, skip 0mm, 24 observations per event type).

fMRI Data Analysis. Functional imaging data were preprocessed and analyzed using the Analysis of Functional NeuroImages (AFNI) software package (Cox, 1996). All analyzed data were free of motion greater than 2.5 mm in any direction. Preprocessing of each individual's images included slice time correction to adjust for temporal differences in slice acquisition within each volume, spatial realignment to correct for head motion, registration to the first volume of each run, spatial smoothing using a 6-mm Gaussian kernel (FWHM) to increase the signal to noise ratio, and transformation into the standard coordinate space of Talairach and Tournoux (Talairach and Tournoux, 1988) with parameters obtained from the transformation of each individual's high-resolution anatomical scan. Talairached transformed images had a resampled resolution of 3 mm³. Timeseries were normalized to percent signal change to allow for comparisons across runs and individuals. The functional runs were concatenated prior to creating two individual-level models for each participant to model activation.

In order to examine activation across the brain, each participant's individual-level model included regressors for each of the stimulus conditions (fearful faces, happy faces, neutral faces

in the context of fearful faces, neutral faces in the context of happy faces) and accuracy. The regressors were created by convolving the stimulus timing files with the canonical hemodynamic response function. Six motion parameters were included as separate regressors. General linear modeling (GLM) was performed to fit the percent signal change time courses to each regressor. Linear and quadratic trends were modeled for each voxel's time course to control for correlated drift. At the group level, parameter estimates (beta weights) were extracted for each participant for the happy and fear conditions from anatomically-defined masks covering the bilateral NAcc as defined by AFNI's Talairach-Tournoux Atlas. Therefore, for the purposes of this study, each participant had an activation value for the happy (happy>BL) and the fear (fear>BL) condition. These values were subjected to analyses within SPSS that tested for EA Group (Comparison, EA) by Age Group (Children, Adolescents) interactions.

Behavioral Data Analysis. For each participant, accuracy was calculated as the total number of correct presses to neutral faces in the context of happy and fear faces minus the total number of errors (commission to happy faces or fear faces and errors of omission to neutral faces), producing two accuracy scores for each participant (neutral with happy, and neutral with fear). We also calculated the mean reaction time for correct hits to neutral in the context of happy or fear faces, producing two reaction time averages for each participant (neutral with happy, and neutral with fear). These values were subjected to analyses within SPSS that tested for PI Group (Comparison, PI by Age Group (Children, Adolescents) interactions.

Parent Report Questionnaires. Parents completed the Revised Child Anxiety and Depression Scales (RCADS-P). The RCADS-P is a parent report 47-item instrument that assesses symptoms of childhood anxiety disorders and depression continuously based on *DSM-IV* criteria. The scale consists of 47 items that on the basis of exploratory factor analysis are

allocated to six subscales including a subscale specific to major depressive disorder (MDD; 10 items; e.g. ‘My child feels sad or empty.’) Each symptom on the scale is scored 1, “never”; 2, “sometimes”; 3, “often”; and 4, “always.” T-scores were calculated based on child gender and grade in school. Chorpita et al. (2000) reported an item set and factor definitions that were consistent with *DSM-IV* depression. For the present study, we used the depression and total anxiety T-scores.

Child Report Questionnaires. Participants completed a 6-item scale mood assessment that was derived from the Positive and Negative Affect Schedule for Children (PANAS-C) (Laurent et al., 1999), which is designed to assess positive affect (PA) and negative affect (NA) in children. Laurent et al. (1999) reported acceptable alpha coefficients (.94 and .92 for negative affect, and .90 and .89 for positive) for the scale development and replication samples, respectively. Good convergent and discriminant validity were also reported, with the NA scale correlating positively with self-reports of depression, and the PA scale correlating negatively with depression. We chose to include 3 items on the PA scale (“Lately, how much have you been feeling:” Cheerful/Joyful/Delighted) and 3 items on the NA scale (“Lately, how much have you been feeling:” Frightened/Miserable/Sad) to abbreviate the testing session based on words that seemed most child-appropriate. Participants were asked to rate the degree to which they have felt during the past few weeks, on a scale of 1 (Very slightly or not at all) to 5 (Extremely). We also obtained acceptable alpha coefficients for the abbreviated version of the questionnaire (PA alpha=.77, NA alpha=.75). Responses were summed to create a PA score and an NA score for each participant.

Results

Depression scores increase between children and adolescent PI youth

Data from the RCADS-P (Chorpita, 2000) was available for 67 participants. A 2X2 (PIGroupXAgeGroup) analysis of variance (ANOVA) yielded a main effect of PI group ($F(1,63)=38.66, p<.001, \text{partial } \eta^2=.38$), which was anticipated based on the selection of a healthy comparison group, such that the average RCADS-P MDD T-score was significantly higher for the PI group (mean(SD)=45.74(9.09)) than for the comparison group (mean(SD)=35.28(3.96)). Importantly, there was a two-way interaction of PIGroupXAgeGroup ($F(1,63)=5.46, p<.025, \text{partial } \eta^2=.08$), and post hoc tests showed that for the PI group only, depression scores significantly increased with age ($F(1,36)=6.25, p<.025$) (Figure 1.1).

As anticipated, analysis of RCADS-P Total Anxiety T-score yielded a main effect of PI group ($F(1,64)=21.19, p<.001, \text{partial } \eta^2=.25$), such that anxiety scores were significantly higher for the PI group (mean(SD)=43.54(9.37)) than for the comparison group (mean(SD)=35.03(5.41)), which was anticipated based on participant recruitment of healthy individuals. Importantly, the PIGroupXAgeGroup interaction that was observed in RCADS depression scores was not observed in RCADS anxiety scores ($F(1,67)=2.47, ps>.05, \text{partial } \eta^2=.04$), showing that unlike the age-related increases in depression scores, anxiety scores remained constant over the two age groups.

In addition to parent report, we included an abbreviated version of the PANAS-C to assess recent mood in all child and adolescent participants. Data was available for 69 participants. Two separate 2x2 (PIGroupXAgeGroup) ANOVAs examining the dependent measures z-scores for positive affect (PA) and negative affect (NA) were performed. For positive affect, there was a main effect of age group ($F(1,59) =6.77, p<.015, \text{partial } \eta^2=.10$), such that reported positive affect was high in all children and was significantly lower for adolescents. For negative affect, there was a main effect for PI group ($F(1,59)=5.96, p<.025, \text{partial } \eta^2=.09$), such

that the PI group reported significantly higher levels of negative affect than the comparison group. Taken together, as shown in Figure 1.2, PI adolescents had the unique combination of low positive affect and high negative affect. These self-reported mood scores were consistent with parent reports of increased depression in PI adolescents.

fMRI Findings

Behavioral Task Performance. Participants were engaged in a simple task of pressing for neutral faces to ensure task engagement. Responses from one child were not included due to technical malfunction. Two separate 2X2X2 (EmotionXPIGroupXAgeGroup) repeated measure ANOVAs were performed on the dependent measures of accuracy and reaction time during correct trials. For accuracy, there was a main effect of age group ($F(1,58)=10.00, p<.005$, partial $\eta^2 = .15$), such that accuracy increased with age. Additionally, there was an PIGroupXAgeGroup interaction ($F(1,58)=5.39, p<.025$, partial $\eta^2 = .09$) and an EmotionXAgeGroup interaction ($F(1,58)=10.52, p<.005$, partial $\eta^2 = .15$). Post hoc tests showed that accuracy improved with age for the comparison group ($p<.0005$; child mean(SD)=.44(.21), adolescent mean(SD)=.78(.21)), but did not change with age for the PI group ($p=.59$; child mean(SD)=.61(.26), adolescent mean(SD)=.66(.26). Additionally, accuracy during the happy face condition improved more ($p<.00005$) from childhood (mean(SD).48(.25)) to adolescence (mean(SD)=.76(.24)) than it did during the fear face condition (child mean(SD)=.56(.26), adolescent mean(SD)=.70(.25)). There were no main effects or interactions for reaction time ($ps>.05$).

NAcc Reactivity Following Early-life Adversity. A 2X2X2 ANOVA (EmotionXPIGroupXAgeGroup) was performed on the extracted beta weights from the anatomically-defined NAcc for happy and fear face conditions. There was a significant PIGroupXAgeGroup interaction ($F(1,65)=7.03, p=.01$, partial $\eta^2=.10$). Post hoc analyses reveal

that, for the typically developing comparison group, mean NAcc activation significantly increased from childhood to adolescence ($t(29)=2.33, p<.01$), while no significant increase was seen in the PI group ($t(36)=.789, ps>.05$) (Figure 1.3). PI adolescents exhibited significantly lower NAcc activation relative to the comparison adolescents ($t(27)=2.26, p<.05$) (Figure 3).

Association between NAcc activity and depression scores. A linear regression was performed on the dependent measure of RCADS MDD T-scores and NAcc activation to happy and to fear entered as independent variables, controlling for age group and PI group. As seen in Figure 1.4, this analysis showed that low nucleus accumbens activation while viewing happy faces predicted higher depression scores ($\beta = -.16, p<.05$), and NAcc response to fearful face was not associated with depression ($\beta = .02, ns$). When only the PI group was examined, the association between NA response to happy faces and depression scores remained ($\beta = -.30, p<.05$).

Discussion

The present study examined the association between EA, depression, and underlying NAcc reactivity. Findings revealed that parent-reported depression increased from childhood to adolescence in PI youth. Parent-report was corroborated by child and adolescent self-report measures of recent mood showing that PI adolescents experienced more negative affect in the absence of positive affect than any other group. Although EA was associated with depression and anxiety, only depression scores increased from childhood to adolescence, whereas anxiety was elevated in both age groups. These differential developmental courses for anxiety and depression have been characterized previously (Angold and Rutter, 1992; Cole, Peeke, Martin, Truglio, & Seroczynski, 1998), with childhood depression being infrequent and an emergence of

depression symptoms appearing in early adolescence. We examined NAcc reactivity as a potential correlate of the increase in depression.

Our findings support the hypothesis that EA would be associated with hypoactivity of the NAcc during adolescence. Unlike the normative increase in NAcc activity during the transition from childhood to adolescence (Galvan et al., 2006; Ernst et al., 2005; van Leijenhorst et al., 2009; Geier et al., 2009) observed in the typically-raised comparison group, NAcc reactivity did not increase with age in the PI group, and as a consequence, was atypically hypoactive in the PI adolescents. That is, there was no observable effect of EA on NAcc reactivity during childhood, as both groups of children demonstrated relatively low levels of NAcc reactivity. The effect of EA on NAcc reactivity was observed in the adolescent group at the same time that reports of depressed behaviors emerged. Importantly, lower NAcc activity was associated with higher levels of depression, consistent with the notion that hypoactivity in the NAcc results in depressive behaviors. Taken together, these findings replicate earlier reports showing that depression associated with EA is associated with NAcc hypoactivity. Moreover, the data suggest that depression typically emerges after childhood because it is after this point that group differences emerge in NAcc activity, with the PI group failing to show the developmentally-typical rise in NAcc reactivity that the comparison group shows. Hypoactivity of the NAcc has been associated with anhedonia (and not other behavioral symptoms; Wacker et al., 2009); therefore the role of the NAcc hypoactivity observed in the current study may increase depressive behaviors in adolescents with EA by increasing anhedonic states, a notion supported by the self-reported mood ratings in PI adolescents (low positive affect, high negative affect).

A scientific advantage of studying previously institutionalized children for EA research is in this population's exposure to a temporally-discrete and severe stressor. Institutional care,

which is sparse, unstable, and regimented (Smyke et al., 2007), is unfortunately a naturally occurring example of early-life adversity in humans. Several research groups have observed that in institutional care, health care, nutrition, and safety needs are often met; however, necessary maternal input is lacking (Groark and McCall, 2011; Groark et al., 2011; Smyke et al., 2007; The St. Petersburg-USA Orphanage Research Team, 2008; Tirella et al., 2008; Vorria et al., 2003; Zych, 2006). Maternal deprivation is a potent stressor for the human infant (as reviewed in Tottenham, 2012), and not surprisingly, emotional health is at significant risk in previously institutionalized children (reviewed in Gunnar, Bruce and Grotevant, 2000). Diagnostically, previously institutionalized children demonstrate an increased rate of internalizing and externalizing emotion regulation disorders such as anxiety, depression, and attention deficit hyperactivity disorder (Zeanah et al., 2009). Importantly, intervention studies suggest that many of the mental health effects of institutionalization are likely to be related to institutionalization itself rather than preexisting genetic or prenatal conditions of the child (Bos et al., 2011; Nelson et al., 2007; The St. Petersburg-USA Orphanage Research Team, 2008). Unlike most other studied populations with a history of EA, previously institutionalized infants are removed from adversity through an adoption process into stable caregiving environments, thereby temporally isolating the duration of the adversity exposure to the infant period. Despite this beneficial and dramatic “intervention” through international adoption, socio-emotional difficulties may remain or even exacerbate into adolescence (Colvert et al., 2008; Verhulst, Althaus, & Versluis-den Bieman, 1990) suggesting that there may be long-term changes in neural systems associated with emotional processes following orphanage care.

There are limitations to the current study. First, due to the nature of international adoption, we do not have access to individual prenatal/developmental histories for PI youths.

This is a common issue for investigators studying this population. However, randomized control intervention work suggests that institutionalization itself may be the most significant factor in children's developmental histories (Zeanah et al., 2009). However, an experimental benefit to studying this population is knowledge of a discrete period of deprivation. A second concern is the task used to assess NAcc activity. In the current study, we employed an emotional face-processing paradigm, requiring only passive viewing of emotional faces interspersed with target neutral faces to maintain attention. Thus, a limitation of our design is that we did not employ a reward-learning paradigm, which might be better suited for examination of the NAcc. However, in both healthy (Somerville, Hare, & Casey, 2011) and children at risk for depression (Monk et al., 2008), emotional faces like happy have been effective in recruiting NAcc activity and effective in separating out diagnostic groups. Low ventral striatum reactivity in response to happy faces has been associated with clinical depression (Epstein et al., 2006). Similarly, low ventral striatum reactivity to happy faces has shown diagnostic specificity to depression, as another fMRI study showed that depression (not anxiety) was inversely correlated with NAcc response to happy faces (Keedwell et al., 2005). Importantly, our results replicate those of Mehta et al. (2009) who used a reward-learning task (i.e., a monetary incentive delay task) and showed NAcc hypoactivity in PI adolescents.

The results from the current study have important implications for understanding how early-life adversity can influence the emergence of depression during adolescence. Consistent with previous research associating adversity-induced dysfunction in the ventral striatum, in particular the NAcc, with depressive behaviors, we observed that NAcc function is hypoactive in PI adolescents.. These findings highlight the importance of identifying individuals at risk for

depression during childhood, as this may be a potential critical period for depression-targeted intervention.

Figure 1.1. Depressive symptoms increase following early-life adversity. The PI group showed significantly higher depression scores (measured dimensionally) in adolescents when compared to children. In contrast, the comparison group did not show any age-related change in depression scores.

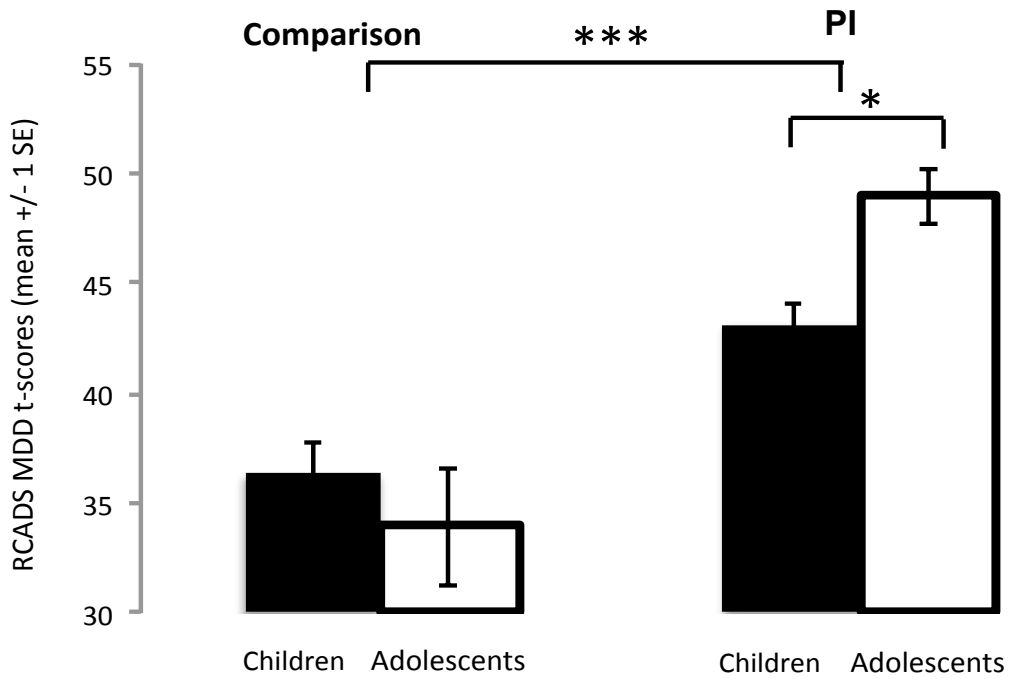


Figure 1.2. Self-report mood. PI adolescents showed a unique combination of low positive affect and high negative affect.

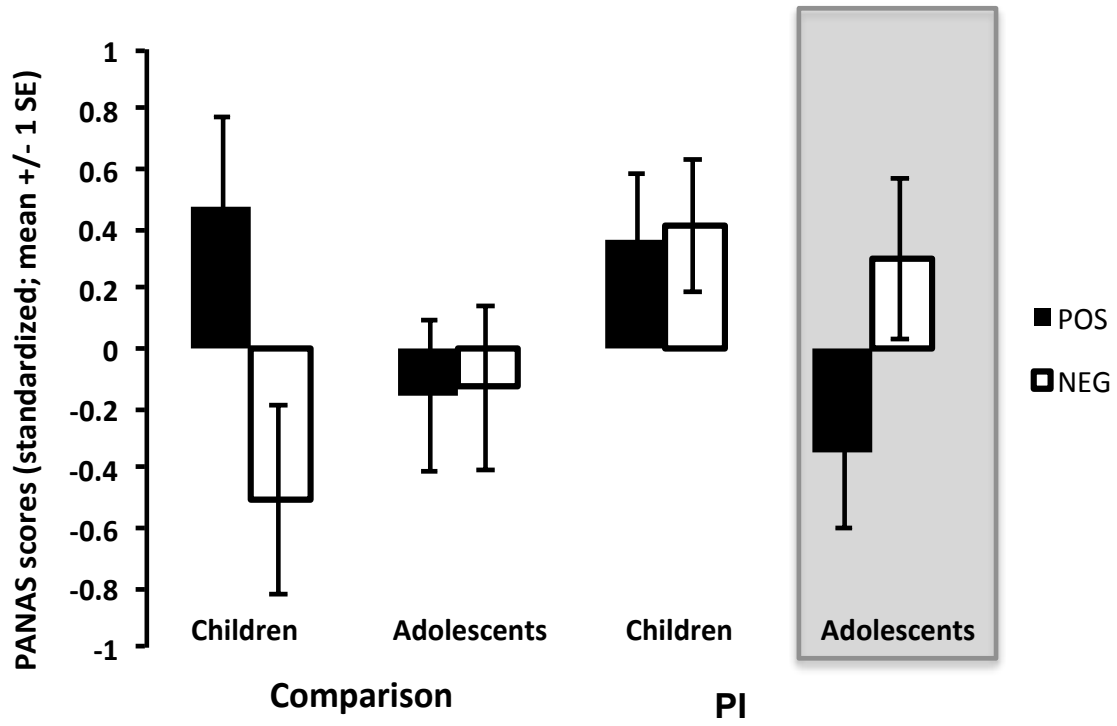


Figure 1.3. NAcc Hypoactivation during adolescence following early-life adversity. Left panel shows anatomically-defined NAcc regions selected for analysis. Right panel shows the normative developmental increase in NAcc activity from childhood to adolescence in the comparison group. In contrast, the PI group did not show any age-related change, resulting in a NAcc hypoactivation in adolescence.

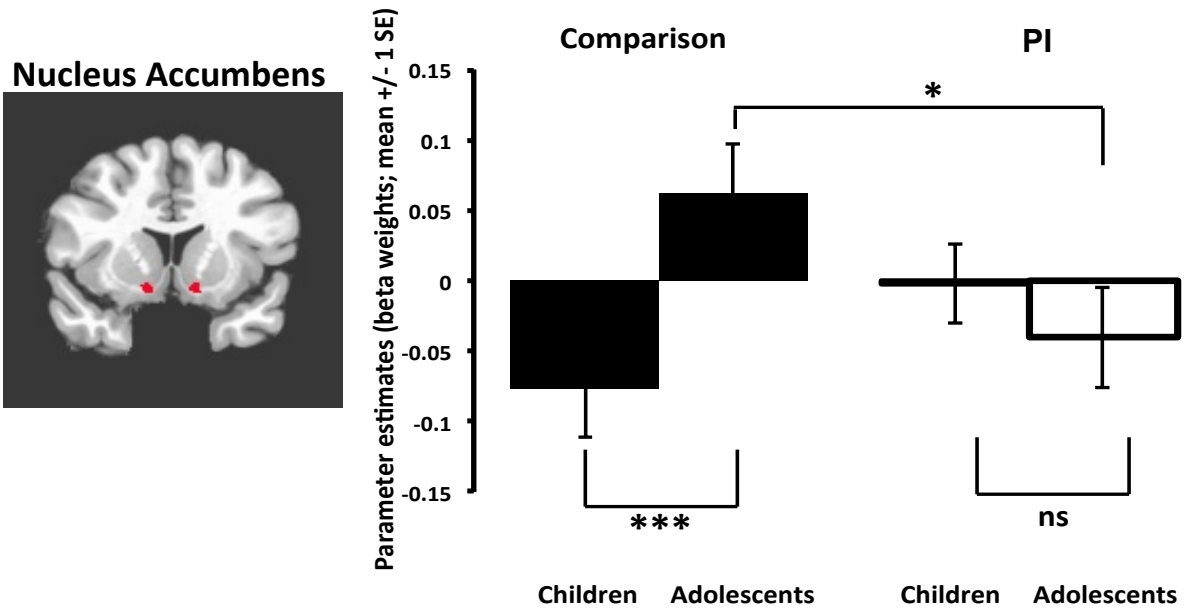


Figure 1.4. Negative association between depression scores and NAcc activation. Lower NAcc activation while viewing happy faces was inversely correlated with parent report of depression scores, controlling for age and group.

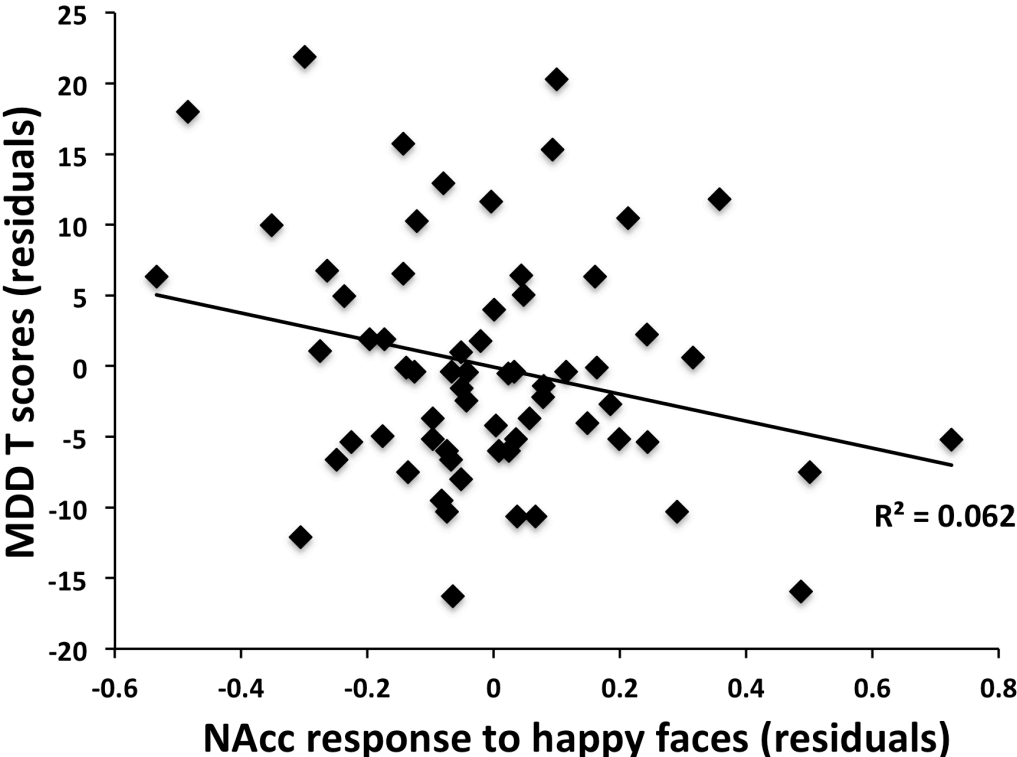


Table 1. Demographic Information for Sample

	PI (n = 38; 24 children, 14 adolescents)	Comparison (n = 31; 15 children, 16 adolescents)
Sex	24 female; 14 male	12 female; 19 male
Mean age in years (SD); range	9.9 (2.6); 6-15	9.7 (3.1); 4-15
Mean (SD) IQ; range	101.1 (14.3); 72-126	111.2 (15.2); 76-143
Country of origin	29 Eastern Europe; 8 East Asia; 1 India	
Mean age orphaned in months (SD); range	7.8 (12.4); 0-54	
Mean age adopted in months (SD); range	30.0 (23.9.2); 6-102	
Mean time with family in months (SD); range	94.7 (35.7); 33-169	

Legend: SD=standard deviation

III. Nucleus Accumbens Reactivity Mediates Relationship Between Human Chromosomal
Modification and Future Early-Life Adversity Induced Depression

Exposure to early-life adversity (EA) has consistently been associated with a range of stress induced (Loman & Gunnar, 2010) negative health outcomes including increased risk for depression (Agid et al., 1999; Brown et al., 1999; Chapman et al., 2004; Heim & Nemeroff, 2001; McCauley et al., 1997; Mullen et al., 1996); however the mechanisms underlying how negative early-life experiences alter psychobiological processes are not fully understood. Associations have been found between depression and caregiver-related EA, including abuse (Anda et al., 2006; Maniglio, 2009; Rainekei et al., 2012), neglect (Gibb, Butler, & Beck, 2003; Spinhoven et al., 2010), institutional care (Johnson, 2002; Loman & Gunnar, 2010), and parental depression (Klein, Lewinsohn, Rohde, Seeley, & Olino, 2005; Tully, Iacono, & McGue, 2008), the effects of which appear to endure into adulthood (Anda et al., 2006; Edwards et al., 2003; Shonkoff et al., 2012), suggesting that EA significantly alters the trajectory of depression.

A large and growing literature shows that depression in adults is associated with compromised genetic material. Telomeres, DNA–protein complexes located at the end of chromosomes, protect the chromosome from deterioration. Several studies have now shown that adulthood depression is associated with shorter telomere length (see Lindqvist et al., 2015 for review). Shorter telomere length has been shown to lead to neurodegeneration in rodent models (Jaskelioff et al., 2011), and in humans, it predicts cognitive decline (Martin-Ruiz et al., 2006). Although the evidence continues to mount regarding the neural effects of shortened telomeres, the literature suggests a potential causative link between telomere length and neural function.

Telomere length shortens with normative aging; however exposure to adversity can hasten telomere shortening and lead to premature cell senescence (Tyrka et al., 2010). It has been hypothesized that this relationship is likely the result of increased cellular turnover resulting from adversity-related oxidative damage, which in turn accelerates the telomere attrition rate

(Epel et al., 2004). Emerging evidence suggests that telomere erosion may also be accelerated as a function of EA (Asok, Bernard, Rosen, Dozier, & Roth, 2014; Drury et al., 2012; Kananen et al., 2010; Kiecolt-Glaser et al., 2011; Mason, Prescott, Tworoger, DeVivo, & Rich-Edwards, 2015; O'Donovan et al., 2011; Savolainen et al., 2014; Shalev, Moffitt, & Caspi, 2013; Surtees et al., 2011; Tyrka et al., 2010) providing insight into the mechanisms underlying how EA alters psychobiological processes at the genetic level. Thus, telomere shortening may represent one mechanism by which EA results in biological alterations at the cellular level.

Indeed, several recent studies have provided support for an association between EA and shorter telomere length. Research in adults has demonstrated that participants who retrospectively recalled adverse events during childhood showed shorter telomere length as compared to adult controls (Kananen et al., 2010; Kiecolt-Glaser et al., 2011; Mason et al., 2015; O'Donovan et al., 2011; Surtees et al., 2011; Tyrka et al., 2010). In the first study to show effects of EA on telomere length in children, Drury et al. (2012) found that greater time spent in institutional care correlated with reduced telomere length in 6-10 year old girls. Similarly, a prospective longitudinal study of children tested at age 5, and again at age 10, found greater telomere shortening in children exposed to two or more forms of violence as compared with children who had less exposure (Shalev et al., 2013)

A separate literature has identified alterations in brain function that are associated with the emergence of depression. In both human studies and non-human animal models, depression has been associated with altered neural activity in the ventral striatum (Corral-Frías et al., 2015; Epstein et al., 2006; Eshel & Roiser, 2010; Monk et al., 2008; D. A. Pizzagalli et al., 2010; Price & Drevets, 2010), a dopamine receptor-rich limbic structure which includes the nucleus accumbens (NAcc). Activation of the NAcc is associated with reward learning and motivation in

response to pleasurable stimuli (Ikemoto and Panksepp, 1999), including monetary gain (Knutson et al., 2001) and the visual presentation of happy faces for humans (Monk et al., 2008).

EA has also been associated with atypically low ventral striatum activity and depression in both humans (Admon et al., 2012; Nikolova, Bogdan, Brigidi, & Hariri, 2012) and non-human animals (Anisman & Matheson, 2005; Leventopoulos et al., 2009). In animal models, electrophysiological and lesion studies have demonstrated a sensitivity of dopaminergic pathways (Hall et al., 1998; Jones et al., 1992; Powell et al., 2003) including the NAcc (Fulford & Marsden, 1998; Jones et al., 1992), and reduced responsiveness to reward (Lapiz et al., 2000) to early adverse experiences, such as social isolation. Similar effects of EA have been observed in humans. Dillon et al. (2009) found that participants with a history of early-life maltreatment displayed dampened behavioral responsiveness to reward and reduced activation in associated striatal structures, such as the NAcc. A longitudinal study examining youth having experienced EA found that greater levels of emotional neglect were associated with blunted activation of reward-related ventral striatal activity across development, and that blunted activation predicted the emergence of depressive symptoms (Hanson et al., 2015). In a noteworthy example of the enduring effects of EA, Mehta et al., (2009) examined children who had experienced maternal deprivation during infancy in the form of institutional care - but had then been adopted into stable families years prior to scanning - found that previously institutionalized (PI) youth showed hyporesponsivity in the ventral striatum in response to reward. These findings were replicated and extended by Goff et al. (2013), such that PI adolescents demonstrated hyporesponsivity in the ventral striatum (specifically the NAcc) in response to reward, and this NAcc hyporesponsivity was negatively correlated with depression symptoms. Collectively, these findings suggest that EA impacts the development of the ventral striatum, resulting in

hyporeactivity and altered reward and motivational processing – a central phenotype of depression.

In the current study, we aimed to bring together these risk factors (EA, telomere erosion, NAcc hypoactivity) for depressive symptoms, which have, to date, been studied independently. Here we characterize EA as those having been exposed to institutional care early in life – PI youth. Institutional care (e.g., orphanage rearing), which is sparse, unstable, and regimented (Gunnar, Bruce, & Grotevant, 2000) is unfortunately a naturally occurring example of EA in humans affecting millions of children worldwide (<http://www.hrw.org>). What makes this population unique is that if a child is removed from the orphanage via adoption, the end date of the adversity is documented, increasing our ability to draw conclusions about the timing of adverse caregiving in a human population. Moreover, this approach precludes the reliance on retrospective reporting of adversity, which can be unreliable (Widom & Shepard, 1996). Although institutionalized infants experience an unknown combination of adverse events and we have no means of isolating these unique experiences, poor caregiving is common to all PI youth (Gunnar et al., 2000) and the odds of developmental delay following this type of caregiving are devastatingly high (Nelson et al., 2009).

Investigation of these associations in a developmental population is important as early childhood likely represents a critical period for the interaction between adversity, cellular aging and neurodevelopment. First, brain development is rapid and highly sensitive to experience during the first years of life. Additionally, early life is a period of rapid telomere attrition as well as the critical time at which an individual's rate of telomere length attrition is established. Taken together, characterizing the associations between EA, depressive symptoms, and both neural and genetic changes would represent a significant advancement for the study of deleterious

psychological outcomes in this population.

In both PI and comparison youth, we measured brain development with functional magnetic resonance imaging (fMRI) and collected telomere measurements via a non-invasive salivary qPCR assay. We examined youth across a wide age range to characterize alternations in NAcc activity and telomere length across development. Additionally, we collected parent-reported continuous measures of depressive symptoms. We hypothesized that depressive symptoms would be increased in PI youth, and this behavioral change would be paralleled by altered NAcc reactivity and telomere length. We further hypothesized that both NAcc reactivity and telomere length would demonstrate a negative association with depressive symptoms. Lastly we hypothesized that NAcc reactivity would mediate the association between telomere length and depressive symptoms.

Methods

Participants

Demographic information for participants is presented in Tables 2.1-2.3. Three-hundred and forty participants (103 PI and 237 comparison) contributed usable telomere data (Table 2.1). One-hundred and twenty-four (56 PI and 68 comparison) contributed usable fMRI data (additional subjects were excluded for either excessive motion during scanning or insufficient accuracy in the task; criteria described below) (Table 2.2). Sixty-four of these participants (35 PI, 29 comparison) were examined in a previous fMRI study (Goff et al., 2013). A subset of 95 participants (52 PI, 63 comparison) contributed usable parent-reported depression measures two years following their fMRI scan (Table 2.3). For a visual timeline of data collection see Figures 2.1 & 2.2.

PI youths were recruited via local international adoption agencies and family networks.

The comparison group, comprised of non-adopted youths who had always lived with their families, was recruited via flyer advertisements within the surrounding community or from state birth records. Participants in the comparison group were only included if they were psychiatrically healthy, free of psychotropic medications, and did not report having experienced early-life trauma. Based on parent-report of mental health from the Child Behavior Checklist questionnaire (CBCL; Achenbach & Rescorla, 2001), a standardized instrument to assess emotional or behavioral problems that includes DSM-Oriented Scales (Nakamura et al., 2009), and the Revised Child Anxiety and Depression Scales – Parent form (RCADS-P; Chorpita et al., 2000), none of the comparison participants scored within clinical range, and for those participants in the PI group with all three assessments (telomere, fMRI, and longitudinal RCADS-P measures), 31% exhibited mental health characteristics within the clinical range (T scores > 70 for internalizing or externalizing problems on the CBCL & depression or total anxiety on the RCADS-P). The protocol was approved by the Institutional Review Board at the University of California, Los Angeles. Parents of participants provided informed consent.

Procedure

In the first lab session, saliva samples (via Oragene) and parent report measures were collected, and all participants were given the opportunity to acclimate to an MRI scanner environment with a mock MRI scanner. CDs of MRI noises were available for families to play at home to participants as further preparation. In the second session, participants returned to complete an fMRI scan, which occurred on a separate day. Two years after the first MRI session, participants returned and completed additional questionnaire measures as part of a larger experimental battery.

Parent Report Measures

Parents completed the Revised Child Anxiety and Depression Scales – Parent form (RCADS-P; Chorpita et al., 2000), which has been shown to be valid and reliable in developing samples (Chorpita et al., 2005). The RCADS-P is a parent report 47-item instrument that assesses symptoms of childhood anxiety disorders and depression continuously based on DSM-IV criteria. Each symptom on the scale is scored 1, “never”; 2, “sometimes”; 3, “often”; and 4, “always.” The questionnaire is reliable in terms of internal consistency (with Cronbach’s alphas between 0.65 and 0.83 for the various subscales) and temporal stability (with 4-week test–retest correlations between 0.79 and 0.85), and displays reasonable parent–child agreement and good convergent and divergent validity. In the current study, the depression subscale was examined from both the first and second laboratory visit occurring 2 years later. T-scores were calculated based on child gender and grade in school using the norms established by the RCADS-P. RCADS-P T-score calculations limit to grades 3-12, thus we adapted the scale by using grade 3 norms for all participants below the grade range, and grade 12 norms for all participants above the grade range in order to accommodate our broad developmental sample. For the present study, we used the depression T-scores.

Telomeres

Average telomere length in saliva was measured by using a validated quantitative polymerase chain reaction (Q-PCR) method (Cawthon, 2002). In brief, relative telomere length was determined by quantitative polymerase chain reaction Q-PCR through two steps of relative quantification. In the first step, the ratio of telomere repeats product to single copy gene product to (*36B4*, encoding acidic ribosomal phosphoprotein PO) was established for each sample by using standard curves. This ratio is proportional to the average telomere length. In the second step, the ratio for each sample was normalized to a calibrator DNA in order to standardize

between different runs. Telomere PCRs and *36B4* PCRs were always performed in separate 96 wells. A standard curve of a diluted reference DNA (the same DNA sample for all runs), as well as the calibrator DNA were included in each run and relative quantification of the samples were allowed.

fMRI Paradigm

During the fMRI scan, participants completed two runs of an emotional faces task. The task consisted of a mixed design with one blocked variable (emotional valence: happy vs. fearful) and one event-related variable (emotion vs. neutral). During each run, participants viewed singly-presented faces that were either emotional or neutral. The order of runs was counterbalanced across participants, and the stimulus order within each run was randomized and fixed. To ensure that participants were paying attention, they were instructed to press a button with their index finger when they saw a neutral face. The faces were selected from the Karolinska Directed Emotional Faces database (Lundqvist et al., 1998). The faces were presented in color at a visual angle of approximately 15 degrees. The probability of a neutral face was 50% on any given trial. Stimuli were jittered (variable inter-trial interval ranging from 3000-9000 msec) and randomized based on a genetic algorithm (Wager and Nichols, 2003) in order to allow for unique estimates of the hemodynamic response for each trial type. Each run contained 48 trials (24 neutral faces, 24 fearful or happy faces). Each face remained on the screen for 500 msec. Given the happy face-related findings in a previous publication (Goff et al, 2013), for the present analyses, we examined the trials in which participants passively viewed happy faces to assess stimulus-elicited activation.

fMRI Data Acquisition

All participants were scanned with a Siemens Trio 3.0-Tesla MRI scanner using a

standard radiofrequency head coil. For the emotion task, we collected two functional scans. T2*-weighted echoplanar images (interleaved) were collected at an oblique angle of $\sim 30^\circ$ to minimize signal drop-out (130 volumes/run; TR, 2000 ms; TE, 30 ms; flip angle, 90° ; matrix size, 64×64 ; field of view (FOV), 192 mm; 34 slices; 4 mm slice thickness; skip 0 mm; 24 observations per event type).

fMRI Data Pre-processing

The functional imaging data were preprocessed and analyzed with the Analysis of Functional NeuroImages (AFNI) software package (Cox, 1996). For each participant's images, preprocessing included discarding the first 4 functional volumes to allow for BOLD signal stabilization, correction for slice acquisition dependent time shifts per volume, rigid body translation and rotation from each volume to the first volume to generate 6 within-subject regressors, and spatial smoothing to an 8mm isotropic full-width half maximum smoothness using 3dBlurToFWHM to ensure that all subjects' data had the same effective spatial smoothness (Scheinost et al, 2014). To allow for comparisons across individuals, timecourses were normalized to percent signal change and transformed to the standard coordinate space of Talairach and Tournoux (Talairach & Tournoux, 1988) using parameters obtained from the transformation of each individual's high-resolution anatomical scan. Talairach transformed images had a resampled resolution of 3mm^3 . Comparison of structural and functional MRI data between young children and adults by registration to standard coordinate spaces like Talairach and Tournoux has previously been shown to be methodologically appropriate (Burgund et al., 2002; Kang, Burgund, Lugar, Petersen, & Schlaggar, 2003). To further verify that the nucleus accumbens region of interest (ROI) in this developmental sample corresponded to that in the adult template space after registration, we created anatomical averages for the participants split

into two age groups: our youngest participants (4-6 years old), and our oldest participants (15-16 years old), and overlaid these averages on the adult template. The anatomical average from each of these developmental groups coincided robustly with the adult template and with the anatomically defined nucleus accumbens ROI, suggesting that registration of subcortical regions across development is not a confounding factor in this study (Supplemental Image 2.1).

Motion Corrections

In keeping with recent recommendations, a strict motion-censoring limit was applied so that any timepoint as well as the immediately preceding timepoint were both censored where the Euclidean norm of the scan-to-scan motion parameters across the 6 rigid-body parameters exceeded .5 mm/degrees (Power et al., 2015).

fMRI Statistical Analysis

In order to examine activation across the brain, each participant's individual-level model included regressors for each of the stimulus conditions (fearful faces, happy faces, neutral faces in the context of fearful faces, neutral faces in the context of happy faces) and accuracy. Participants with accuracy rates lower than 50% on the emotion task were excluded from further analysis (six participants; these participants were not included in the demographic data). The regressors were created by convolving the stimulus timing files with the canonical hemodynamic response function. Six motion parameters were included as separate regressors. General linear modeling (GLM) was performed to fit the

percent signal change time courses to each regressor. Linear and quadratic trends were modeled for each voxel's time course to control for correlated drift. Implicit baseline (BL) comprised unmodeled events (fixation) during the inter-trial intervals. At the group level, parameter estimates (beta weights) were extracted for each participant for the happy and fear

conditions from anatomically-defined masks covering the bilateral NAcc as defined by AFNI's Talairach-Tournoux Atlas. Therefore, for the purposes of this study, each participant had an activation value for the happy (happy>BL) condition. These values were subjected to correlational analyses within SPSS.

Results

Blunted telomere length in PI youth

Telomere data was available for 340 participants (103 PI, 237 comparison). A univariate analysis of variance (ANCOVA) on telomere length including the between-subject factor of group type (PI, comparison) and age as a covariate revealed a significant main effect of group type ($F(1,339)=9.77, p<.01, \text{partial } \eta^2=.03$), such that average telomere length for the PI group (mean(SD);range=8.55(4.35);99-23.17) was significantly shorter than the comparison group (mean(SD);range=12.00(7.66);2.53-67.97). There was a main effect of age such that shorter telomere length was associated with increasing age ($F(1,339)=11.65, p=.001, \text{partial } \eta^2=.03$). This effect was qualified by a significant GroupXAge interaction ($F(1,339)=3.95, p<.05 \text{ partial } \eta^2=.01$), and post hoc tests revealed that for the comparison group there was a significant negative association between telomere length and age ($t(233)=-5.05, p<.001$), however among PI participants there was no significant association between telomere length and age ($t(103)=-1.21, p>.05$). To visualize these differences across development we divided our sample into three age groups; young children between the ages of 3-5, children between the ages of 6-10, adolescents between the ages of 11-17 (Figure 2.3).

Longitudinal changes in depression scores in PI youth

Data from the RCADS-P (Chorpita, 2000) was available for 117 PI participants and were compared with 117 comparison participants selected to match the PI participants based on age

and sex in order to ensure comparison of equal groups. For 99 participants (50 PI, 49 comparison) data was available at two time points. A linear mixed-effect model (LMM) was used for repeated-measures of RCADS-P T-scores to assess age-related changes in depression over time with fixed effects of group type, sex, age (linear), age (squared), and the interaction between age (squared) and group type. This procedure prevented listwise deletion due to missing data. Statistical analysis was performed using the SPSS[®]v20 statistical program. Analyses revealed a significant interaction between group type and changes in depression scores over time ($F=3.99, p=.047$). As seen in Figure 2.4, for the PI group, there was a significant quadratic effect of age on changes in depression scores over time, while no significant age effect was seen in the comparison group. We calculated the turning point, or the moment when depression scores reached a developmental peak, in the predicted quadratic slope seen in the PI group [$- \text{linear coefficient of age} / (2 \times \text{quadratic coefficient of age}) = - 2.8025 / (2 \times .2264)$] and identified 12 years of age as the turning point in the data.

Association between telomere length and depressive symptoms

A linear regression was performed on the dependent measure of RCADS-P MDD T-scores at time 2 (collected two years following age of telomere length collection) and telomere length as the independent variable, controlling for group type, sex, age, RCADS MDD-T scores at time 1, groupXage, and the difference in age between collection of RCADS and telomere data centered at 24 months. As seen in Figure 2.5, this analysis showed that shorter telomere length predicted higher depression scores two years later ($\text{beta} = -.21, p < .025$). A linear regression performed on the dependent measure of telomere length and independent variables, quality and quantity of institutional care in PI youth, respectively, as the independent variables did not reveal significant effects ($\text{beta} = .07, p > .05$; $\text{beta} = .12, p > .05$)

NAcc reactivity in PI youth

A 2X2 ANOVA (GroupXAgeGroup) was performed on the extracted beta weights from the anatomically-defined NAcc for happy faces. There was a significant GroupXAgeGroup interaction ($F(1,120)=3.96, p<.05, \text{partial } \eta^2=.03$). Post hoc analyses reveal that, for the PI group, mean NAcc activation significantly decreased from childhood to adolescence ($t(29)=2.33, p<.01$), while no significant change was seen in the comparison group ($t(36)=.789, ps>.05$) (Figure 3). PI adolescents exhibited significantly lower NAcc activation relative to the comparison adolescents ($t(27)=2.26, p<.05$) (Figure 2.6).

Association between telomere length and NAcc reactivity

A linear regression was performed on the dependent measure of NAcc activation to happy faces and telomere length as the independent variable, controlling for group type, sex, age, groupXage, and the difference in age between collection of fMRI and telomere data. As seen in Figure 2.7, this analysis showed that longer telomere length predicted greater NAcc activation ($\text{beta} = .24, p<.025$).

Association between NAcc reactivity and depressive symptoms

A linear regression was performed on the dependent measure of RCADS-P MDD T-scores scores at time 2 (collected two years following age of fMRI) and NAcc activation to happy faces entered as independent variables, controlling for group type, sex, age, and the difference in age between collection of fMRI and RCADS-P data. As seen in Figure 2.8, this analysis showed that low nucleus accumbens activation while viewing happy faces predicted higher depression scores ($\text{beta} = -.19, p<.05$).

Nacc reactivity mediates relationship between telomere length and depression

In order to examine potential mediators of the association between telomere length and

RCADS MDD T-scores, we tested a mediation model of telomere length and RCADS MDD-tscores (collected two years following age of telomere length collection) with NAcc reactivity as a mediator (PROCESS Model 4). The results showed a significant indirect effect of NAcc reactivity (Est.=-.15 [SE=.1], 95% CI [-.49, -.02]). The inverse was also tested and was not significant; mediation tests of NAcc reactivity as the independent variable and telomere length as a mediator revealed the indirect effect of telomere length on NAcc reactivity and depression to be not significant (Est.=-1.3 [SE=1.12], 95% CI [-4.13, .32]) (Figure 2.9).

Discussion

The present study examined the association between depressive symptoms, NAcc reactivity, and telomere length across a 2-year period in a sample of PI youth and a comparison group (never institutionalized) across a wide developmental age range. Findings revealed that PI youth showed greater levels of depressive symptoms than the comparison group. Longitudinal analyses revealed that and these depressive symptoms increased significantly from childhood to early adolescence, and remained high during the adolescent period - a developmental course that has been characterized previously (Angold, Costello, & Worthman, 1998; Angold & Rutter, 1992; Cole, Peeke, Martin, Truglio, & Seroczynski, 1998). Findings further revealed that NAcc reactivity was significantly dampened in the adolescent PI youth relative to the comparison group. While the comparison group demonstrated a normative increase in NAcc activity from childhood to adolescence (Galvan et al., 2006; Ernst et al., 2005; van Leijenhorst et al., 2009; Geier et al., 2009) the PI youth showed atypically hypoactive NAcc activity in adolescents. Interestingly, the effect of EA on NAcc reactivity was observed in adolescents at the same time that reports of depressive symptoms increased, and lower NAcc activity was associated with higher levels of depression two years later, findings which are consistent with the notion that

reduced reactivity of the Nacc to reward may later result in depressive behaviors (Wacker, Dillon, & Pizzagalli, 2009).

PI youth did not show the typical age-related decline in telomere length that was seen in the comparison group but instead demonstrated flattened, significantly shorter, telomere length than the comparison group even from the preschool period, providing additional support for the idea that EA may induce lasting epigenetic alterations at a very early age (Blaze, Asok, & Roth, 2015; Naumova et al., 2012; Oberlander et al., 2008), including changes in telomere biology (Asok et al., 2014). While both NAcc reactivity and depression scores demonstrated age related change following EA, particularly during the early adolescent period, the lack of age effects seen in telomere length may further suggest that these adversity-related telomere alterations occur much earlier in life. Consistent with previous cross-sectional findings in adults (Chen & Shu, 2007; Hartmann et al., 2010; Hoen et al., 2011; Karabatsiakos, Kolassa, Kolassa, Rudolph, & Dietrich, 2014; Simon et al., 2006; Teyssier et al., 2011; Verhoeven et al., 2014; Wikgren, Maripuu, et al., 2012; Wolkowitz et al., 2011; Zhang et al., 2010) demonstrating a correlation between telomere length and depression, in our longitudinal sample we found an association between telomere length and subsequent depressive symptoms such that increased telomere length was correlated with decreased depressive symptoms two years later in both PI and comparison youth. Here, we show this association in a developmental sample, which suggests the role of accelerated aging as a mechanism contributing to the link between EA and depressive outcomes (Agid et al., 1999; Brown et al., 1999; Chapman et al., 2004; Heim & Nemeroff, 2001; McCauley et al., 1997; Mullen et al., 1996). Additionally, we found an association between telomere length and reactivity of the NAcc to reward, a novel demonstration of the relationship between telomeres and functional neural activation. Although future studies are needed to better

establish the relationship between telomere length and brain alterations, research in humans has shown a correlation between shorter telomere length and greater degree of subcortical atrophy (Wikgren et al., 2014), and in a recent post-mortem study researchers found an association between shortened telomere length in the brain and hippocampal volume reductions in those with depression (Mamdani et al., 2015). While not yet fully understood, it is theoretically plausible that peripheral telomere length may correlate with telomere length in the brain as telomere length is often correlated across tissues (Daniali et al., 2013; Gadalla, Cawthon, Giri, Alter, & Savage, 2010; Mitchell et al., 2014; Takubo et al., 2010). Peripheral telomere length has also been associated with alterations in cognitive function (Martin-Ruiz et al., 2006; Wikgren, Karlsson, et al., 2012). Importantly, whereas many studies have shown a correlation between telomere length and depressive symptoms (Ridout et al., 2016), the current study shows that telomere shortening preceded brain and behavioral phenotypes associated with depression symptoms.

Given the aforementioned associations we tested a mediation model of telomere length and RCADS MDD-t-scores with NAcc reactivity. Results demonstrated that NAcc reactivity mediated the relationship between telomere length and depressive symptoms two years later. Upon reversing the model, mediation tests of NAcc reactivity as the independent variable and telomere length as a mediator did not reveal significant results. Thus, our findings suggest the potential causative role of telomeres in neural and depressive outcomes. Consistent with this interpretation, evidence from telomerase-deficient rodent models has demonstrated the effects of telomere attrition on neurodegeneration, which included reduced proliferation of neural progenitor cells, restricted neurogenesis, and atrophy of white matter tracts. Remarkably, these degenerative effects were reversed following reactivation of telomerase activity (Jaskelioff et al., 2011). Thus, these data suggest that telomere length may provide an early marker for deleterious

alterations in neural function which that can be detected as early as the childhood period, and neural alternations - particularly those involved in reward processing - may provide further insight into future depressive outcomes.

While our study has notable strengths, we acknowledge its limitations. First, due to the nature of international adoption, we do not have access to individual prenatal/developmental histories for PI youth. However, randomized control intervention work suggests that institutionalization itself may be the most significant factor in children's developmental histories for future psychiatric outcomes (Zeanah et al., 2009). A second concern is the task used to assess NAcc activity. In the current study, we employed an emotional face-processing paradigm, requiring only passive viewing of emotional faces, which may not be best suited for examination of the NAcc. However, in both healthy youth (Somerville, Hare, & Casey, 2011) and those at risk for depression (Monk et al., 2008) emotional (e.g., happy) faces have been effective in recruiting the NAcc and effective in distinguishing diagnostic groups. Additionally, low ventral striatum reactivity to happy faces has shown diagnostic specificity to depression, as another fMRI study showed that depression was inversely correlated with NAcc response to happy faces (Keedwell, Andrew, Williams, Brammer, & Phillips, 2005). Importantly, our results replicate those of Mehta et al. (2009) who used a reward-learning task (i.e., a monetary incentive delay task) and showed NAcc hypoactivity in PI youth. Additionally, although we hypothesized that telomere length is related to the overall adversity associated with institutional care, we cannot exclude the possibility that a particular aspect of institutional care contributed to this outcome. Tests for correlations between telomere length and quality and quantity of care did not reveal any significant associations in the PI youth, however future research examining the association of telomere length in children with more specific measurements of individual level exposures

including nutrition, toxins and adverse life events may help to refine this distinction. That said, our findings are consistent with previous studies demonstrating associations between telomere length and EA (Kananen et al., 2010; Kiecolt-Glaser et al., 2011; Mason et al., 2015; O'Donovan et al., 2011; Surtees et al., 2011; Tyrka et al., 2010), including studies specific to PI youth that have used experimental design (Drury et al., 2012) providing support for our hypothesis that institutionalization on the whole is the primary cause of this association. Lastly, this study examined telomere length using salivary DNA and not DNA extracted from peripheral blood. Although differences in telomere length between cell types do exist, there is also evidence to support a strong association between telomere length in different cell types (Daniali et al., 2013). While the majority of studies have utilized DNA from whole blood - which contain predominately a mixed cell population of lymphocytes - or buccal cells, previous research has also demonstrated that telomere length from salivary DNA is associated with childhood adversity (Theall, Brett, Shirtcliff, Dunn, & Drury, 2013). Saliva contains both lymphocytes and buccal epithelial cells, and thus has important similarities to previously utilized sources of DNA in telomere studies. Although significant research is still needed to examine the correlation between telomere length obtained from different cell types, the establishment of a reliable and standardized telomere length measurement from non-invasive sources, particularly as pertaining to adversity in developmental populations, would provide a significant advancement for the field.

The results from the current study have important implications for understanding the associations between EA and both neural and genetic changes that may influence later depressive outcomes. Investigation of these associations in a developmental population is paramount, as early childhood may represent a critical period for the interaction between adversity, cellular aging, and neurodevelopment. Consistent with previous research demonstrating adversity-

induced alterations in telomere length, and an increased prevalence of depressive outcomes, we observed shorter telomere length and increased rates of depression across development following EA. We also observed adolescent hypoactivation of the NAcc in response to reward in those having experienced EA. Together we found an association between telomere length and depression two years later that was mediated by NAcc reactivity. Although future studies are needed to establish a direct link between accelerated telomere shortening, alterations in neural function, and depression, our data provide support for the notion that accelerated aging may be one mechanism by which EA results in depressive outcomes. Further elucidation of this relationship and may potentially reveal novel pathways for intervention to reduce the detrimental effects of depression in this population.

Figure 2.1. Ages of participants at time 1 and time 2. Participants with 1 point had telomere data but no follow-up information on depression.

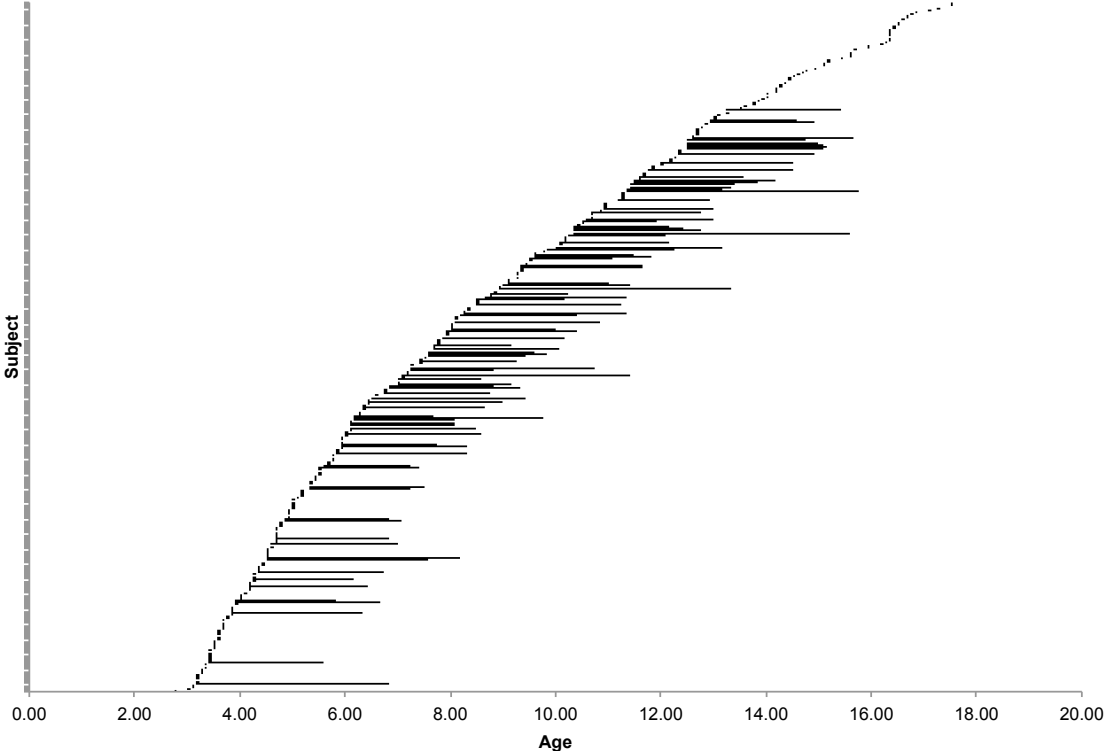


Figure 2.2. Data collection timeline.

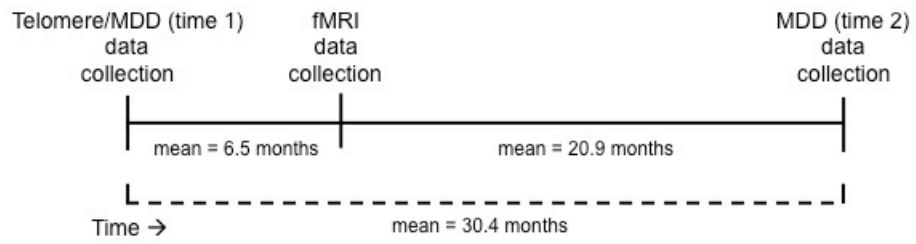


Figure 2.3. Telomere length is blunted in PI youth. The PI group showed significantly shorter telomere length than the comparison group. The comparison group showed a normative age decline in telomere length (measured dimensionally) and no age related changes in telomere length were seen in the PI group.

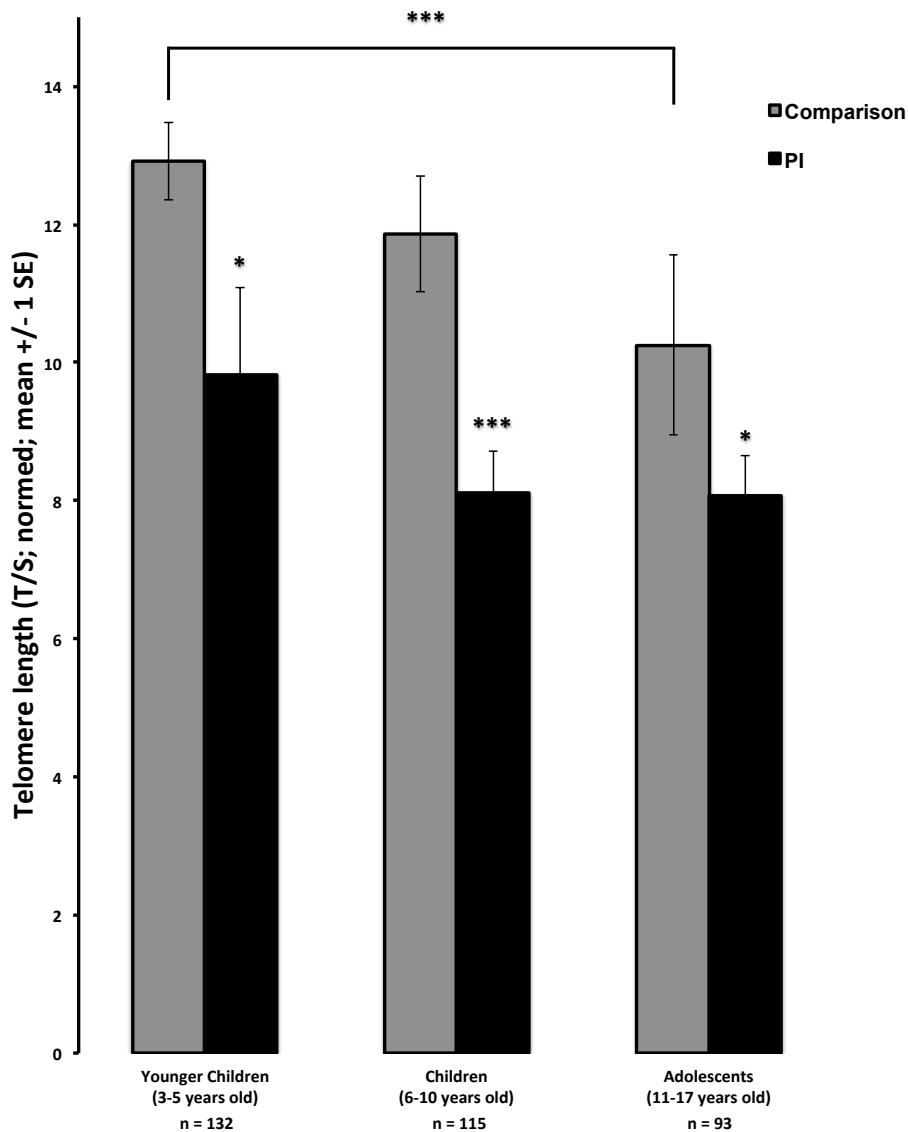


Figure 2.4. Parent-reported depression changes quadratically over time in PI youth. The black arrow marks age 12 years that post-hoc computation identified as the turning point, or moment when depression scores reached a developmental peak. The comparison group did not show any age-related change in depression scores.

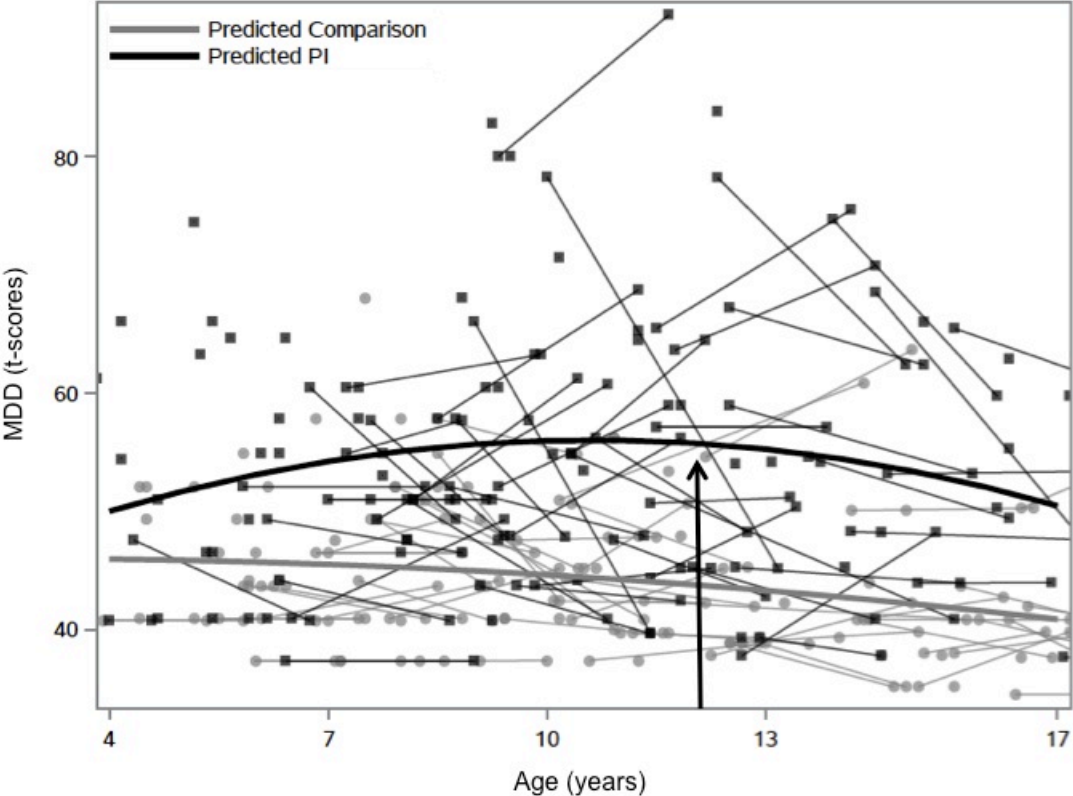


Figure 2.5. Telomere length was inversely correlated with parent report of depression scores, controlling for group type, sex, age, depression scores at time 1, and the difference in age between collection of depression and telomere data centered at 24 months.

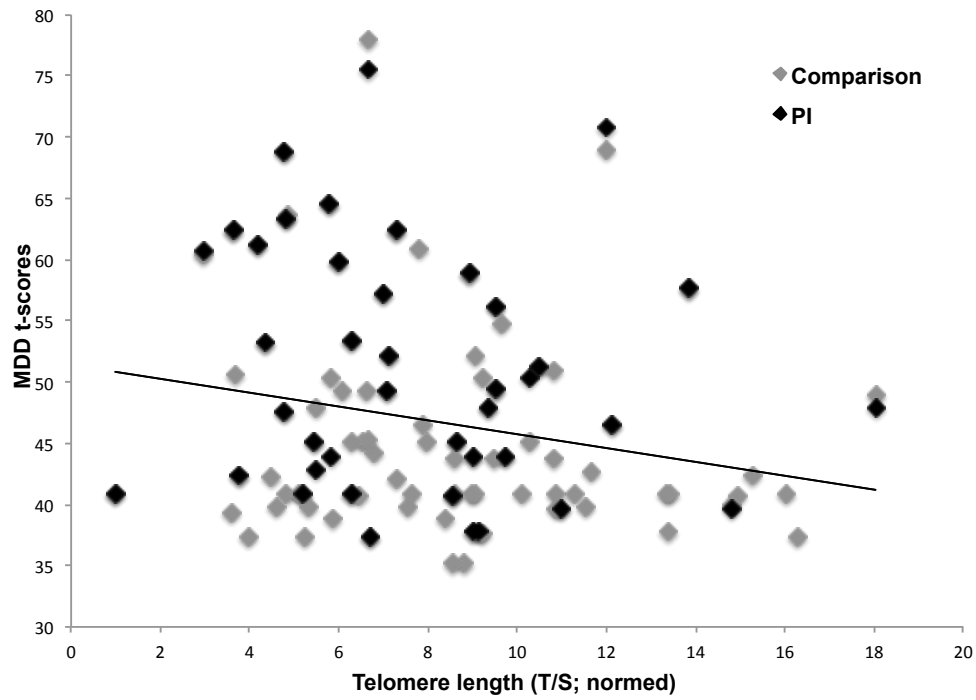


Figure 2.6. Left panel shows anatomically-defined NAcc regions selected for analysis. Right panel shows that, for the PI group, mean NAcc activation significantly decreased from childhood to adolescence. PI adolescents exhibited significantly lower NAcc activation relative to the comparison adolescents.

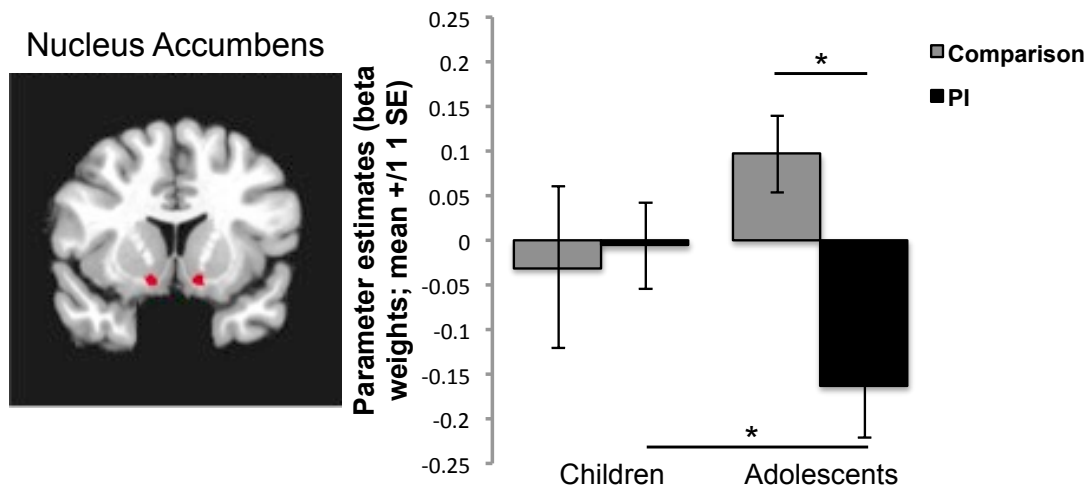


Figure 2.7. Telomere length was positively correlated with NAcc activation while viewing happy faces, controlling for group type, sex, age, and the difference in age between collection of fMRI and telomere data.

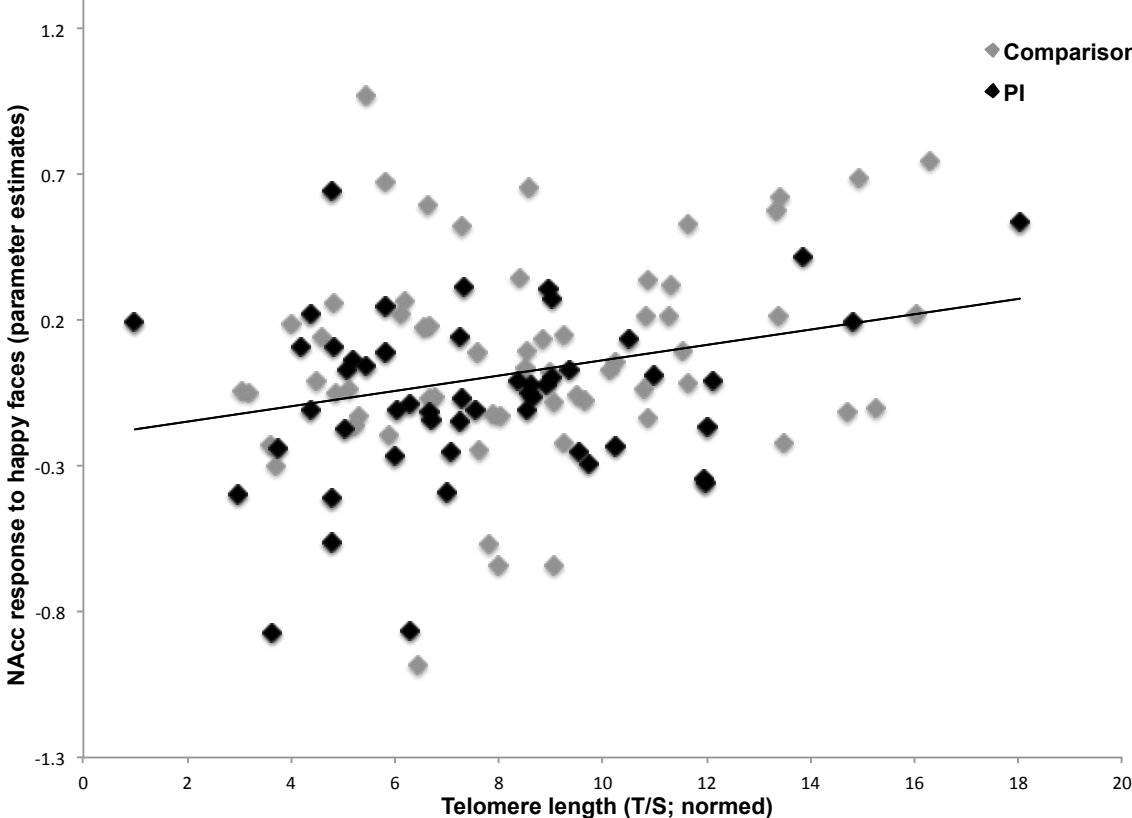


Figure 2.8. Lower NAcc activation while viewing happy faces was inversely correlated with parent report of depression scores two years later, controlling for group type, sex, age, and the difference in age between collection of fMRI and depression data.

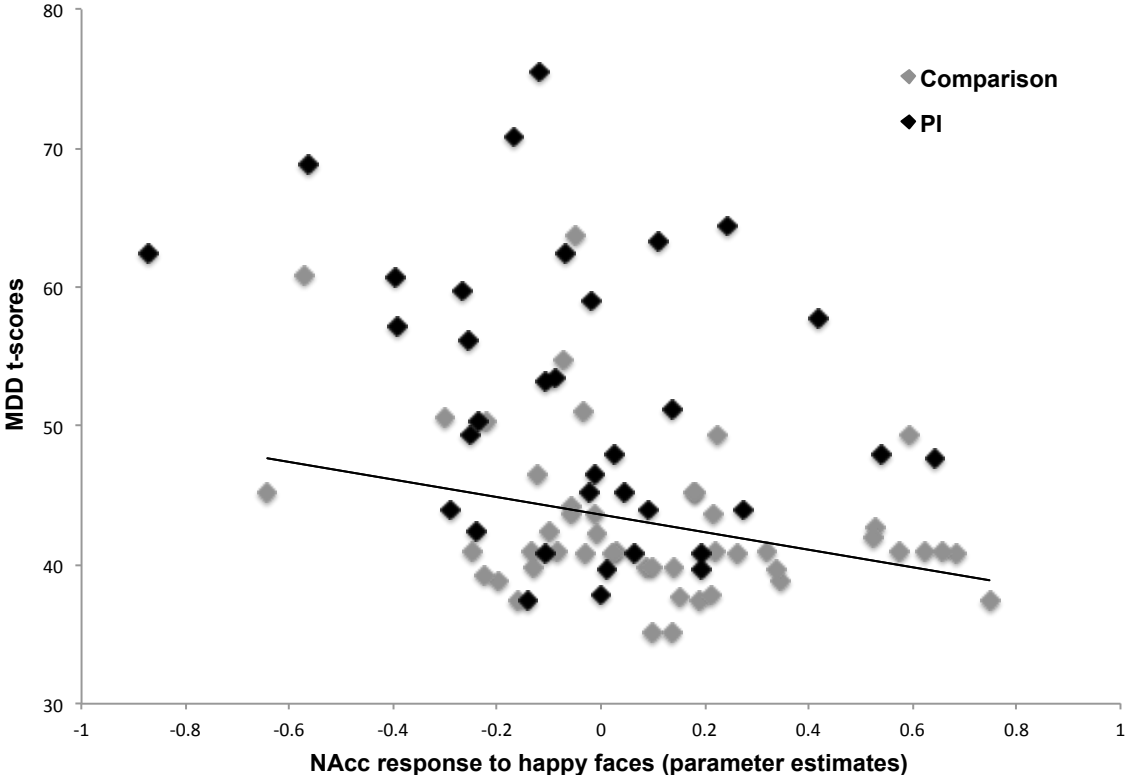
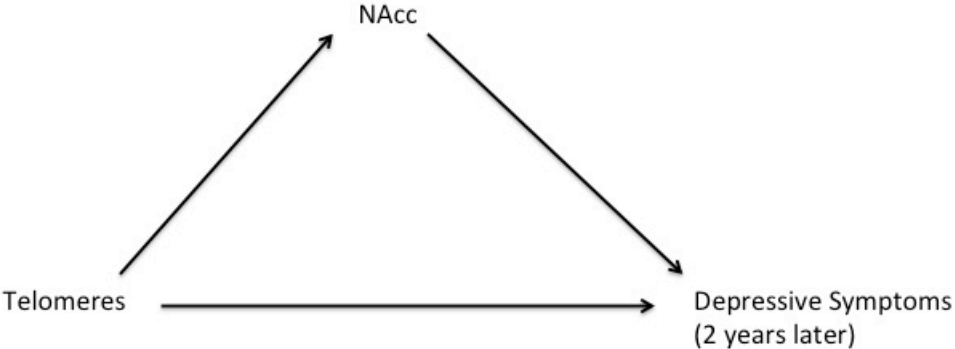
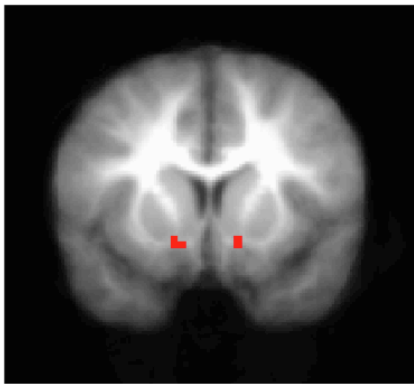


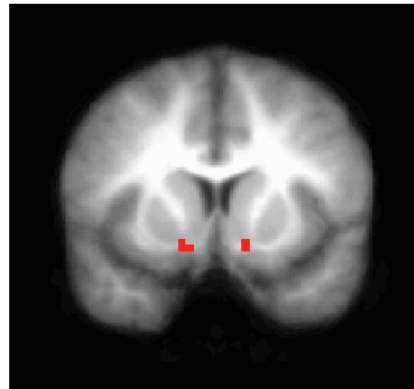
Figure 2.9. NAcc activation mediated the relationship between telomere length and depressive symptoms two years later.



Supplemental Image 2.1. Anatomical averages for youngest (4-6 years old) and oldest participants (15-16 years old) overlaid on adult template.



NAcc (5-6 year olds)



NAcc (15-16 year olds)

Table 2.1: Demographic Information for Sample (with Telomere data)

N:	PI 103	Comparison 237
Baseline Age (range) in years:	3.0 – 17.1	2.8 – 17.5
Sex:	31.4% Male	47.3% Male
Handedness:	82.9% R	85.6% R
IQ (mean [SD]):	102.5 (17.1)	110.4 (16.1)
Income level (median):	85,001-100,000	100,000+
Ethnicity:		
African American	0.0%	14.0%
Asian American	11.1%	7.6%
American Indian	0.0%	1.3%
European American	52.4%	50.2%
Other	2.0%	8.6%
Hispanic	5.7%	8.4%
Country of Origin:		
Azerbaijan	1.9%	
Belarus	1.0 %	
China	33.3%	
Guatemala	1.9%	
Hungary	1.0%	
India	2.9%	
Kazakhstan	13.3%	
Romania	1.0%	
Russia	25.7%	
Slovak Republic.	1.0%	
South Korea	1.9%	
Taiwan	1.0%	
Ukraine	2.0%	
Vietnam	2.9%	
Age placed in institutional care (years; mean [SD]; range)	.54 (13.92); 0-6.0	
Age at adoption (years; mean [SD]; range)	2.1 (2.1); .1-10.0	
Time spent with adoptive family (years; mean [SD]; range)	7.3 (3.8); .6-15.7	
Parent reported quality of institutional caregiving (1=very poor caregiving, 10=very good caregiving; mean [SD]; range)	6.5 (2.6); 1.0-10.0	
Parent reported quantity of caregiving (1=too few caregivers, 10=many caregivers; mean [SD]; range)	5.5 (2.9); 1.0-10.0	

Table 2.2: Demographic Information for Sample (with NAcc data)

N:	PI 56	Comparison 68
Baseline Age (range) in years:	6.2 – 15.8	4.8 – 15.8
Sex:	30.8% Male	44.4% Male
Handedness:	91.8% R	89.4% R
IQ (mean [SD]):	102.6 (14.9)	114.3 (16.2)
Income level (median):	85,001-100,000	100,000+
Ethnicity:		
African American	0.0%	33.3%
Asian American	23.8%	23.8%
American Indian	0.0%	3.2%
European American	40.4%	58.7%
Other	10.9%	11.2%
Hispanic	5.8%	9.5%
Country of Origin:		
Azerbaijan	2.0%	
China	20.2%	
Guatemala	1.0%	
India	1.0%	
Kazakhstan	7.1%	
Romania	1.0%	
Russia	14.1%	
Slovak Republic.	1.0%	
Ukraine	2.0%	
Age placed in institutional care (years; mean [SD]; range)	.56 (1.1); 0-6.0	
Age at adoption (years; mean [SD]; range)	2.2 (1.9); .5-10.0	
Time spent with adoptive family (years; mean [SD]; range)	8.5 (3.3); 1.6-15.0	
Parent reported quality of institutional caregiving (1=very poor caregiving, 10=very good caregiving; mean [SD]; range)	5.1 (3.1); 1.0-10.0	
Parent reported quantity of caregiving (1=too few caregivers, 10=many caregivers; mean [SD]; range)	6.0 (2.7); 1.0-10.0	

Table 2.3: Demographic Information for Sample (with RCADS data)

N:	PI 39	Comparison 56
Baseline Age (range) in years:	5.8 – 15.1	5.6 – 17.8
Follow-up Age (range) in years:	8.1 – 18.0	5.6 – 17.5
Sex:	29.3% Male	40.4% Male
Handedness:	90.4% R	83.8% R
IQ (mean [SD]):	104.4 (14.6)	114.4 (15.6)
Income level (median):	85,001-100,000	100,000+
Ethnicity:		
African American	0.0%	35.3%
Asian American	39.0%	21.6%
American Indian	0.0%	1.9%
European American	43.9%	64.7%
Other	19.4%	11.4%
Hispanic	7.3%	7.7%
Country of Origin:		
Azerbaijan	2.2%	
China	17.2%	
Guatemala	2.2%	
Hungary	1.1%	
Kazakhstan	7.5%	
Russia	12.9%	
Slovak Republic.	1.1%	
Age placed in institutional care (years; mean [SD]; range)	.69 (1.3); 0-6.0	
Age at adoption (years; mean [SD]; range)	2.6 (2.4); .5-10.0	
Time spent with adoptive family (years; mean [SD]; range)	8.2 (3.5); 1.6-14.3	
Parent reported quality of institutional caregiving (1=very poor caregiving, 10=very good caregiving; mean [SD]; range)	6.5 (2.5); 1.0-10.0	
Parent reported quantity of caregiving (1=too few caregivers, 10=many caregivers; mean [SD]; range)	5.8 (3.0); 1.0-10.0	

Legend: SD=standard deviation, IQ measured by Wechsler Abbreviated Scale of Intelligence

IV. Effects of Physical Activity on Depressive Symptoms in Children and Adolescence
Following Institutional Care

Depression is one of the most prevalent disorders in development, with an estimated 5 to 10 percent of children and adolescents presenting subsyndromal symptoms of major depressive disorder (Boris Birmaher, Arbelaez, & Brent, 2002). Youth with depressive symptoms are likely to suffer broad impairments across numerous domains including psychosocial, emotional, and academic dysfunction (Costello, Mustillo, Erkanli, Keeler, & Angold, 2003). Relative to adult-onset depression, youth onset depression tends to be more chronic and debilitating, with higher risk for substance abuse and other psychiatric comorbidities (Cook, Peterson, & Sheldon, 2009). Moreover, youth-onset depression often persists into adulthood (Lewinsohn, Rohde, Klein, & Seeley, 1999). Given the potency and persistence of depression in development, recent work has sought to understand the risk factors contributing to youth-onset depression.

This body of work has consistently identified early-life adversity (EA) as one prominent risk factor for youth-onset of depressive symptoms (e.g. Chapman et al., 2004; Heim & Nemeroff, 2001). Associations have been found between depression and a wide range of caregiver-related adverse early-life experiences including abuse (Anda et al., 2006; Maniglio, 2009; Raine et al., 2012), neglect (Gibb et al., 2003; Spinhoven et al., 2010), maternal deprivation (Johnson, 2002; Loman & Gunnar, 2010), and parental depression (Klein et al., 2005; Tully et al., 2008), among others. Regardless of its form, those with a history of EA have a risk of developing depression nearly a two-fold that of youth not having experienced EA (NCANDS, 2012; Sedlak et al., 2010; Spinazzola et al., 2014). Evidence further suggests a dose response relationship between EA and depression (Edwards et al., 2003) such that the severity of adversity predicts the probability of developing depression later in life (Anda et al., 2006; Chapman et al., 2004). Thus, EA increases vulnerability for depression, and this vulnerability may increase linearly with both the quantity and severity of EA.

Conversely, research focusing on factors ameliorating depressive phenotypes has identified physical activity as a particularly promising approach. Observational research in adults has consistently found a cross-sectional association between high levels of physical activity and better mental health, including low rates of depression in adults. Intervention studies utilizing randomized control trials have also overwhelmingly shown that exercise improves depressive symptoms in both clinical and non-clinical adult populations when compared with no treatment or control intervention (for review see Ströhle, 2009) in adults. Furthermore, a dose response relationship has been demonstrated such that those prescribed to a level of exercise consistent with public health recommendations was an effective treatment for depression, while lower levels of exercise revealed no effect (Dunn et al., 2005; Singh et al., 2005). A smaller longitudinal literature confirms these associations for both deliberate exercise and leisure time physical activity in adulthood (Pereira, Geoffroy, & Power, 2014; for review see Ströhle, 2009).

The relation between physical activity and depression in children and adolescents has not been well-characterized, however. Preliminary meta-analytic research has generally concluded that in both correlational and intervention-based studies in youth the association between physical activity and depression is evident, but research designs are often weak and effects are small (Biddle & Asare, 2011; Calfas & Taylor, 1994; Larun et al., 2006). Importantly, the effects of physical activity on depressive symptoms have yet to be examined longitudinally in a population of children.

Moreover, the effects of physical activity on EA induced depression have yet to be examined directly. However, there is promising research suggesting that the depressive effects of EA may be attenuated, or even reversed, by physical activity. For example, adolescents with a history of EA showed greater self-reported psychological wellbeing and lower rates of problem

behaviors, such as substance abuse, when regularly engaged in physical activity (Field et al., 2001; Kirkcaldy et al., 2002). In rodents, physical exercise has also been shown to produce physiological benefits like increased neurotrophin expression in brain areas critical to depression outcomes like the ventral striatum, prefrontal cortex, and hippocampus (Griffin et al., 2011; Maniam & Morris, 2010; Neeper, Gómez-Pinilla, Choi, & Cotman, 1996). Thus, exercise may serve as an important mechanism by which EA-induced depressive phenotypes may be ameliorated.

In the current study we aim to probe the association between EA, depression, and physical activity in a longitudinal developmental sample. Here we characterized EA as those having been exposed to institutional care early in life – previously institutionalized (PI) youth. Institutional care (e.g., orphanage rearing), which is sparse, unstable, and regimented (Gunnar, Bruce, & Grotevant, 2000) is unfortunately a naturally occurring example of EA in humans affecting millions of children worldwide (<http://www.hrw.org>). What makes this population unique is that if a child is removed from the orphanage via adoption, the end date of the adversity is documented, increasing our ability to draw conclusions about the timing of adverse caregiving in a human population. Moreover, this approach precludes the reliance on retrospective reporting of adversity, which can be unreliable (Widom & Shepard, 1996). Although institutionalized infants experience an unknown combination of adverse events and we have no means of isolating these unique experiences, poor caregiving is common to all PI youth (Gunnar et al., 2000) and the odds of atypical developmental outcomes following this type of caregiving are devastatingly high (Nelson et al., 2009). We examined children and adolescents with and without a history of institutionalization to explore the effects of physical activity on depression across time. We collected dimensional behavioral measures of depression to both chart its developmental course

and to examine associations between physical activity and depression. We hypothesized high levels of physical activity during childhood and adolescence would moderate the association between a history of institutional caregiving and depression over time.

Methods

Participants

A total of 120 individuals (50 PI and 70 comparison, never-institutionalized) including children between the ages of 3 and 11 years-old (35 PI, 52 comparison) and adolescents between the ages of 12 and 17 years-old (15 PI, 18 comparison) participated in a longitudinal depression study whose characteristics are described in Table 3.1. Sixty-four of these participants (35 PI, 29 comparison) were examined in a previous study of depressive outcomes (Goff et al., 2013). All participants contributed Revised Child Anxiety and Depression Scales – Parent questionnaires (RCADS-P; Chorpita, Yim, Moffitt, Umemoto, & Francis, 2000) at two time points approximately two years apart, and a subset of 87 participants (41 PI, 46 comparison) contributed usable Child Behavior Checklist questionnaire data (CBCL; Achenbach, 1991). PI youth were recruited via local international adoption agencies and family networks. The comparison group, comprised of non-adopted youths who had always lived with their families, was recruited via flyer advertisements within the surrounding community or from state birth records. Participants in the comparison group were only included if they were psychiatrically healthy, free of psychotropic medications, and did not report having experienced early-life trauma. Based on parent-report of mental health from the CBCL (Achenbach, 1991) (a standardized instrument to assess emotional or behavioral problems that includes DSM-Oriented Scales (Nakamura, Ebesutani, Bernstein, & Chorpita, 2009), and the RCADS-P (Chorpita et al., 2000), none of the comparison participants scored within clinical range, and 20 of the

participants from the PI group exhibited mental health characteristics within the clinical range (T scores > 70 for internalizing or externalizing problems on the CBCL & depression or total anxiety on the RCADS-P). The protocol was approved by the Institutional Review Board at the University of California, Los Angeles. Parents of participants provided informed consent.

Procedure

Depression. Parents completed the Revised Child Anxiety and Depression Scales – Parent form (RCADS-P; Chorpita et al., 2000), which has been shown to be valid and reliable in developing samples (Bruce F. Chorpita, Moffitt, & Gray, 2005). The RCADS-P is a parent report 47-item instrument that assesses symptoms of childhood anxiety disorders and depression continuously based on DSM-IV criteria. Each symptom on the scale is scored 1, “never”; 2, “sometimes”; 3, “often”; and 4, “always.” The questionnaire is reliable in terms of internal consistency (with Cronbach’s alphas between 0.65 and 0.83 for the various subscales) and temporal stability (with 4-week test–retest correlations between 0.79 and 0.85), and displays reasonable parent–child agreement and good convergent and divergent validity. In the current study, the depression subscale was examined from both the first and second laboratory visit occurring 2 years later. T-scores were calculated based on child gender and grade in school using the norms established by the RCADS-P. RCADS-P T-score calculations limit to grades 3-12, thus we adapted the scale by using grade 3 norms for all participants below the grade range, and grade 12 norms for all participants above the grade range in order to accommodate our broad developmental sample. For the present study, we used the depression T-scores.

Physical Activity. Parents completed the Child Behavior Checklist (CBCL; Achenbach, 1991), a 113-item parent-reported rating scale that has been normed on a large sample of children and possesses excellent test-retest and inter-rater reliability, as well as adequate to

excellent internal consistency (Achenbach & Rescorla, 2001). As part of this measure, parents indicate number (0-3) and extent of extracurricular activities (e.g., sports, art, clubs, etc.) during the preceding 6 months, providing an “activities” subscale. Parents were asked to list the activities in which their children participate plus rate children’s degree of involvement. Responses were scored on a 4 - point scale ((0 (don’t know), 1 (less than average), 2 (average), 3 (more than average)) for each activity. From these questions, we were able to isolate the activities that were physical in nature and compute a measure of physical activity by multiplying the number of sports by the child’s level of involvement resulting in a 10 – point scale from 0 (low activity) to 9 (high activity).

Results

Group Differences in Depression Over Time

A repeated measures analysis of covariance (ANCOVA) was performed to examine group differences in RCADS-P MDD T-scores at two time points. The ANOVA included the within-subjects factor of Time (time1, time2) and the between-subjects factor of Group Type (PI or comparison) on the dependent measure of depression scores. Participant’s sex, age at time 1, and the age difference between time 1 and time 2 (centered at 24 months) were entered as covariates. There was a main effect of Group Type ($F(1, 115)=34.08, p<.0000001, \text{partial } \eta^2=.18$) such that depression scores for the PI group (mean(SD)=52.82(8.63)) were significantly higher than those of the comparison group ((mean(SD)=45.11(8.37)). There were no other main effects or interactions, including no significant differences between depression scores at time 1 and time 2 for the PI or comparison groups ($F(1, 117)=.167, p>.05, \text{partial } \eta^2=.001$) (Figure 3.1).

Physical Activity Predicts Changes in Depression in PI Youth

A repeated measures ANCOVA was performed to examine the effects of CBCL Physical

Activity (PA) scores on changes in depression scores over time. The ANCOVA included the within-subjects factor of Time (time1, time2), and the between-subjects factors of group type (PI, comparison) and PA on the dependent measure of RCADS-P depression scores. Participant's sex, age at time 1, and the age difference between time 1 and time 2 (centered at 24 months) were entered as covariates. There was a main effect of group type ($F(1, 80)=7.54, p<.01, \text{partial } \eta^2=.09$) such that depression scores for the PI group (mean(SD)=44.57(8.88)) were significantly higher than those of the comparison group (mean(SD)=53.25(9.48)). A significant TimeXPA interaction ($F(1, 80)=4.51, p<.05, \text{partial } \eta^2=.05$) and TimeXPAXGroupType interaction ($F(1, 80)=4.27, p<.05, \text{partial } \eta^2=.05$) were also revealed.

Given the significant TimeXPAXGroupType interaction, covarying for participant's sex, age at time 1, and the age difference between time 1 and time 2 (centered at 24 months), post-hoc simple effects tests were run to characterize the interaction between group type and time for three PA categories (Low=0, Average =4.8, High=9) (Figure 3.2). The simple effects tests were performed within the ANCOVA model described above with pairwise comparisons (adjusted for multiple comparisons with a Bonferroni correction) of the estimated marginal means for each PA category. Results showed that when PA was High the PI group demonstrated a significant decrease in depression scores ($p<.01$) between time 1 (mean(SE)= 54.08(2.72)) and time 2 (mean(SE)= 44.8(3.36)). However, for the comparison group, no significant change in depression scores was seen between time 1 (mean(SE)= 45.26(3.54)) and time 2 (mean(SE)= 44.7(4.36)) ($p>.05$). When PA was Low the PI group demonstrated a significant increase in depression scores ($p<.025$) between time 1 (mean(SE)= 53.9(4.0)) and time 2 (mean(SE)= 63.77(4.94)). However, for the comparison group, no significant change in depression scores was seen between time 1 (mean(SE)= 44.54(1.2)) and time 2 (mean(SE)= 44.36(1.6)) ($p>.05$). When

PA was Average the PI group demonstrated no significant change in depression scores ($p > .05$) between time 1 (mean(SE)= 54.0(1.52)) and time 2 (mean(SE)= 53.65(1.87)). Likewise, for the comparison group, no significant change in depression scores were seen between time 1 (mean(SE)= 44.54(1.2)) and time 2 (mean(SE)= 44.36(1.6)) ($p > .05$). No significant group differences in depression scores were seen between time 1 and time 2 ($p > .05$). There were no other main effects or interactions.

Control analyses

The same repeated measures ANCOVA was performed to examine CBCL Activities scores in place of PA scores and revealed no significant main effects or interactions. Additionally, a repeated measures ANCOVA was performed to examine the effects of RCADS-P depression scores on changes in PA scores over time. The ANCOVA included the within-subjects factor of Time (time 1, time 2), and the between-subjects factors of group type (PI, comparison) and depression scores on the dependent measure of PA. Participant's sex, age at time 1, and the age difference between time 1 and time 2 (centered at 24 months) were entered as covariates. There was a main effect of sex ($F(1, 80)=12.54, p < .00001, \text{partial } \eta^2=.13$) such that average PA scores were significantly higher for males (mean(SD)=6.02(1.78)) than for females (mean(SD)=4.74(1.77)). There were no other main effects or interactions. Additionally, ANCOVA was performed to examine the effects of PA scores on concurrent depression scores at time 1. The ANCOVA included the between-subjects factors of group type (PI, comparison) and PA on the dependent measure of RCADS-P depression scores. Participant's sex and age were entered as covariates. Results revealed no significant main effects or interactions. Lastly, we included psychiatric medication use as a covariate in the ANCOVA model, which revealed no significant change in the effects of PA on depressive symptoms for those with high levels of PA.

Discussion

The present study tested whether physical activity could ameliorate depressive symptoms in PI youth during development. We found that parent-reported depression in PI youth was high and remained elevated across 2 years for both children and adolescents. Although at the group level no changes were seen in the developmental course of depressive symptoms, differences in physical activity levels across youth modulated later depressive symptoms in PI youth. Specifically, we observed that high levels of physical activity predicted decreases in depressive symptoms over time and low levels of activity predicted increases in depressive symptoms. These effects were specific to both children and adolescents in the PI group, as they were not observed in the comparison youth participants.

Our findings showed no association between physical activity and depressive symptoms at time 1 suggesting that the current findings are not simply an artifact of concurrent physical and mental health. Furthermore, we found no effects of depression on changes in physical activity over time, providing support for the causal role of physical activity in changes in depressive symptoms in a developmental sample. These findings provide evidence that physical activity may be beneficial for alleviating depression symptoms in youth during development (Biddle & Asare, 2011; Calfas & Taylor, 1994; Larun et al., 2006). We found that both children and adolescents across a wide developmental sample, 3-18 years of age, demonstrated changes in depressive symptoms dependent upon their initial level of physical activity. Many studies in adults have examined the effects of physical activity on depression utilizing randomized control trials (for review see Ströhle, 2009). Here, we show that in a naturalistic setting (self-driven participation in recreational sports), physical activity in youth can positively influence depressive outcomes. Moreover, our results specifically support a possible dose response relation between

physical activity and symptom amelioration during development, consistent with prior reports in adults (Dunn et al., 2005; Singh et al., 2005).

Although the current study could not directly address the mechanisms through which physical activity reduces later depression symptoms, there are several potential pathways. One plausible mechanism by which exercise may ameliorate depressive symptoms in PI youth involves Brain-Derived Neurotrophic Factor (BDNF), a protein enhancing brain health and plasticity that may be protective against adversity-induced neuronal insults (see Daskalakis, De Kloet, Yehuda, Malaspina, & Kranz, 2015 for review). Research has shown that EA can negatively impact neuronal structure and function (for review see Teicher et al., 2003), including those brain regions implicated in depression, such as the ventral striatum, in youth (Goff et al., 2013; Hanson, Hariri, & Williamson, 2015; Mehta et al., 2010). Recent research also suggests that low levels of BDNF are associated with depression (Aydemir & Deveci, 2009 ; Duman & Monteggia, 2006; Hashimoto, Shimizu, & Iyo, 2004). Importantly, physical activity has been shown to increase BDNF in humans (see Huang, Larsen, Ried-Larsen, Møller, & Andersen, 2014 for a review). While still not fully elucidated in a human population, a study performed on rodents exposed to EA revealed that physical activity was correlated with increases BDNF levels in the striatum and decreases in depressive symptoms (Marais, Stein, & Daniels, 2009). Thus increases in BDNF could help to limit or repair depression-related neuronal damage caused by adversity, suggesting a potential mechanism by which depressive symptoms may be improved as the result of physical activity. Future studies probing the relationship between physical activity, BDNF, and those brain regions implicated in depressive outcomes following EA may help to further elucidate this relationship.

Currently psychotherapy and pharmacological interventions are common treatments for

youth with depression. However psychotherapy is often expensive and in short supply (Biddle & Asare, 2011), and lingering concerns remain about the safety of antidepressant use in youth (Kratochvil et al., 2006) - with poor overall response even when antidepressant efficacy has been proven (Emslie et al., 1997, 2002; Hughes et al., 2007). To date, research examining resilience following EA has focused heavily on the moderating effects of individual psychological characteristics (Cicchetti, Rogosch, Lynch, & Holt, 1993) as well as environmental factors including parental care, quality of inter-personal relationships, and a stable home environment (for review see Afifi & MacMillan, 2011) as being protective in long-term mental health outcomes. Research has also highlighted genetic factors as important in psychological resilience following EA (Gatt et al., 2009). Indeed, resilience outcomes following EA are likely driven by the interaction between genetics, individual characteristics, and environmental influence. Though often times these factors are determined outside of an individual's control, here we provide evidence for a behavioral intervention that may provide PI youth with some agency in altering the trajectory of future depressive outcomes. Specifically we demonstrated the positive effect of physical activity on depressive symptoms in PI youth. Participation in physical activity is an age-appropriate enterprise garnering few negative side effects, which can be self-driven and self-sustaining, in that individuals can maintain it once the basic skills have been established (Larun et al., 2006). As such, physical activity may serve as a viable alternative treatment for EA-induced depressive symptoms.

While our study has notable strengths, we acknowledge it also has several limitations. First, due to the nature of international adoption, we do not have access to individual prenatal/developmental histories for PI youth thus somewhat limiting the conclusions we can draw in regard to depressive outcomes following institutionalization. However, randomized

control intervention work does suggest that institutionalization itself may be the most significant factor in children's developmental histories for future psychiatric outcomes (Zeanah et al., 2009). A second concern is that our questionnaires for both depression and physical activity were parent-reported measures that may not reflect the self-reported responses of the participants, though both the RCADS-P and CBCL demonstrate reasonable parent-child agreement (Chorpita et al., 2005; Rey, Schrader, & Morris-Yates, 1992). In addition to self-report, future work should also include more objective measures of physical activity (eg. direct observation, actigraphy, heart rate monitoring, etc.) Furthermore the number of sports permitted on the CBCL (3) may have limited our construct for physical activity in that we may not have been able to capture the full scale of involvement in physical activities in this sample. Lastly, while we did provide evidence for the causal role of physical activity in the amelioration of depressive symptoms in PI youth, future studies across species will be required to test potential mechanisms.

Youth-onset depression following EA is a prevalent and developmentally detrimental. The results from the current study demonstrate that physical activity may reduce or even reverse the emergence of depressive symptoms in PI children and adolescents. These findings suggest a potential non-pharmaceutical, self-driven behavioral intervention for depressive symptoms in an at-risk developmental population, therefore highlighting the importance of efforts by clinicians, parents, schools, and public health officials in reinforcing youth's participation in physical activity.

Figure 3.1. The PI group showed significantly greater depression scores than the comparison group at both time 1 and time 2. The pattern of results was the same in both PI children (ages 4-11 years) and adolescents (ages 12-17 years).

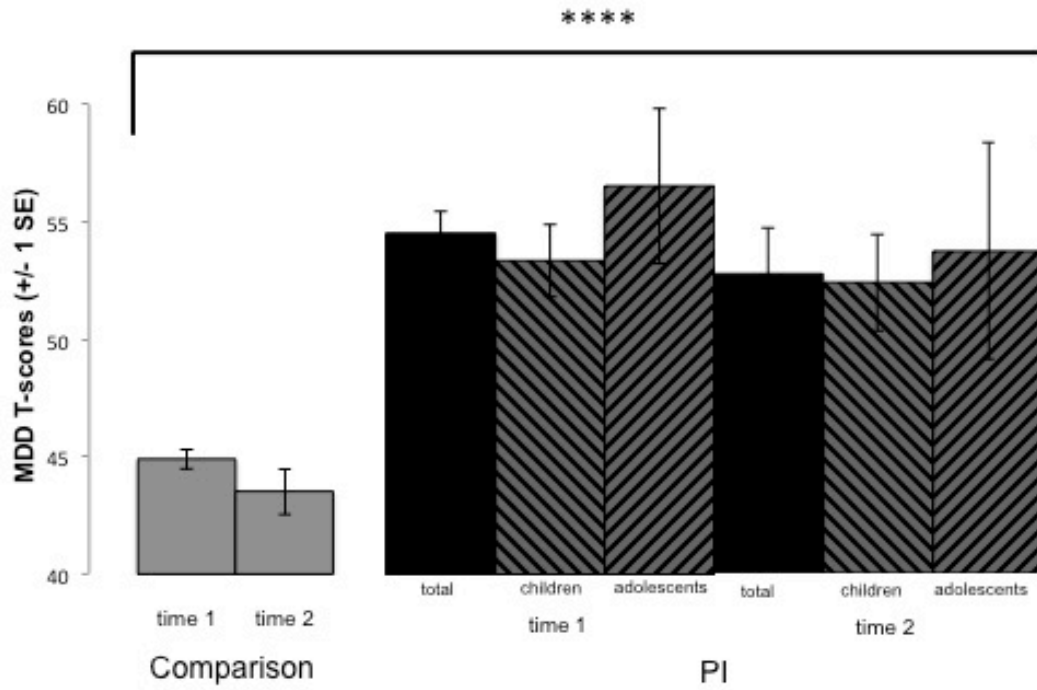


Figure 3.2. Longitudinal changes in depression scores in PI youth when Physical Activity was Low, Average, and High. The pattern of results was the same in both PI children (ages 4-11 years) and adolescents (ages 12-17 years). There was no significant difference in depression scores at time 1 for PI participants regardless of level of Physical Activity. No changes were observed in the comparison group.

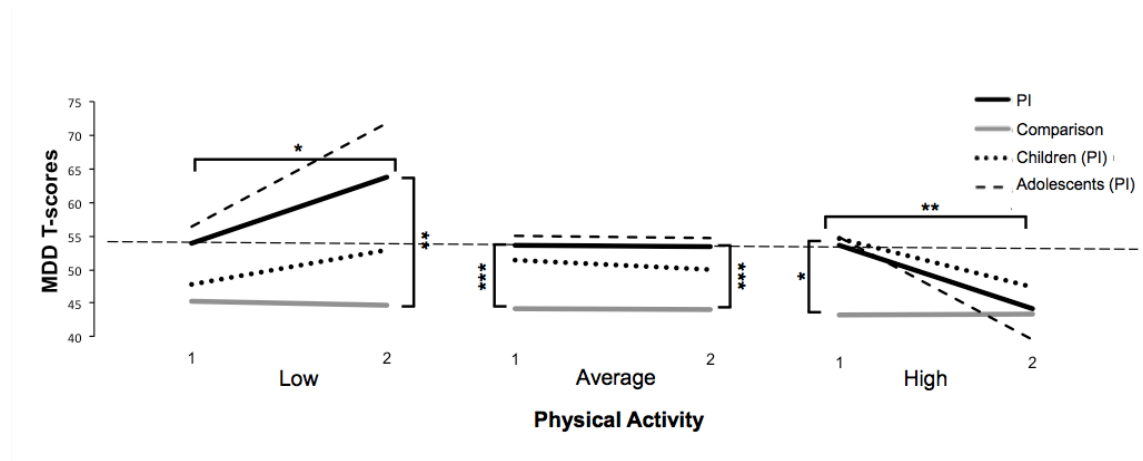


Table 3.1: Demographic Information for Sample

	PI	Comparison
N:	50	70
Baseline Age (range) in years:	4.3 – 17.1	3.2 – 17.5
Follow up age (range) in years:	6.8 – 18.7	5.6 – 20.3
Sex:	30.0% Male	38.6% Male
IQ (mean [SD]):	104.7 (14.9)	115.7 (15.7)
Income level (median):	150,001- 200,000	150,001- 200,000
Ethnicity:		
African American	0.0%	21.4%
Asian American	44.0%	27.1%
American Indian	2.0%	2.9%
European American	52.0%	42.9%
Other	2.0%	7.2%
Hispanic	2.0%	4.3%
Age placed in institutional care (years; mean [SD]; range)	.67 (1.4); 0-6.0	
Age at adoption (years; mean [SD]; range)	2.7 (2.4); .1-10.0	
Time spent with adoptive family (years; mean [SD]; range)	7.4 (4.0); .6-15.7	
Parent reported quality of institutional caregiving (1=very poor caregiving, 10=very good caregiving; mean [SD]; range)	6.6 (2.4); 1.0-10.0	
Parent reported quantity of caregiving (1=too few caregivers, 10=many caregivers; mean [SD]; range)	5.7 (2.9); 1.0-10.0	

Legend: SD=standard deviation, IQ measured by Wechsler Abbreviated Scale of Intelligence

V. General Discussion

Exposure to EA has consistently been associated with a range of negative health outcomes that include increased risk for psychopathology, in particular disorders of emotion regulation such as depression (Phillips, Hammen, Brennan, Najman, & Bor, 2005). Numerous studies have documented these associations, however the mechanisms that underlie how negative early-life experiences alter psychobiological processes remain unclear. Therefore, this dissertation aimed to probe how EA alters psychobiological processes by targeting three mechanisms. The first aim was to empirically test the theory that adolescent-emergent depressive symptoms following EA are associated with alterations in underlying reward-related neural circuitry. The second aim was to identify EA induced modifications of chromosomal structure (i.e., telomere length) and test associations with youth depression and related neurobiology. And lastly, because EA is such a potent risk factor for depression, the third aim was to examine potential behavioral interventions for depressive outcomes in this population. These studies provide evidence for an increased prevalence of depressive outcomes following EA that may be mechanistically associated with adversity-induced alterations in telomere length across development and atypical adolescent hypoactivation of the NAcc in response to reward. Furthermore, we provide evidence that physical activity may ameliorate depressive symptoms following EA in both children and adolescents.

Our results support the notion that mechanisms underlying depression following EA involve dysfunction of reward related processes. Here we provide evidence to suggest that atypical positive affective processing, or the inability to experience pleasure, may underlie depressive outcomes in this population. More specifically, anhedonic phenotypes may reflect atypical responsivity to rewarding information. Indeed, our finding that early adolescence is the typical age of onset for increased depressive symptoms following EA may provide support for,

and additional insight into, the role of altered positive affect in these outcomes. It is well documented that adolescence is the time at which increases in reward-related behavior (Dahl & Spear, 2004) and enhanced reward responsiveness most commonly emerge (Larson, Csikszentmihalyi, & Graef, 2014). Furthermore, these reward-seeking behaviors correspond temporally with the period at which the NAcc reaches its developmental peak (Ernst et al., 2005; Galvan et al., 2006; Geier & Luna, 2009; Urošević et al., 2012; Van Leijenhorst et al., 2010). Importantly, the NAcc is vulnerable to adversity-induced alterations and thus the typical developmental NAcc changes expected in early-adolescence may cause this period to be one of even greater vulnerability to positive affect dysregulation following EA via atypical functional development of the NAcc.

Addressing the role of positive affect in youth depression may have important implications for developing effective treatments, specifically treatments that target anhedonic symptoms during the adolescent period – a time at which onset of depressive symptoms leads to higher risk for developing other negative outcomes including suicidal behavior, substance abuse, physical disorders, early unwanted pregnancy, and compromised work, academic and psychosocial functioning (Birmaher et al., 1996; Brent, 1995). Treating symptoms of dysregulated positive affect may also play an important role in reducing recurrence of depression over the lifespan. Indeed research suggest that reduced responsiveness to rewarding stimuli is associated with poor depression recovery (Rottenberg, Kasch, Gross, & Gotlib, 2002). Though future research is still needed to establish the most efficacious treatments for positive affect dysregulation, successful enhancement of positive affect may have implications for targeted periods of intervention, likelihood of recurrence, and amelioration of other negative psychosocial outcomes following EA.

Beyond these systems level mechanisms, we provide evidence to suggest that telomere erosion may lend additional insight into the relationship between EA and depression. That is, telomere length may serve as a cellular biomarker of EA-induced depressive outcomes. Importantly, depression (Musselman, Evans, & Nemeroff, 1998), EA (Danese & McEwen, 2012), and shortened telomere length (Cawthon, Smith, O'Brien, Sivatchenko, & Kerber, 2003) have all been associated with chronic somatic diseases that are generally considered to be diseases of aging. This relationship stands to reason as telomere length declines with cell replication, and this effect can be further accelerated by adversity-related factors such as inflammation (Jurk et al., 2014) and oxidative stress (Correia-Melo, Hewitt, & Passos, 2014), which are also implicated in depressive outcomes (Michel, Pülschen, & Thome, 2012; Raison, Capuron, & Miller, 2006). Though more work is necessary to establish causality, perhaps accelerated aging is one mechanism by which EA results in depressive outcomes. Our findings that depressive symptoms could be prospectively predicted by telomere length, and that NAcc hypoactivity mediated this relationship suggest a causal role of telomere length in both neural and behavioral outcomes following EA. These findings further suggest the importance of integrating physical health markers, in addition to the behavioral and psychological symptoms the field has focused on, in treatments for depression for this population.

Lastly, our findings suggest that physical activity may ameliorate depressive symptoms in both children and adolescents following EA. Thus the present study provides promising support for the notion that adverse experiences in early life are not deterministic in predicting depressive outcomes, rather exercise may prevent, or even reverse depression in this population. While we can only speculate as to the mechanisms by which physical activity reduces later depression, there is evidence for the role of biological aging in the efficacy of this intervention. For example,

research has shown that physical activity in adults can increase brain volume in regions associated with age-related decline (Colcombe et al., 2006), possibly as the result of exercise-induced increases in BDNF (see Huang, Larsen, Ried-Larsen, Møller, & Andersen, 2014 for a review). There is also evidence to suggest that telomere length is positively correlated with regular vigorous aerobic exercise in aging humans (LaRocca, Seals, & Pierce, 2010). This effect was not seen in healthy young adults, thus perhaps the beneficial effects of physical activity on telomeres can only be observed in populations demonstrating blunted telomere length, such as those having experienced EA. Future research will be required to more directly examine the mechanisms underlying these effects.

Although the current studies could not address this directly, BDNF may play an important role in understanding the relationship between telomeres, Nacc hypoactivity, and physical activity in EA related depressive outcomes. Indeed, EA has been shown to induce long-term changes in BDNF expression (Lippmann, Bress, Nemeroff, Plotsky, & Monteggia, 2007) and reductions in BDNF have been robustly associated with depression (Dwivedi, 2009; Karege et al., 2005; Lee & Kim, 2010; Shimizu et al., 2003). Importantly, physical activity has been shown to increase BDNF in humans (see Huang, Larsen, Ried-Larsen, Møller, & Andersen, 2014 for a review). Furthermore, a study performed on rodents exposed to EA revealed that physical activity was correlated with increases BDNF levels in the striatum and decreases in depressive symptoms (Marais et al., 2009). Thus perhaps exercise induced increases in BDNF could help to limit or repair depression-related neuronal damage caused by adversity, thus ameliorating symptoms of depression following EA. Telomerase, a reverse transcriptase enzyme that rebuilds telomere length - thereby delaying cell senescence, apoptosis, and cell death - may also involve mechanisms of BDNF. There is evidence in rodent models for a neuroprotective relationship

between BDNF and telomerase such that telomerase may mediate the BDNF signaling pathway in promoting neuronal survival (Fu, Lu, & Mattson, 2002; Niu & Yip, 2011). Though further investigation is required, perhaps telomerase serves as a mechanism for the neuroprotective function of BDNF, suggesting a new direction for therapeutic strategies involving psychological disorders associated with atypical neural function, such as EA induced depression. Thus, future research on BDNF within this context may thus tie together the three pathways from EA to depression targeted in this dissertation.

Taken together, these studies provide a valuable advancement in elucidating the mechanisms underlying depression following EA, as well as a potential treatment option for these negative outcomes. Investigation of these associations in a developmental population is paramount, as early childhood may represent a critical period for the interaction between adversity, cellular aging, and neurodevelopment. Further elucidation of this relationship may potentially further reveal novel pathways for intervention to reduce the detrimental effects of depression in this population.

Appendix A

PANAS-C

Lately, how much have you been feeling:

	Not at all	A little	Moderately	Quite a bit	Extremely
Cheerful	1	2	3	4	5
Frightened	1	2	3	4	5
Miserable	1	2	3	4	5
Joyful	1	2	3	4	5
Delighted	1	2	3	4	5
Sad	1	2	3	4	5

Appendix B

RCADS-P

Please put a circle around the word that shows how often each of these things happen for your child.

1. My child worries about things	Never	Sometimes	Often	Always
2. My child feels sad or empty	Never	Sometimes	Often	Always
3. When my child has a problem, he/she gets a funny feeling in his/her stomach	Never	Sometimes	Often	Always
4. My child worries when he/she thinks he/she has done poorly at something	Never	Sometimes	Often	Always
5. My child feels afraid of being alone at home	Never	Sometimes	Often	Always
6. Nothing is much fun for my child anymore	Never	Sometimes	Often	Always
7. My child feels scared when taking a test	Never	Sometimes	Often	Always
8. My child worries when he/she thinks someone is angry with him/her	Never	Sometimes	Often	Always
9. My child worries about being away from me	Never	Sometimes	Often	Always
10. My child is bothered by bad or silly thoughts or pictures in his/her mind	Never	Sometimes	Often	Always
11. My child has trouble sleeping	Never	Sometimes	Often	Always
12. My child worries about doing badly at school work	Never	Sometimes	Often	Always
13. My child worries that something awful will happen to someone in the family	Never	Sometimes	Often	Always

14. My child suddenly feels as if he/she can't breathe when there is no reason for this	Never	Sometimes	Often	Always
15. My child has problems with his/her appetite	Never	Sometimes	Often	Always
16. My child has to keep checking that he/she has done things right (like the switch is off, or the door is locked)	Never	Sometimes	Often	Always
17. My child feels scared to sleep on his/her own	Never	Sometimes	Often	Always
18. My child has trouble going to school in the mornings because of feeling nervous or afraid	Never	Sometimes	Often	Always
19. My child has no energy for things	Never	Sometimes	Often	Always
20. My child worries about looking foolish	Never	Sometimes	Often	Always
21. My child is tired a lot	Never	Sometimes	Often	Always
22. My child worries that bad things will happen to him/her	Never	Sometimes	Often	Always
23. My child can't seem to get bad or silly thoughts out of his/her head	Never	Sometimes	Often	Always
24. When my child has a problem, his/her heart beats really fast	Never	Sometimes	Often	Always
25. My child cannot think clearly	Never	Sometimes	Often	Always
26. My child suddenly starts to tremble or shake when there is no reason for this	Never	Sometimes	Often	Always
27. My child worries that something bad will happen to him/her	Never	Sometimes	Often	Always

28. When my child has a problem, he/she feels shaky	Never	Sometimes	Often	Always
29. My child feels worthless	Never	Sometimes	Often	Always
30. My child worries about making mistakes	Never	Sometimes	Often	Always
31. My child has to think of special thoughts (like numbers or words) to stop bad things from happening	Never	Sometimes	Often	Always
32. My child worries what other people think of him/her	Never	Sometimes	Often	Always
33. My child is afraid of being in crowded places (like shopping centers, the movies, buses, busy playgrounds)	Never	Sometimes	Often	Always
34. All of a sudden my child will feel really scared for no reason at all	Never	Sometimes	Often	Always
35. My child worries about what is going to happen	Never	Sometimes	Often	Always
36. My child suddenly becomes dizzy or faint when there is no reason for this	Never	Sometimes	Often	Always
37. My child thinks about death	Never	Sometimes	Often	Always
38. My child feels afraid if he/she has to talk in front of the class	Never	Sometimes	Often	Always
39. My child's heart suddenly starts to beat too quickly for no reason	Never	Sometimes	Often	Always
40. My child feels like he/she doesn't want to move	Never	Sometimes	Often	Always

41. My child worries that he/she will suddenly get a scared feeling when there is nothing to be afraid of	Never	Sometimes	Often	Always
42. My child has to do some things over and over again (like washing hands, cleaning, or putting things in a certain order)	Never	Sometimes	Often	Always
43. My child feels afraid that he/she will make a fool of him/herself in front of people	Never	Sometimes	Often	Always
44. My child has to do some things in just the right way to stop bad things from happening	Never	Sometimes	Often	Always
45. My child worries when in bed at night	Never	Sometimes	Often	Always
46. My child would feel scared if he/she had to stay away from home overnight	Never	Sometimes	Often	Always
47. My child feels restless	Never	Sometimes	Often	Always

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