ABSTRACT

Title of Dissertation:	EFFECTS OF EARLY AND CONCURRENT PARENTING AND CHILD CORTISOL REACTIVITY ON HIPPOCAMPAL STRUCTURE AND FUNCTIONAL CONNECTIVITY DURING CHILDHOOD: A PROSPECTIVE, LONGITUDINAL STUDY
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Offspring of depressed mothers are at increased risk for emotional and behavioral disorders and social impairment. One proposed mechanism of risk transmission is through exposure to maladaptive parenting styles, as depressed mothers display higher levels of hostility and lower levels of support than non-depressed mothers. Rodent models indicate that the early parenting environment programs the endogenous stress response system, the hypothalamic-pituitary-adrenal (HPA) axis, through a cascade of epigenetic processes, ultimately elevating levels of glucocorticoid stress hormones (i.e., cortisol in humans). Elevated cortisol levels have been linked to both structural and functional changes in the hippocampus, a medial temporal lobe structure implicated in regulation of the HPA axis and the pathophysiology of depressive disorders. Despite elucidation of the pathways through which parenting influences neurobiological development in rodents, research examining these associations in humans is only emerging. The present study aimed to translate the rodent literature by examining the effects of early and concurrent parenting on hippocampal structure and functional connectivity during childhood, with a specific emphasis on exploring the mediating role of cortisol reactivity, in a longitudinal sample of offspring of depressed mothers and a community comparison group. At 3-6 and 5-10 years, observational measures of parenting and children's salivary cortisol responses to a laboratory stressor were assessed. At 5-10 years, children completed structural and resting-state functional MRI scans. Findings revealed timing- and region-dependent associations. Early positive parenting predicted larger hippocampal head volumes whereas concurrent positive parenting predicted smaller body volumes. Early cortisol reactivity predicted larger body volumes whereas concurrent cortisol reactivity predicted smaller tail volumes. Concurrent parenting (positive and negative) predicted hippocampus subregion connectivity with regions of the cerebellum. Early cortisol reactivity predicted increased hippocampal

connectivity with the cuneus and regions of the cingulate gyrus. There was a significant indirect effect of greater T1 Negative Parenting on smaller left hippocampal tail volume through increased concurrent cortisol reactivity. Significant interactions with maternal depression were also observed. This research provides a necessary translation of the rodent literature and elucidates possible timing-dependent neurobiological pathways through which early experience may confer increased risk for poor outcomes in human offspring.

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by

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Dedication

To two of the most important men in my life who were taken all too soon: my baby brother, Paul Allan Blankenship, Jr. (December 8, 1994 – May 22, 2015), and my Poppop, Robert Francis Hertzog (August 1, 1936 – May 31, 2014). I looked forward to having you both by my side as I accomplished this goal and embarked on the next steps of my life.

Thank you both for always believing in me, encouraging me, and reminding me to keep things in perspective. Thank you for being my first inspiration into the power of family in shaping who we become.

Poppop, thank you for encouraging my pursuit of new knowledge and experiences. Thank you for introducing me to new places and ideas and for being my greatest travel partner. Thank you for being my forever field-trip and science fair chaperone. Thank for being a source of stability and comfort when my mom got sick. Thank you for teaching me the healing power of cuddling and a good nap. Without your unconditional love and support (and your occasional tough love), I would not be here today. Thank you for everything.

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AUCg: Area under the curve with respect to ground, a measure of total magnitude of cortisol release

AUCi: Area under the curve with respect to increase, a measure of total change in cortisol

CRF: Corticotrophin release hormone/factor

DMN: Default mode network, a network of brain regions that demonstrate high temporal coherence in the absence of an overt task (i.e., at rest)

dlPFC: Dorsolateral prefrontal cortex

FD: Framewise displacement, a measure of volume-to-volume movement calculated within as the Euclidean distance traveled from the previous volume

MRI: Magnetic Resonance Imaging

Rs-fcMRI: Resting-state functional connectivity Magnetic Resonance Imaging

Chapter 1: Introduction

Decades of research has established that maternal depression is associated with poor offspring outcomes including increased risk for psychopathology, social difficulties, and cognitive deficits beginning in childhood and persisting into the adult years (Cummings & Davies, 1994; Goodman & Gotlib, 1999; Letourneau, Tramonte, & Willms, 2013; Weissman et al., 2006). For instance, compared to the offspring of non-depressed mothers, the offspring of depressed mothers demonstrate higher rates of internalizing and externalizing disorders (Goodman et al., 2011), increased negative and decreased positive affect (Goodman et al., 2011), lower receptive vocabulary and IQ (Jensen, Dumontheil, & Barker, 2014; Letourneau et al., 2013), greater inattentiveness and lower inhibitory control (Jensen et al., 2014; Letourneau et al., 2013), and deficits in social cognition (Jensen et al., 2014). With over 10% of mothers in the United States experiencing a depressive episode each year (Ertel, Rich-Edwards, & Koenen, 2011), the association between maternal depression and negative offspring outcomes poses a significant public health concern.

Identification of the mechanisms through which maternal depression affects child development will enable more targeted interventions and effective strategies for prevention. Unfortunately, at present, the mechanisms of transmission, that is, *how* maternal depression influences offspring outcomes, are poorly understood. Although many have searched for specific hereditary factors, genetic influences have not been able to fully predict the emergence of poor outcomes in high risk offspring (Cummings & Davies, 1994; Flint & Kendler, 2014). This has drawn researchers' focus towards investigations of environmental mechanisms and gene x environment interactions. One

suggested environmental risk factor that has gained attention, and is the focus of this proposal, is the role of parenting in the intergenerational transmission of risk for poor psychosocial outcomes in high risk offspring of depressed mothers.

Maternal Depression and Parenting Behaviors

Parenting has been proposed as a potential environmental risk factor based on observational evidence that maternal depression is associated with maladaptive parenting practices (for review, see Goodman & Gotlib, 1999, 2002; Goodman, 2007; Lovejoy, Graczyk, O'Hare, & Neuman, 2000). For instance, currently depressed mothers demonstrate more hostility, more intrusiveness, and less support and warmth towards their children (Azak & Raeder, 2013; Beeber et al., 2014; Campbell, Matestic, von Stauffenberg, Mohan, & Kirchner, 2007; Goodman, 2007; Lovejoy et al., 2000; Murray, Fiori-Cowley, Hooper, & Cooper, 1996). Depressed mothers have been reported to talk, lay, and play with their children less frequently, with many choosing not to breastfeed, potentially leading to significant reductions in mother-child physical contact during early life (McLearn, Minkovitz, Strobino, Marks, & Hou, 2006). The interactions that do occur are marked by fewer affirmations and more criticisms (Murray et al., 1996). Additionally, depressed mothers are reported to be more disengaged and less responsive to child cues, which may have lasting effects on offspring cognition and emotion (Kiernan & Huerta, 2008). Finally, depressed mothers are less likely to follow routines, resulting in less consistent, structured environments for children (Field, 2010; McLearn et al., 2006).

In contrast to meta-analytic findings, which suggest maternal depression is associated with global deficits in parenting behaviors (i.e., increased negativity, decreased positivity, and increased withdrawal) (Lovejoy et al., 2000), some researchers

have proposed that depressed mothers' parenting deficits may fall into discrete parenting profiles. For instance, Malphurs et al. (1996) proposed depressed mothers may either engage in withdrawn (e.g., low on both positive and negative interactions) or intrusive (e.g., high on negative interactions) interaction styles. Wang and Dix (2013) expanded upon this hypothesis and found that depressed mothers fall under three parenting profiles: high intrusive, high intrusive/high withdrawn, and low intrusive/low withdrawn. The potential utility of these distinctions is highlighted by evidence that the nature of the specific parenting behaviors may have unique effects on the developing child (Field, 1998; for extended discussion, see section on *Parenting Dimensions* below). Despite inconsistent hypotheses regarding the generality or variations of parenting deficits observed in depressed parents, it remains clear that depression can influence the nature, quality, and frequency of a mother's interactions with her children.

Parenting behaviors characterized by increased hostility and decreased warmth are likely attributable to the cognitive-emotional processes implicated in the onset and maintenance of depressive symptoms. For instance, poor emotion regulation and deficits in inhibitory control may contribute to difficulties participating in consistent, responsive parenting practices (Goodman, 2007; Wang & Dix, 2013). Similarly, fatigue and irritability, which are hallmarks of depressive disorders, have been linked to both less positive involvement and increased hostility (Letourneau, Salmani, & Duffett-Leger, 2010; Lovejoy et al., 2000; Murray, Cooper, & Hipwell, 2003). Interestingly, there is evidence that parenting deficits persist even during periods of remission (Hipwell, Goossens, Melhuish, & Kumar, 2000; Lovejoy et al., 2000), supporting the theory that individual personality characteristics such as neuroticism, agreeableness, and

extraversion, may simultaneously influence parenting behaviors and the onset of depressive disorders (McCabe, 2014). Whether through pre-existing personality-dependent cognitive-emotional impairments or as a consequence of the depressive disorder itself, the experience of depressive symptoms is associated with compromised parenting abilities, resulting in more hostile, less warm, and less consistent parenting behaviors, which may be detrimental to overall child development and may play a role in the intergenerational transmission of risk.

Links between maternal depressive symptoms and parenting behaviors have also been identified in rodent species. The rodent analogue of parenting behaviors relies on measuring the frequency of licking and grooming behaviors (LG), where greater frequency is associated with more attentive and nurturing parenting. Although naturally-occurring variations in LG exist (Champagne, Francis, Mar, & Meaney, 2003), making it a valid model for studying individual differences in parenting behaviors on offspring outcomes, there is also evidence that LG may function as a model of maternal depression (Newport, Stowe, & Nemeroff, 2002; Pryce et al., 2005). For instance, rodent genetic models of depression display decreased LG (Lavi-Avnon, Yadid, Overstreet, & Weller, 2005), induction of depressive symptoms via maternal separation results in simultaneous decreases in LG behaviors (Boccia et al., 2007), and experimentally manipulating LG by exogenously administering mothers with glucocorticoids induces impulsive symptoms in adult offspring (Brummelte, Pawluski, & Galea, 2006). Therefore, rodent LG behaviors serve as a useful model for examining the hypothesis that the altered parenting behaviors in maternal depression are associated with offspring outcomes.

Effects of Parenting on Offspring Development

Understanding the links between parenting behaviors and child development has mesmerized academics for millennia (Cline, 2015). After all, it is a concept that has personal relevance to every human being on earth. Review of over a century of parenting research is beyond the scope of the present report, but suffice it to say, parenting behaviors have been linked to a host of child outcomes spanning cognitive, affective, social, and neurobiological domains (Belsky & de Haan, 2011; Borkowski, Ramey, & Brisol-Power, 2002). Despite abounding evidence that the early parenting environment is associated with offspring outcomes, what is of primary importance, here, is understanding *how* parenting affects the developing child.

Before we can begin to address this question, it is necessary to briefly review the available empirical evidence, which enables us to confidently suggest parenting itself, rather than other experiential, contextual, or genetic factors, has specific effects on the developing child. Due to ethical concerns, human research cannot isolate specific effects of parenting through controlled experimental manipulations, forcing researchers to rely on correlational studies and special populations who naturally experience variations in parenting behaviors (e.g., abuse, neglect, institutional rearing, adoption; Belsky & de Haan, 2011; Marceau et al., 2013; McLaughlin et al., 2015). These studies have consistently reported links between extreme variations in early parenting behaviors and later cognitive, affective, social, and neural outcomes (e.g., Cicchetti & Toth, 2005; Kaplan, Pelcovitz, & Labruna, 1999; Trickett & McBride-Chang, 1995). Unfortunately, these methods cannot completely account for all variables confounded with parenting behaviors, such as household income, requiring the much-debated process of statistical

control of confounding variables (i.e., covariates). Therefore, the most compelling evidence has come from animal research.

One of the most elegant designs that directly links parenting behaviors themselves, rather than previously theorized genetic mechanisms, to specific effects on developing offspring used a cross-fostering paradigm to isolate the effects of the postnatal parenting environment on offspring development. Liu and colleagues (2000) cross-fostered the biological offspring of naturally high- or low- LG mothers to dams demonstrating the opposite phenotype. By comparing the adult offspring's behavioral phenotypes to controls, researchers were able to examine the effect of postnatal rearing on offspring development. Analyses revealed adult phenotypes of cross-fostered offspring were better predicted by the phenotype of their postnatal rearing mother than their biological mother. These results indicate that early postnatal parenting behaviors play a specific role in shaping maladaptive offspring behaviors.

Neurobiological Pathways of Parenting

Investigating how the early parenting environment "gets under the skin" (Fox, Levitt, & Nelson, 2010; McEwen, 2012) is paramount to understanding the role of early parenting behaviors in shaping offspring outcomes. Emerging work has focused on the neurobiological pathways through which parenting affects the developing child. The past two decades of carefully-designed rodent research and converging human evidence point to the role of the early parenting environment in the epigenetic programming of the developing hypothalamic-pituitary-adrenal (HPA) axis, an endogenous stress response system preserved across mammalian species.

Hypothalamic-Pituitary-Adrenal (HPA) Axis.

The HPA axis is a regulatory feedback loop, which, as its name suggests, consists of nodes in the hypothalamus, the anterior pituitary, and the adrenal glands. When an organism is presented with a stressor, the amygdala processes the potential threat and disinhibits corticotropin-releasing factor (CRF) release from the paraventricular nucleus (PVN) of the hypothalamus, which stimulates the release of adrenocorticotropic hormone (ACTH) from the anterior pituitary, resulting in the release of the stress hormone cortisol (corticosterone in rodents) from the adrenal glands (Figure 1). Cortisol enables adaptive coping to stressors by regulating key biological systems including blood pressure, immune responses, and conserving energy stores. Circulating cortisol stimulates two receptors, expressed throughout the brain, but in relatively high densities within the hippocampus: the mineralocorticoid receptor (MR) and the glucocorticoid receptor (GR). Activation of hippocampal GRs stimulates a negative feedback loop whereby CRF synthesis is inhibited, thus halting excess cortisol release (Jacobson & Sapolsky, 1991). Thus, the function of a healthy HPA response is heavily dependent on the actions of hippocampal GRs in shutting down the extended release of cortisol. However, with chronic or extreme stressors, the HPA axis can become dysregulated[1], resulting in high

[1] Associations between early parenting and offspring cortisol reactivity are discussed in terms of successful regulatory processes and dysregulation of these systems. It should be noted, however, that the use of "dysregulated" and "maladaptive" are relative terms. That is, the degree to which HPA function can be considered adaptive or regulated is dependent on its influence on the child's healthy psychosocial functioning. From an evolutionary perspective supported by empirical evidence, the changes in HPA function associated with early experiences, both pre- and post-natally, may be the result of adaptive biological processes which have evolved over hundreds of thousands of years. Many hypotheses have been generated which emphasize that what may be adaptive in one context may be maladaptive in another. For example, according to the match-mismatch hypothesis (Oitzl, Champagne, van der Veen, & de Kloet, 2010), although an exaggerated cortisol response may be maladaptive during low-stress cognitive tasks, offspring exposed to early negative parenting behaviors (low LG) fare better under high-stress cognitive challenges in comparison to their high LG counterparts (Champagne et al., 2008). Therefore, under high-stress conditions, high stress reactivity provides offspring with a cognitive advantage; however, under low-stress conditions, the offspring's stress response may not be appropriately matched to the context and

and increasing or blunted cortisol levels in response to stress (Kudielka & Wüst, 2015; Sánchez, Ladd, & Plotsky, 2001).

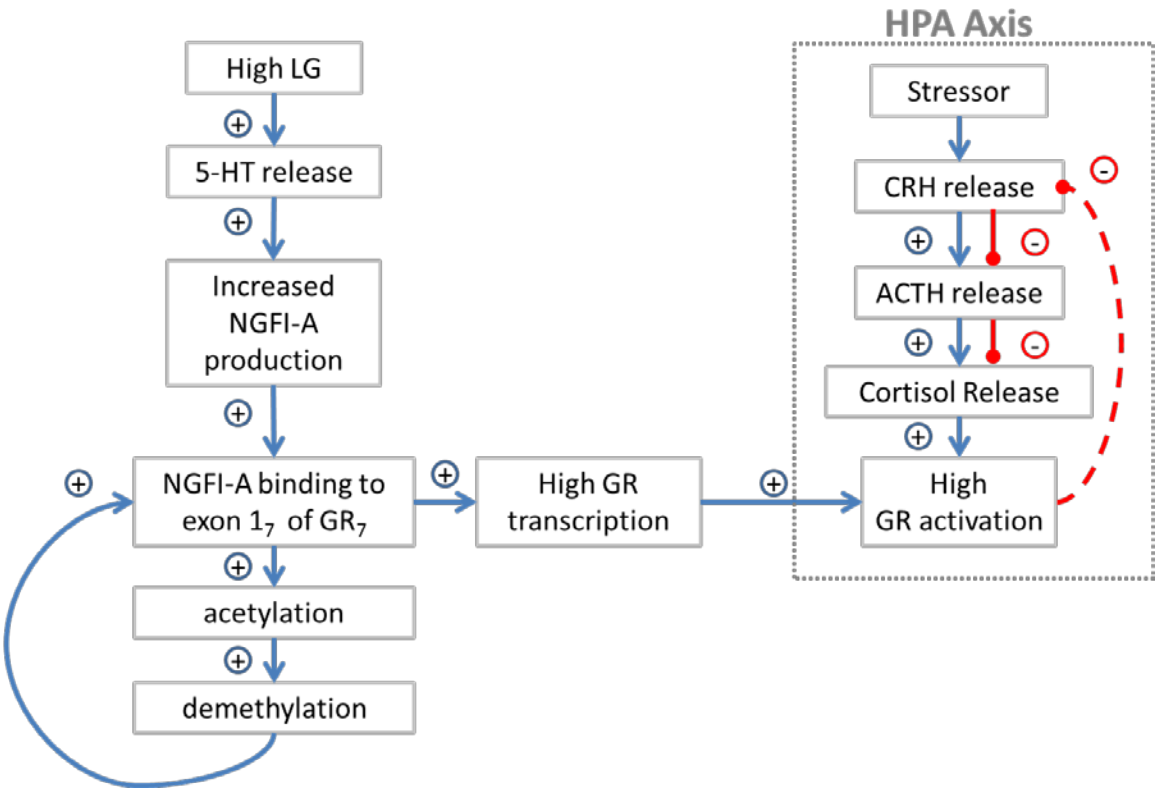


Figure 1. Illustration of the epigenetic pathway through which the early parenting environment (LG behaviors) influences the developing HPA axis. Greater frequency of LG (high LG) leads to the transcription of greater hippocampal GRs enabling more efficient cessation of the HPA response. Low LG offspring lack appropriate hippocampal GR density to effectively stop cortisol release, resulting in high and increasing cortisol levels in response to a stressor. Blue lines represent positive feed-forward or feedback loops. Red lines represent negative feedback or inhibition.

deemed dysregulated. The differential susceptibility hypothesis (Belsky & Pluess, 2009) and the biological sensitivity to context model (Ellis & Boyce, 2008) further suggest that high stress reactivity may be a marker of global plasticity – making an individual both more sensitive to adverse environments and more likely to thrive in supportive environments. Therefore, the degree to which heightened stress reactivity may confer increased risk may be dependent on current contextual demands. Thus, it is important to keep in mind why these systems adapt and that the trends described herein may not be representative of faulty processes per se, but rather the unfortunate situation of having an adaptive biological system being poorly matched, or particularly sensitive, to the current context.

Parenting and HPA Dysregulation

Rodents. Rodent work has demonstrated that the early parenting environment acts to program the developing HPA axis to adaptively respond to stressors. For instance, in their seminal paper, Liu and colleagues (1997) reported that offspring of low LG mothers demonstrated elevated corticosterone levels in response to acute stressors. Similarly, using a cross-fostering paradigm, Barha et al. (2007) reported that natural variations in maternal LG behaviors predicted female offspring corticosterone levels in response to an acute stressor. Moreover, it was found that the tactile stimulation of LG behaviors seems to be the critical factor: when stroked with a soft brush, offspring of low LG mothers have similar stress responses as offspring raised by high LG mothers (Hellstrom, Dhir, Diorio, & Meaney, 2012). Subsequent studies have replicated these results (Weaver et al., 2004), and more importantly, have elucidated the entire biomolecular pathway through which the somatosensory stimulation of LG behaviors program the HPA axis.

Evidence supports that parenting behaviors program the HPA axis through epigenetic mechanisms: processes which act upon the genome (e.g., to alter the functional or structural output of gene transcription), but do not make permanent changes to the DNA (Caldji, Hellstrom, Zhang, Diorio, & Meaney, 2011, for review). Specifically, the tactile stimulation evident in high LG postnatal environments stimulates serotonin (5-HT) release, leading to an increase in nerve growth factor-inducible protein A (NGFI-A) through cyclic adenosine monophosphate (cAMP)-dependent pathways. Increased binding of NGFI-A to the response element of the exon 1_7 promoter region of the GR gene – a gene which codes for glucocorticoid receptors - results in a cascade of acetylation and demethylation. Demethylation increases the affinity of the promoter

region for NGFI-A binding, ultimately resulting in increased gene transcription and a subsequent increase in GRs (Meaney & Szyf, 2005; Weaver et al., 2004). Therefore, increased circulating serotonin in response to tactile stimulation in high LG offspring sets an epigenetic cascade in motion, culminating in an increased density of hippocampal GRs (Weaver et al., 2004, 2007; see Figure 1, left panel). In contrast, low LG offspring do not receive this serotonin influx, which keeps the exon 1_7 methylated throughout development and results in relatively lower levels of GR transcription.

Because of the critical role of hippocampal GRs in shutting down the HPA response to stress (Jacobson & Sapolsky, 1991), relative differences in hippocampal GR transcription among high- and low- LG offspring make them, respectively, more and less capable of regulating an HPA response. Thus, if an individual has lower GR expression in the hippocampus, they have greater feedback control over cortisol release via inhibition of CRF synthesis. Therefore, offspring from nurturing environments (with high GR expression) are better able to shut down their stress response and effectively cope, whereas offspring who receive less warmth and nurturance (with low GR concentrations) demonstrate exaggerated responses to stress marked by elevated and increasing cortisol levels. According to the glucocorticoid cascade hypothesis (Conrad, 2009; Sapolsky, Krey, & McEwen, 1986), disruptions of the HPA axis are perpetuated by a positive feedback loop whereby the amygdala becomes more sensitive to incoming stressors, effectively reducing the threshold for an HPA response which lacks an intact regulatory system, ultimately resulting in poorer hippocampal feedback and increased sensitivity to stress.

Humans. Human evidence has largely replicated the links between the early parenting environment and HPA axis programming, though with somewhat less consistent results. For example, while many have found associations between early maladaptive parenting practices and evidence of hypercortisolism (increased reactivity, higher basal cortisol, increased awakening responses) (Bugental, Martorell, & Barraza, 2003; Ellenbogen & Hodgins, 2009; Kuhlman, Olson, & Lopez-Duran, 2014; Taylor et al., 2013), others have found evidence of hypocortisolism (Engert et al., 2010; Marsman et al., 2012; Narita et al., 2012; Zalewski, Lengua, Kiff, & Fisher, 2012). These inconsistencies may be due to methodological differences such as the method for measuring indices of parenting and HPA axis function as well as the age at which these measurements are taken. For instance, while Taylor et al. (2013) found that observational measures of intrusive-overcontrolling parenting at 30 months predicted increases cortisol reactivity at 72 months, Engert et al. (2010) found that retrospective questionnaire reports of parenting quality (collapsed across dimensions of control and warmth) in adults was associated with decreased cortisol reactivity. Use of different parenting measures (observational versus retrospective self-report) and different ages at cortisol measurement could explain these divergent results. Moreover, there is evidence that acute versus chronic exposure to stressors may differentially influence the developing HPA system, with chronic stress exposure related to lower cortisol levels (Fries, Hesse, Hellhammer, & Hellhammer, 2005; Kudielka & Wüst, 2015). Similarly, each cortisol metric (reactivity, baseline, diurnal slope) reflects a different aspect of HPA functioning and may have unique antecedents, effects, and developmental trajectories. For example, cortisol reactivity has been shown to undergo developmental change, with greater reactivity in

adolescence (Gunnar, Wewerka, Frenn, Long, & Griggs, 2009). Therefore, multiple methodological and developmental factors may contribute to observed inconsistencies in the direction of effects. However, despite these inconsistencies, HPA function has been consistently linked to parenting in human offspring.

Evidence of associations between the early parenting environment and cortisol dysregulation is particularly important given observed links between HPA axis dysfunction and psychopathology. Of critical importance, HPA axis dysregulation is recognized as one of the most consistent biomarkers in depression (Pariante & Lightman, 2008), with evidence of dysregulation in both adults (Varghese & Brown, 2001; Vreeburg et al., 2009) and children (Lopez-Duran et al., 2015; Luby et al., 2003) with depressive disorders, making it a popular index of risk in the parenting and maternal depression literatures. Patterns of HPA axis hyperactivity have been demonstrated in the pre-school aged (Dougherty, Klein, Rose, & Laptook, 2011; Dougherty et al., 2013; Lupien, King, Meaney, & McEwen, 2000) and adolescent (Barry et al., 2014; Halligan, Herbert, Goodyer, & Murray, 2004) offspring of depressed mothers, providing support for the hypothesis that associations between maternal depression and HPA dysregulation may be mediated by parenting behaviors. Interestingly, in two independent samples, Dougherty et al. (2011, 2013) found the combination of maternal depression history and current hostile parenting behaviors was associated with increased cortisol reactivity in preschool-aged children, and this effect was specific to the offspring who were exposed to maternal depression during their life. In contrast, Murray, Halligan, Goodyer, and Herbert (2010) reported postnatal withdrawal behaviors were associated with elevated morning cortisol at 13 years, even when controlling for postnatal maternal depression

exposure. Thus, although maternal depression has been linked to cortisol dysregulation, it remains uncertain how maternal depression status and parenting behaviors influence child outcomes, namely HPA axis function. It has been proposed that the links between HPA axis dysregulation and depressive symptoms and subsequent risk are the result of the effects of excess cortisol on developing neural substrates (Sapolsky, 2000).

Effects of cortisol on the hippocampus

Rodents. The inability to regulate the HPA axis can result in excessive release of cortisol, which has been associated with deleterious effects on neural structure and function (Sapolsky, Uno, Rebert, & Finch, 1990; Sapolsky, 1988; Sapolsky, 1987; Uno et al., 1994; for review see Conrad, 2009). The neurotoxicity hypothesis proposes that elevated levels of circulating glucocorticoids are associated with functional and structural alterations in neural regions that express glucocorticoid receptors (Virgin et al., 1991). Although effects have been found throughout the brain, given the high expression density of GRs in the hippocampus, the majority of rodent research and the attempts at human translations have focused on hippocampal indices. Woolley, Gould, and McEwen (1990) demonstrated glucocorticoid toxicity experimentally by injecting rodents with exogenous doses of glucocorticoids and measuring hippocampal changes. They found decreased dendritic branching, shorter dendritic lengths, and smaller cell bodies in apical CA3 (hippocampal) pyramidal cells. Elevated corticosterone levels have also been associated with a host of other cellular changes within the hippocampus, including: a reduced hippocampal serotonin (5-HT) response (Joëls, Karten, Hesen, & de Kloet, 1997), reduced neurogenesis in the dentate gyrus (Gould & Tanapat, 1999), reduced BDNF expression in the dorsal hippocampus (Liu et al., 2000), and decreased neuronal

complexity in CA1 (Alfarez et al., 2009), with similar trends demonstrated in non-human primates (Uno et al., 1994). It is thought that these effects are not a direct result of glucocorticoids, but instead, excess glucocorticoids make neurons more susceptible to a range of metabolic insults (Sapolsky, 1987).

Humans. Emerging neuroimaging techniques provide a means to translate findings in rodents to human populations and to explore the effects of cortisol on neural structure and function in humans. The majority of studies have assessed associations between HPA axis function and hippocampal structure (for a review see Frodl & O'Keane, 2013). High cortisol levels following the dex/CRH test, higher evening cortisol, and increased morning cortisol have been associated with decreased hippocampal volumes in geriatric populations (Knoops, Gerritsen, van der Graaf, Mali, & Geerlings, 2010; Sudheimer et al., 2014). In contrast, in younger adults, greater cortisol release on the dex/CRH test (Narita et al., 2012), greater cortisol awakening response (Pruessner, Pruessner, Hellhammer, Bruce Pike, & Lupien, 2007; cf Dedovic et al., 2010) and greater cortisol reactivity to a social stressor (Pruessner et al., 2007) were associated with larger hippocampal volumes. In a sample of 7-12 year-old children, morning basal cortisol was not associated with total hippocampal volume, but was associated with regionally-specific inward and outward deformations in lateral and anterior regions of the hippocampus (Wiedenmayer et al., 2006). In a prospective longitudinal sample, early cortisol levels in children ages 3-6 years mediated the associations between both genetic risk (as determined by a genetic profile consisting of genes implicated in depression risk) and early life stress on later hippocampal volumes (7-12 year-olds), where higher cortisol levels were associated with decreased hippocampal volumes (Pagliaccio et al., 2014).

These patterns of results suggest an age-related change in the association between cortisol levels and hippocampal volume, with possible negative associations in childhood and old age and positive associations in mid-life adulthood. Similar anomalous findings in young adults have been demonstrated in associations between depression status and hippocampal volumes. For instance, children and middle-aged and older adults with depressive disorders demonstrated decreased hippocampal volumes whereas young adults showed no volume reduction (for a review see McKinnon, Yucel, Nazarov, & MacQueen, 2009). Thus, it is possible that glucocorticoids exert differential effects on neural substrates at different points in development (see *Considerations* section for extended discussion of Developmental Timing). Additionally, discrepancies in these studies may be attributable to sample demographics and selection criteria or sample size. For instance, Narita et al. (2012) excluded participants who demonstrated an elevated cortisol response on the dex/CRH test and Pagliaccio et al. (2014) used a sample of children in which 75% had a psychiatric diagnosis at the time of scanning.

Most recently, studies have utilized resting-state functional connectivity metrics to explore associations between hippocampal function and HPA activity. The resting-state functional connectivity magnetic resonance imaging (rs-fcMRI) method measures the coherence of spontaneous low-frequency oscillations in brain activity while an individual lies passively in the scanner. It is based on evidence that regions of the brain that are highly correlated at rest have a history of co-activation in task (Biswal, Yetkin, Haughton, & Hyde, 1995). In this way, the resting-state method allows for measurement of neural networks in the absence of an explicit task. Functional associations are expected given evidence from rodent models that cortisol causes alterations in dendritic arbors, the

site of long range connections, and reduces hippocampal long-term potentiation (Pavlides, Watanabe, & McEwen, 1993; Woolley et al., 1990). Moreover, because biological structure often dictate function, observations of altered hippocampal structure will likely be preceded by or follow functional changes. For example, in a sample of 7-15 year-olds, Thomason, Tocco, Quednau, Bedway, and Carré (2013) reported greater cortisol reactivity at the time of scanning was associated with greater hippocampal resting-state connectivity with the default mode network (DMN), a network of distributed brain regions involved in the baseline processes of the resting brain (Greicius, Krasnow, Reiss, & Menon, 2003) which has been implicated in the pathophysiology of depressive disorders (Hamilton et al., 2011; Marchetti, Koster, Sonuga-Barke, & De Raedt, 2012; Sheline et al., 2009). In contrast, in a sample of young adults, cortisol reactivity in response to a social stressor was not associated with hippocampal connectivity within the DMN (Sripada, Swain, Evans, Welsh, & Liberzon, 2014), perhaps mirroring the age-related results seen in structural studies. Additionally, in a small sample of young adult males, Kiem et al. (2013) found greater cortisol levels in response to the dex/CRH test (signaling cortisol hypersecretion) predicted lower left to right hippocampal connectivity, suggesting that hippocampal hemispheric asynchrony is associated with dysregulated HPA function. Together, these results suggest cortisol levels are associated with hippocampal functional connections throughout the brain, which likely influence information processing.

Parenting and the Hippocampus

As reviewed above, the rodent literature has characterized the pathway from early parenting to hippocampal alterations through HPA dysregulation. For example, Liu et al.

(1997) demonstrated that the early parenting environment altered the HPA response to stress and subsequent protein expression in the hippocampus. Additionally, high LG behaviors have been linked to increased hippocampal cholinergic innervation, NMDA receptor expression, and BDNF mRNA (Liu et al., 2000). Similarly, Champagne et al. (2008) demonstrated low LG behaviors were linked to shorter dendritic branches, small spine density, and reduced LTP in CA1 under basal conditions. However, to date, human examinations of the link between parenting and neural development are only emerging.

In a recent review of the extant literature linking the early parenting environment to neural development in humans, Belsky and deHaan (2011) concluded that the majority of pre-existing human literature has exclusively focused on extreme forms of parenting such as maltreatment and neglect. Unsurprisingly, these studies largely replicate the rodent literature – with many reports of early physical and sexual abuse linked to hippocampal volume reductions in adulthood. For example, Teicher, Anderson, and Polcari (2012) found that childhood maltreatment was associated with volumetric reductions in adult hippocampal subfields (CA3, dentate gyrus, subiculum). Similarly, Stein, Koverola, Hanna, Torchia, and McClarty (1997) found that women who experienced sexual abuse had 5% hippocampal volume reductions in comparison to never-abused controls. Early maltreatment has also been associated with hippocampal functional deficits in emotion processing and olfaction (for review of neurofunctional deficits in maltreatment, see Hart & Rubia, 2012). For example, 9-18 year-old children exposed to deprivation and emotional neglect displayed greater hippocampal responses to fearful and angry faces (Maheu et al., 2010). It has been widely speculated that these hippocampal changes emerge as a result of glucocorticoid toxicity (Sapolsky, 2000).

Despite overwhelming behavioral evidence on the effects of individual differences in parenting on offspring development, to date, little efforts have been made towards elucidating the neurodevelopmental effects of less severe parenting practices.

In the past few years, Belsky and de Haan's call has been met with attempts to characterize the effects of individual differences in parenting on neural development; however, results have been equivocal. For instance, Rao et al. (2010) reported greater maternal nurturance at age 4 predicted smaller hippocampal volume in adolescence. In contrast, Luby et al. (2012) reported greater maternal support in early childhood (3-6 years) was associated with larger hippocampal volume at school age (4-7 years). Narita et al. (2012) did not find an association between retrospective perceived parenting (collapsed across overprotection and care) and hippocampal gray matter volume in adults, despite finding a positive association between parenting and cortisol. Similarly, Whittle and colleagues (2014) reported that the frequency of positive maternal behaviors during a conflict interaction at age 12 was not associated with hippocampal volumes at age 16. There are no straightforward interpretations of these data, but many factors may contribute to divergent findings (see *Considerations* for extended discussion). For instance, Luby et al. (2012) oversampled children with pediatric depression, Whittle et al. (2014) measured parenting behaviors relatively late in development (12 years), Narita et al. (2012) excluded participants who demonstrated hypercortisolism on the dex/CRH test, and Rao et al. (2011) used a sample which included children exposed to drugs prenatally. To date, no research has examined the effects of early parenting on hippocampal task-based or resting-state function beyond what has been found in the maltreatment literature.

Together, these methodological differences make it difficult to form firm conclusions from the available evidence.

Depression Risk and the Hippocampus

HPA axis dysregulation has been identified as one of the most consistent biomarkers and risk factors for depressive disorders (Pariante & Lightman, 2008; Varghese & Brown, 2001; Vreeburg et al., 2009) and has been considered to be the source of hippocampal volume reductions commonly found in depressed adults (Campbell, Marriott, & Macqueen, 2004; Sapolsky, 2000). Similar evidence of hippocampal volume reductions have been reported in depressed adolescent populations (Chen, 2010; MacMaster & Kusumakar, 2004); however, investigations in pediatric samples are more rare and less consistent (Hulvershorn, Cullen, & Anand, 2011). In adults, volume reductions are associated with illness duration (McKinnon et al., 2009) and have been reversed with antidepressant treatment in humans (Arnone et al., 2013) and rodents (Malberg, Eisch, Nestler, & Duman, 2000) providing support for the notion that hippocampal changes are associated with depressive disorders and are possibly attributable to extended exposure to glucocorticoids (Sapolsky et al., 1990).

Many researchers have moved towards neurocircuitry models of depression (Drevets, Price, & Furey, 2008; Hamilton et al., 2011; Peng et al., 2014; Price & Drevets, 2010; Wang, Hermens, Hickie, & Lagopoulos, 2012; Wang et al., 2015; Zeng et al., 2012), with an emphasis on dysregulated connectivity in large scale brain networks. For instance, Zeng et al. (2012) found that multivariate pattern analysis could reliably discriminate adults with depression based on patterns of resting-state functional connectivity. The authors concluded that given its high discriminative power, the

hippocampus likely plays a role in the pathophysiology of depressive disorders. McCabe and Mishor (2011) reported that hippocampal connectivity with the dorsomedial prefrontal cortex (DMPFC) was reduced with antidepressant treatment, perhaps suggesting that heightened connectivity may be a neural basis of depressive symptoms. Hippocampal connectivity findings have been reported in adolescents with depression, with reduced amygdala-hippocampal connectivity associated with greater depressive symptoms, dysphoria, and lassitude (Cullen et al., 2014). Additional evidence suggests depressed adolescents demonstrate increased connectivity, relative to controls, between the subgenual anterior cingulate cortex (sgACC) to a functional region encompassing the amygdala and extending into the hippocampus and parahippocampal gyrus (Connolly et al., 2013) . To our knowledge, no studies have used rs-fcMRI to examine pediatric depression in children younger than 13 years-old.

Of relevance to the association between parenting and hippocampal development is a separate body of literature examining maternal depression and hippocampal development. If we accept the hypothesis that maternal depression alters parenting behaviors, the maternal depression literature may contribute to our understanding of the associations between early parenting experiences and hippocampal development (for review, see Foland-ross, Hardin, & Gotlib, 2013). Consistent with depressed adults, adolescents, and children, high familial risk for depression is associated with reduced hippocampal volumes during childhood (Chen, Hamilton, & Gotlib, 2010; Rao et al., 2010), though this finding is inconsistent, with some reporting null associations between maternal depression and offspring hippocampal volume (Lupien et al., 2011). Similarly, never-depressed adult siblings (Baaré et al., 2010) and first-order relatives (Amico et al.,

2011) of depressed individuals demonstrated decreased hippocampal volumes, suggesting that reduced hippocampal volumes may be a risk factor for depression, rather than a byproduct of depressive disorders. Men exposed to moderate levels of maternal depressive symptoms during development demonstrated increased amygdala to hippocampal ratio volumes (Gilliam et al., 2014). This increased amygdala volume coupled with decreased hippocampal volume is consistent with the glucocorticoid cascade hypothesis, which proposes that an epigenetic cascade results in increasingly larger and hyperactive amygdalae and increasingly smaller and hypoactive hippocampi (Lupien, McEwen, Gunnar, & Heim, 2009). Finally, de Geus et al. (2007) found that monozygotic twins who had differing risk for depression and anxiety (based on personality questionnaire metrics) showed differences in hippocampal volume, with the high-risk twin demonstrating reduced posterior hippocampal volume. Because differences in risk are presumably due to environmental versus genetic factors in the twin study design, the authors concluded that observed hippocampal differences were likely induced by experience rather than genetic factors. Despite the existence of some null associations (e.g., Lupien et al., 2011), the majority of evidence suggests that having familial risk for depression is linked to reduced hippocampal volumes, though it remains unclear whether these effects are induced by genetic predispositions or environmental factors (such as exposure to maladaptive parenting practices). To date, task-based fMRI investigations in high-risk offspring have focused on emotion regulation (Joormann, Cooney, Henry, & Gotlib, 2012) and reward processing (Henry & Joormann, 2010; Kujawa, Proudfit, & Klein, 2014; Olino et al., 2013; Sharp et al., 2014) in adolescent

populations. However, no fMRI studies have examined tasks-based or resting-state hippocampal function in high-risk offspring.

Considerations

As highlighted above, in comparison to the rodent literature, human research is riddled with many inconsistencies regarding the direction of effects: in some cases early parenting behaviors are associated with high and increasing cortisol responses (Bugental et al., 2003; Ellenbogen & Hodgins, 2009; Kuhlman et al., 2014; Taylor et al., 2013) and in others they are associated with low and blunted responses (Engert et al., 2010; Marsman et al., 2012; Narita et al., 2012; Zalewski et al., 2012); similarly, in some situations the early parenting environment is associated with increased hippocampal volumes (Luby et al., 2012) and in others it is associated with reduced volumes (Rao et al., 2010); moreover, cortisol levels have been linked to increased (e.g., Pruessner et al., 2007), decreased (e.g., Knoops et al., 2010), or unchanged hippocampal volumes (e.g., Kremen et al., 2010). Two factors that may account for these divergent findings are *Developmental Timing* and *Parenting Dimensions*.

Developmental Timing

Perhaps the most important factor to consider is the effect of timing on neural development. Failure to account for timing, both in terms of the timing of early experiences and in the timing of cortisol and hippocampal measurements, likely accounts for many of the inconsistencies in the literature reviewed above.

Wiesel & Hubel (1965) were the first to establish that sensitive periods, phases during which neural substrates are more sensitive to certain modalities of sensory information, exist throughout development. Decades of research have replicated this

finding in different sensory systems, in different species, and in different neural regions (for a review see Knudsen, 2004). Sensitive periods are likely induced by periods of neurodevelopmental plasticity during which discrete brain regions may be more susceptible to both positive and negative experiences. That is to say, regions that are undergoing rapid neurodevelopmental change may be the most susceptible to the effects of environmental inputs. This is important to consider in the present investigation in light of evidence that the hippocampus is undergoing structural (Demaster, Pathman, Lee, & Ghetti, 2014) and functional maturation (Blankenship, Redcay, Dougherty, & Riggins, 2016) during early childhood. Many sources of research suggest sensitive periods and developmental timing are especially relevant to the investigation of the effects of early experience on the epigenetic programming of the HPA axis and the developing hippocampus (Sánchez et al., 2001; Tottenham & Sheridan, 2009). For instance, in a rodent model, offspring separated from their mothers at postnatal day 3 exhibited HPA axis *hyper*responsivness to stressors whereas offspring separated at postnatal day 11 demonstrated HPA axis *hypo*responsiveness (van Oers, de Kloet, & Levine, 1997). This evidence has strong implications for inconsistencies in the human literature regarding whether adverse parenting is associated with an increased or decreased cortisol response. In a human sample of institutionalized Romanian children, a context characterized by low quality of caregiving, only those children who were placed into foster care (i.e., improved caregiving environment) before 24 months showed normative HPA axis function in response to a social stressor (McLaughlin et al., 2015), suggesting a sensitive period during which the caregiving environment has maximal effects on the development of the stress response system. This finding is consistent with additional lines of research, which

indicate the effects of maternal depression on offspring cortisol function and behavior are specific to exposure during early development (Barry et al., 2014; Brennan, Pargas, Walker, Green, & Newport, 2008; Dougherty et al., 2013). The maltreatment literature has mirrored these effects, with reports of abuse occurring between 3-5 years associated with adult hippocampal volume reductions; however, when abuse occurred between 14-15 years, adults displayed no differences in hippocampal volume, but demonstrated decreased frontal gray matter volumes (Andersen et al., 2008), suggesting early childhood may be a period of hippocampal sensitivity to adverse experience. Together, this evidence highlights that consideration of the timing of early experiences may have drastic effects on predicted outcomes.

Additionally, the timing of measurement may influence experimental results and conclusions. One of the most surprising findings from the maltreatment literature is that despite consistent findings of hippocampal volume reductions in adults who experienced childhood trauma, little evidence exists to suggest this volumetric reduction is evident during childhood (for review, see Frodl & O'Keane, 2013). This finding converges with evidence from the depression literature which reports hippocampal reductions more consistently in adults with depressive disorders than children (Hulvershorn, Cullen, & Anand, 2011 cf. Campbell et al., 2004). Three possible, though not mutually-exclusive, explanations for this finding are outlined below. First, these findings may be a consequence of the limitations of human neuroimaging methods. It is possible that early differences exist, but current neuroimaging methods do not have the resolution to capture subtle volumetric differences, especially in small high-risk child and adolescent populations. Second, the volumetric reductions reported in depressive disorders and in

association with dysregulated HPA responses may emerge as a consequence of the cumulative exposure to elevated glucocorticoid levels across development. Therefore, it is only after decades of exposure that reductions emerge. Finally, the emergence of hippocampal volume reductions later in development may be explained by sleeper effects (Maurer, Mondloch, & Lewis, 2007), whereby observable effects emerge after prolonged delays. Evidence for this latter hypothesis comes from Andersen and Teicher (2004) who found that maternal separation in rat pups had a delayed effect on hippocampal structure in comparison to non-separated controls. Specifically, synaptic density was equivalent to non-separated controls until day 35, at which point, CA1 and CA3 densities dropped more than ~30% that which was observed in control animals. In addition, in a recent review, Tottenham and Sheridan (2009) concluded that the effects of early life stressors are more immediately observable in the amygdala whereas hippocampal changes may be more protracted. Similar concerns of measurement timing may be relevant to cortisol metrics, as cortisol reactivity responses appear to change across development with the greatest increase occurring in adolescence (Gunnar et al., 2009). In sum, the timing of hippocampal and cortisol measurements may influence the interpretation of results in the extant literature. Therefore, it is important to consider both the timing of the adverse experience as well as the timing of measurements within its developmental context. Null findings should be interpreted with caution, as failure to find an association does not necessarily indicate that associations do not exist, but rather that associations may not exist *yet*.

Parenting Dimensions

As noted above, there is evidence that the parenting deficits induced by maternal depression may present in two ways: as increased hostility and intrusiveness or as decreased warmth and withdrawal. Important to note, these behaviors may not exist on opposite ends of a continuum (i.e., lack of warmth does not imply high hostility), and rather, may represent two orthogonal dimensions or parenting behaviors. The importance of this theoretical distinction is highlighted by a recent proposal by Sheridan and McLaughlin (2014; McLaughlin, Sheridan, & Lambert, 2014), which hypothesizes that the neurocognitive effects of early adversity can be best explained when the nature of the adverse experiences are classified along the dimensions of deprivation and threat. Similarly, Field (1998) reported maternal withdrawal and negative control are associated with unique and divergent child outcomes. This theory highlights how the absence of expectable positive inputs (e.g., maternal warmth, support) can have drastically different effects on a developing child than the presence of harmful stimulation (e.g., maternal hostility). Failure to recognize and account for these dimensions may contribute to inconsistencies in the literature. For example, Engert et al. (2010) collapsed across warmth and control dimensions and found reduced cortisol reactivity whereas Taylor et al. (2013) exclusively examined overcontrolling-intrusive parenting behaviors and found increased cortisol reactivity. Therefore, operationalization of parenting behaviors should be carefully considered, as these may have significant effects on observed outcomes.

Literature Summary

- Maternal depression is associated with multiple negative offspring outcomes.
- Depressed mothers demonstrate impaired parenting practices.

- The effects of parenting on offspring's developing stress response system and the downstream effects on neural architecture have been clearly defined in the animal literature, with consistent effects documented in the hippocampus.
- Emerging evidence suggests similar patterns of effects observed in animal models may also be present in human populations, particularly with respect to linking parenting and maternal depression to offspring's HPA axis function and hippocampal structure.
- Moreover, similar neuroendocrine and hippocampal differences are evident in depressed adults, providing support for the hypothesis that these neurobiological factors may put an individual at increased risk for poor outcomes.
- Neuroimaging investigations are beginning to address these associations in young human populations; however many gaps remain.

Gaps in the Literature

Despite rapid advances in the examination of the effects of parenting on brain development, major gaps in our knowledge remain. First, although studies have examined pairwise comparisons between parenting, neuroendocrine functioning, and brain structure in a piecemeal fashion, no study has examined the full model in a young longitudinal population. Therefore, the interconnectedness of all variables within a single human sample is currently unknown. This marks a clear deficit in directly translating the animal literature to human populations.

Second, investigations of the effects of individual differences in negative parenting behaviors on the offspring's brain is only emerging – most pre-existing literature has focused solely on extreme versions of parenting including abuse and

neglect. With an entire body of rodent literature and an emerging human literature suggesting variations in parenting behavior are associated with child neurobiological functioning, this critical gap demands addressing.

Finally, and critically, no study to date has used a multimodal imaging approach to investigate associations between the early parenting environment and hippocampal development. The majority of studies have used metrics of hippocampal volume to characterize the neural effects of maternal depression, parenting, and HPA dysregulation; however, it remains difficult to interpret inconsistencies between studies due to variability in populations (e.g., pediatric depression, prenatal drug exposure), timing of measurements (e.g., adolescence, adulthood), and independent measures (e.g., cortisol reactivity vs. basal cortisol; maternal hostility vs. low maternal warmth). Replications are necessary to help elucidate mechanisms and trends, which are currently obscured in the extant human literature.

Although structural data provide important insight into gross neural changes, as briefly discussed above, due to constraints on the resolution of the technology or the timing of the emergence of structural changes, structural imaging techniques may not capture early-emerging differences. Moreover, given the reciprocal nature of biological structure-function relationships, it is likely that functional changes may emerge before and may even drive the emergence of gross morphological changes, making the use of functional imaging methods critical to the investigation of the effects of the early parenting environment and cortisol reactivity on the developing hippocampus. Task-based paradigms are the most popular method of measuring functional brain differences; however, this method has a number of limitations, which make it poorly equipped to

address the aims of the present proposal. First, task-based investigations require targeted hypotheses regarding specific cognitive processes. For instance, a task-based paradigm would be well-suited for research motivated by the hypothesis that episodic memory performance is impaired in individuals with a history of maltreatment. In this way, researchers can design a task aimed to engage episodic memory and compare neural activation between maltreated individuals and controls. However, this method fails in the absence of a directed hypothesis regarding a cognitive process. Second, differences in neural activation elicited from task-based studies are constrained by the specifics of the experimental paradigm. For instance, in an episodic memory paradigm, the nature of the stimuli presented (e.g., auditory vs visual) may differentially influence the evoked neural response, making comparisons between studies more challenging. Finally, of particular concern in high-risk samples, performance on a given task and the neural responses which are elicited may be confounded by factors associated with an individual's risk status. For example, in offspring of depressed mothers, deficits in executive function (Hughes, Roman, Hart, & Ensor, 2013) may induce attentional difficulties which alter task performance and patterns of neural activation between groups. This may lead researchers to incorrectly conclude that fundamental differences in episodic memory exist.

One method for circumventing the challenges and limitations imposed by task-based analyses is resting-state functional connectivity MRI (rs-fcMRI). Rs-fcMRI allows participants to lie passively in a scanner while functional imaging data are collected. This method reduces the cognitive demands placed on the child and mitigates potential effects of executive functioning on performance (though, it should be noted, differences in

executive function may influence a child's ability to remain motionless in the scanner, thus still influencing experimental results), making it a method well-suited for investigations in young children. The greatest strength of rs-fcMRI is that it enables examination of task-independent whole-brain functional connectivity. Instead of being limited to examining hippocampal function within an experimental context, as in task-based studies, rs-fcMRI allows examination of the full range of hippocampal connections spanning the many cognitive processes that engage the hippocampus (e.g., HPA regulation, episodic memory, fear learning, and spatial navigation). Therefore, resting-state functional connectivity may unveil altered functional connections that may represent early biomarkers for disrupted cognitive processes. For example, increased hippocampal connectivity with the amygdala may signal an early marker of heightened attention to and memory for affectively-charged information, a cognitive bias which has been documented in individuals with (Disner, Beevers, Haigh, & Beck, 2011) and at risk for (Joormann, Talbot, & Gotlib, 2007) depressive disorders. Identifying these regions of differing connectivity in rs-fcMRI may stimulate hypotheses best tested in a task-based approach, providing complementary indices of neural function. In this way, resting-state MRI is a more appropriate method when wide-spread context-independent neural activity is of interest, whereas task-based imaging is most fruitful when the approach is motivated by a specific cognitive deficit. Because no study, to date, has examined hippocampal function in a young high-risk sample, inclusion of rs-fcMRI will fill a prominent gap in the literature and expand upon pre-existing structural findings. This multi-method approach is critical to fully capturing the neurobiological effects of the early parenting environment on offspring hippocampal development as it may provide greater sensitivity

to early-emerging hippocampal changes as well as provide insight into the neural basis of later cognitive, affective, and behavioral difficulties.

Chapter 2: Study Overview

The present proposal seeks to address the current gaps in the literature with an overarching aim of investigating the association between parenting and cortisol reactivity on hippocampal structure and function in a high risk longitudinal sample of offspring of depressed mothers and a non-depressed comparison group drawn from the same community. Oversampling for mothers with a lifetime history of depressive disorders provides greater variability in predictor (e.g., parenting, cortisol) and outcome (e.g., hippocampal structure and function) variables in the present design. At Time 1, parents and their preschool-aged children (ages 3-6 years) completed an observational assessment of parenting, and children were exposed to a laboratory-based, standardized stressor paradigm during which five salivary cortisol levels were collected to assess early cortisol reactivity. Approximately three years later (Time 2) when children were 5-10 years-old, children completed another battery of parent-child interaction tasks, a new laboratory stressor, and a neuroimaging assessment during which structural MRI and resting state functional MRI data were collected (Figure 2).

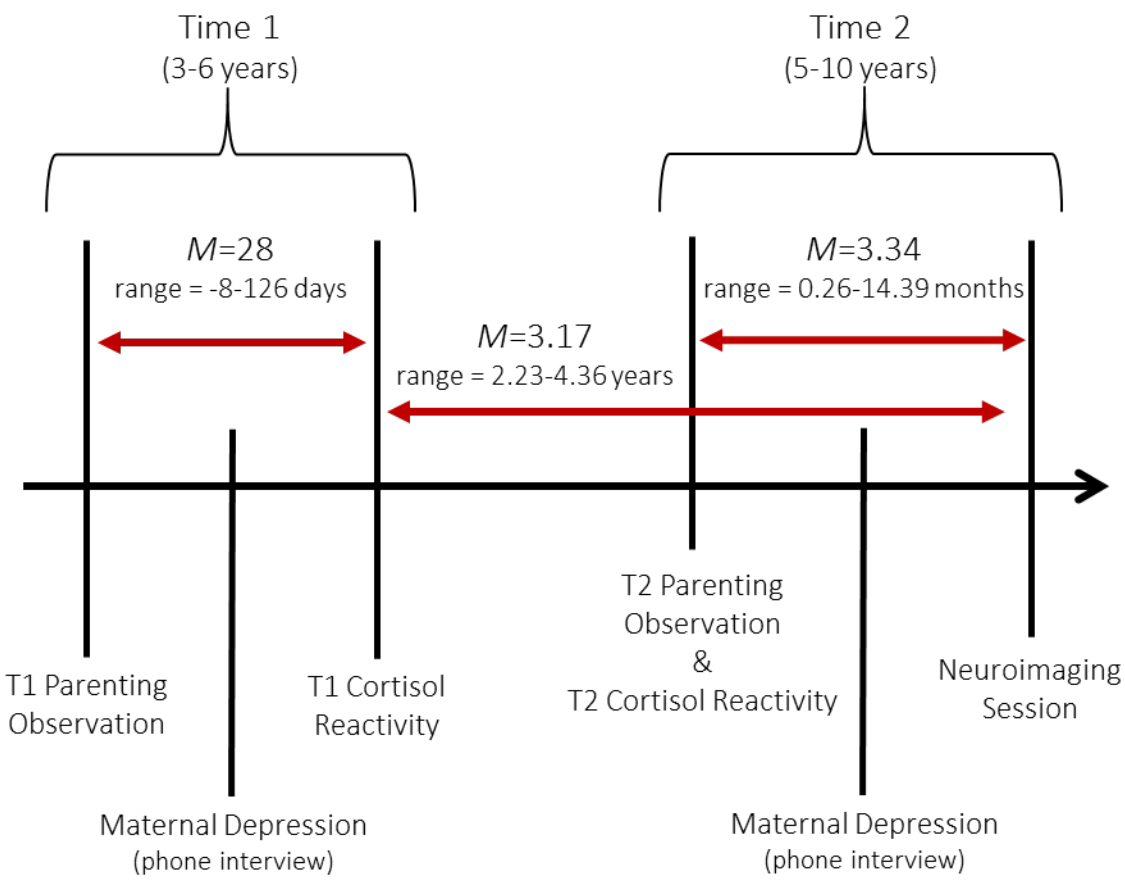


Figure 2. Study timeline.

Prospective Design

The present proposal aimed to investigate the association between early (3-6 years) and concurrent (5-10 years) parenting and cortisol reactivity on later hippocampal development (5-10 years). A prospective longitudinal approach was chosen based on the likely contribution of timing to observed hippocampal effects. The extant literature suggests that the hippocampus may be differentially susceptible to stressors at different developmental times (Tottenham & Sheridan, 2009). In particular, the maltreatment literature suggests childhood (3-5 years) may be a period when the hippocampus is particularly sensitive to the effects of environmental stressors (Andersen et al., 2008). If we are to assume that the parenting environment may serve as an early life stressor or represent a sensitive period whereby hippocampal development relies on expectable inputs from the parenting environment, it remains that 3-6 years may be the optimal time to assess the prevalence of these stressors in a child's life. Thus, our measurements of parenting and cortisol in preschool-aged children represent a time when the parenting environment and excess glucocorticoids may have the most pronounced effects on the developing hippocampus. Moreover, the effects of these early insults may only be manifest as volumetric reductions when measured at points later in development (Andersen & Teicher, 2004). Therefore, measurements of hippocampal volume 3 years after the hypothesized stressor (at 5-10 years-old) may enable greater sensitivity than studies that have used concomitant measures of stress and hippocampal volume. Finally, by including measurements of early (3-6 years) and later (5-10 years) parenting and cortisol reactivity, we can begin to piece apart the timing-dependent nature of these factors on hippocampal structure and function during middle to late childhood (5-10

years). Therefore, the present sample is optimized for measuring the effects of early stressors at a proposed point of peak hippocampal sensitivity as well as for measuring hippocampal indices at a later developmental period.

Chapter 3: Aims & Significance

Aim 1: Examine the timing-dependent associations between early (3-5 years) and concurrent (5-10 years) parenting on hippocampal volume and functional connectivity at 5-10 years (Figure 3).

Working Hypothesis: Early (3-5 years), but not concurrent (5-10 years), maladaptive parenting (high hostility, low warmth) will be associated with smaller hippocampal volumes and differences in hippocampal functional connectivity at school age (5-10 years). This hypothesis is driven by evidence of volume reductions in maltreated children, individuals with depressive disorders, and animal work suggesting early parenting deficits are associated with hippocampal volume reductions. Early, but not concurrent, associations are hypothesized given evidence of a possible sensitive period in hippocampal development that occurs between 3-5 years of age (Andersen et al., 2008). Due to the relative dearth of literature examining the association between parenting on hippocampal structure and function in humans, a priori region of interest (ROI) analyses are not possible. Drawing from literature on early life stress (McLaughlin et al., 2014) and depressed adults, it is possible altered connectivity will be evident between the hippocampus and nodes of the fear learning and reward circuits, the default mode network, and regions involved in episodic memory.

Aim 2: Examine the timing-dependent associations between early (3-6 years) and concurrent (5-10 years) cortisol reactivity on hippocampal volume and functional connectivity at 5-10 years (Figure 3).

Working Hypothesis: Greater early (3-6 years) and concurrent (5-10 years) cortisol reactivity 3-6 will be associated with smaller hippocampal volumes and

differences in hippocampal functional connectivity at school age (5-10 years). It is hypothesized that more elevated levels of cortisol in response to a stressor will be associated with neurotoxic effects associated with extreme levels of circulating glucocorticoids as evidenced in the rodent literature (Sapolsky, Krey, & McEwen, 1985). Because individual differences in cortisol have been linked to concurrent changes in neural functioning (e.g., Kiem et al., 2013), a timing-dependent effect is not hypothesized. A longitudinal association is predicted given evidence that detectable hippocampal morphologic changes emerge after prolonged exposure to glucocorticoids (for extended discussion, see *Timing*). Glucocorticoid effects have been linked to the prefrontal cortex, orbitofrontal cortex, and amygdala, making these viable structures to demonstrate altered hippocampal connectivity.

Aim 3: Test the full mediation model examining whether cortisol reactivity mediates the association between parenting and hippocampal structure and function (ages 5-10 years) (Figure 3).

Working Hypothesis: Early cortisol reactivity will mediate the association between early parenting and school age hippocampal structure and function, with maladaptive parenting predicting increased cortisol reactivity and smaller hippocampal volumes and altered connectivity. This aim seeks to test the full pathway, as demonstrated in the rodent literature, whereby parenting causes HPA Axis dysregulation and hippocampal atrophy. Only partial mediation is expected in light of evidence that maternal depression status (Dougherty et al., 2011) and genetics (Dougherty, Klein, Congdon, Canli, & Hayden, 2010; Hayden et al., 2010), as well as other factors, may moderate these hypothesized associations.

Exploratory Aim: Explore the role of maternal depression status on associations between parenting and children's cortisol reactivity and hippocampal structure and function.

The present proposal aims to elucidate the mechanisms through which maternal depression may confer increased risk for developing children with an emphasis on the role of the early parenting environment. The sample used in the present study was over-selected for mothers with a history of depression, with 60.3% of mothers in the imaging subsample with a lifetime history of depressive disorders, which affords us the ability to study a range of parenting behaviors on cortisol reactivity and hippocampal indices. However, the role of maternal depression on the hypothesized associations in Aims 1-3 is unknown. Some research suggests maternal depression may moderate the association between parenting and offspring cortisol (Dougherty et al., 2013, 2011), whereas others have proposed parenting may mediate the association between maternal depression and offspring cortisol reactivity (Murray et al., 2010). Although there are numerous ways maternal depression could be hypothesized to influence observed associations, due to limitations of low power, the purpose of this aim is to explore the role maternal depression may play in moderating the associations between parenting and cortisol reactivity with hippocampal structure and functional connectivity. In offspring of depressed mothers, the effects of parenting and cortisol reactivity on hippocampal volume and functional connectivity are hypothesized to resemble hippocampal structural and functional changes observed in depressed adults.

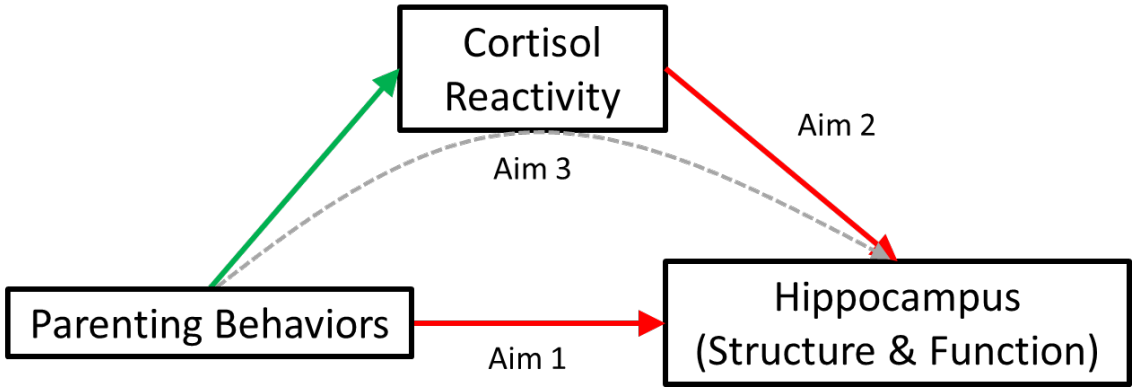


Figure 3. Theoretical model. Solid lines demonstrate the hypothesized model. Gray dashed line represents the full mediation model tested in Aim 3. Green lines represent hypothesized positive associations. Red line represent hypothesized negative associations.

Significance

The present research provides multiple novel and significant contributions to the literature. First, the present research strategy aims to translate our understanding of the effects of parenting and the HPA axis on neural development gained from rodent research to the examination of human development. In particular, despite piecemeal associations between each factor within the model (e.g., HPA axis, parenting, hippocampal development; Figure 3), no study, to date, has examined the full model in a young sample. Second, the longitudinal nature of the sample is well-suited to answer these questions. Given what we know about the timing effects of stress and the hippocampus in humans, the present research is well-equipped to answer questions about longitudinal associations between parenting and cortisol reactivity with brain development. Third, the present study has a larger sample of children than most other human neuroimaging work investigating the effects of parenting on brain development, providing increased power to detect neural effects. Fourth, the present study can examine associations with multiple

parenting dimensions. Most previous work has combined parenting behaviors into a single factor encompassing dimensions of deprivation (i.e., decreased warmth) and threat (i.e., increased hostility). Finally, and critically, the present proposal demonstrates the first attempt to examine the effects of the early parenting environment and cortisol reactivity on hippocampal functional connectivity. This is a critical contribution to the literature as functional differences may be detectable before structural differences. Additionally, examination of alterations in functional connectivity may provide greater insight into neural sources underlying the cognitive, behavioral, and affective deficits associated with exposure to early negative parenting practices.

Chapter 4: Methods

The present analyses were performed on a subset of children (*n's*=41-59) from a longitudinal dataset (*N*=175) of high-risk offspring of depressed mothers and a non-depressed community comparison group (see Dougherty et al., 2013 for a full description of the sample). At Time 1, children and their parents completed two laboratory behavioral sessions and a phone interview (see Figure 2 for the study timeline). At Time 2, children and their parents completed one behavioral visit during which parenting and cortisol reactivity data were collected, followed by a neuroimaging session at the Maryland Neuroimaging Center (MNC). Sample sizes vary for each analysis, as some children did not provide data on all measures (Table 1).

Table 1
Sample sizes (n) for functional and structural analyses.

Hippocampal Volume Analyses									
		1	2	3	4	5	6	7	8
1.	T1 Parenting	60	-	-	-	-	-	-	-
2.	T2 Parenting	59	59	-	-	-	-	-	-
3.	T1 & T2 Parenting	59	59	59	-	-	-	-	-
4.	T1 Cortisol Reactivity	56	55	55	59	-	-	-	-
5.	T2 Cortisol Reactivity	59	58	55	58	62	-	-	-
6.	T1 & T2 Cortisol Reactivity	55	54	54	58	58	58	-	-
7.	Cumulative Exposure	59	58	58	58	61	57	57	-
8.	Maternal Lifetime History of Depressive Disorders	60	59	59	59	62	58	57	63
Functional Connectivity Analyses									
		1	2	3	4	5	6	7	8
1.	T1 Parenting	45	-	-	-	-	-	-	-
2.	T2 Parenting	44	44	-	-	-	-	-	-
3.	T1 & T2 Parenting	44	44	44	-	-	-	-	-
4.	T1 Cortisol Reactivity	43	42	42	46	-	-	-	-
5.	T2 Cortisol Reactivity	44	43	42	45	47	-	-	-
6.	T1 & T2 Cortisol Reactivity	42	41	41	45	45	45	-	-
7.	Cumulative Exposure	44	43	43	45	46	44	47	-
8.	Maternal Lifetime History of Depressive Disorders	45	44	44	46	47	45	47	48

Participants

Recruitment. Participants (*N*=175) were recruited through flyers distributed to local schools, daycares, and healthcare providers (73.1%) and through a commercial mailing list (26.9%). A subset of children were targeted based on a maternal history of lifetime depression via advertisements. At Time 1, eligible children were between three to five years of age; had an English-speaking biological parent with at least 50% legal custody; had no parent-reported history of significant medical conditions or developmental disabilities; and had biological parents without a history of bipolar or psychotic disorders. 174 families seen at Time 1 were invited to participate in Time 2 approximately 3 years later to capture the transition to primary school entry (one family was not invited to participate due to the child's inability to speak or understand English). Families who completed the Time 2 behavioral session (*n*=104) were invited to complete the neuroimaging visit; of these, 64 chose to participate. A total of 63 completed scanning and contributed possible data for analysis (1 child did not complete any scans due to claustrophobia).

Demographics and Descriptive Statistics. Demographic data are reported in Table 2 on the sample of 63 children (32 girls, 50.8%) who may be included in the present neuroimaging analyses. During the Parent-Child Interaction task during Time 1, participants were between 3-5 years of age (M = 4.23 ± .84 years, range = 3.00-5.96 years). Children completed the stressor task approximately 28 days later (M = 27.77 ± 18.21, range = -8-110 days; M = 4.31 ± 0.85, range = 3.11 – 6.10 years-old), with one child completing the Parent-Child Interaction task 8 days after the stressor task. The Time 2 behavioral assessment occurred approximately 3 years later (M = 2.91 ± .45, range =

2.09–3.90 years; 7.20 ± .89, range = 5.57–10.00 years-old). The neuroimaging session occurred approximately 3 months after the Time 2 behavioral assessment (*M* = 103.06 ± 102.85 days, range = 8-438 days) when children were 5-10 years old (*M* = 7.48 ± .88 years, range = 5.85-10.24 years). Participants were racially diverse, household income ranged from <$20,000 to >$100,000 per year, and the majority of children had at least one parent with a 4-year college degree. Thirty-eight (60.3%) mothers had a lifetime history of depressive disorders (major depressive disorder and/or dysthymic disorder).

Table 2
Demographic characteristics of sample.

Demographic variable	
Child age (in years) at T1 Parenting Assessment, [Mean (SD)]	4.22 (0.84)
Child age (in years) at T1 Cortisol Assessment, (*n*=60) [Mean (SD)]	4.31 (0.85)
Child age (in years) at T2 Assessment, [Mean (SD)]	7.20 (0.89)
Child age (in years) at Scan, [Mean (SD)]	7.48 (0.88)
Child sex, [*n* (%)]	
Male	31(49.2%)
Child race [*n* (%)]	
White, European-American	30 (47.6%)
African-American	22 (34.9%)
Asian	0 (0%)
Multi-Racial/Other	11 (17.4%)
Child ethnicity (*n*=62) [*n* (%)]	
Hispanic/Latino descent	9 (14.5%)
Single parent household [*n* (%)]	
Lives with only one parental figure	15 (23.8%)
Family income [*n* (%)]	
<$20,000	5 (7.9%)
$20,001 to $40,000	4 (6.3%)
$40,001 to $70,000	13 (20.6%)
$70,001 to $100,000	15 (23.8%)
>$100,000	26 (41.3%)
Parental education [*n* (%)]	
At least one parent with a four-year college degree	47 (74.6%)
Maternal lifetime history of depressive disorders [*n* (%)]	
Lifetime history present	38 (60.3%)
Any lifetime exposure to maternal depressive disorders (*n*=62) [*n* (%)]	29 (46%)
Proportion of total months from birth to present exposed to maternal DD (*n*=62) [Mean (SD)]	0.19 (0.31)

Note. *n*=63 unless otherwise noted; DD = Depressive Disorders, including Major Depressive Disorder or Dysthymic Disorder; T1: Time 1; T2: Time 2

The subsample of children included in the present analyses did not significantly differ from the full Time 1 sample on gender ($\chi^2(1, N=175)<.001$, $p=.990$), income ($\chi^2(4, N=170)=.89$, $p=.926$), race ($\chi^2(4, N=171)=5.78$, $p=.216$), ethnicity ($\chi^2(1, N=170)=.91$, $p=.341$), parental education ($\chi^2(2, N=173)=.87$, $p=.647$), maternal lifetime history of

depressive disorders ($\chi^2(1, N=167)=3.15$, $p=.076$), proportion of total months exposed to maternal depressive disorders, $t(107)=-0.91$, $p=.364$, age (in months) at Time 1 parenting assessment, $t(102)=0.26$, $p=.795$, or age (in months) at Time 2 behavioral assessment, $t(102)=1.70$, $p=.091$).

Measures

Maternal Depression.

At Time 1, mothers completed the Structured Clinical Interview for DSM-IV Disorders (SCID) (First, Spitzer, Gibbon, & Williams, 1996) over the phone with a trained masters-level diagnostician to assess a lifetime history of depressive disorders (i.e., major depressive disorder or dysthymic disorder). Phone interviews provide diagnoses consistent with in-person interviews (Rohde, Lewinsohn, & Seeley, 1997). For mothers who completed a T1 SCID, a follow-up SCID was conducted at Time 2 to assess any new depressive episodes. If a mother did not complete a SCID at Time 1, she completed the full SCID at Time 2. Data from T1 and T2 were combined to yield a dichotomous variable of lifetime maternal depression (i.e., present or not present). Inter-rater agreement based on 7 interviews from T2 resulted in a κappa (κ) of 1.00. Additionally, at T1 and T2 mothers reported the total number of months they were depressed during each year of their child's lifetime. These scores were converted into a measure reflecting the cumulative proportion of the child's lifetime (in months) during which they were exposed to maternal depression.

Observed Parenting Behavior.

During the first laboratory visits at Time 1 and Time 2, children and their parents worked together to complete standardized tasks, modified from the Teaching Tasks

Battery (Egeland et al., 1995), which were designed to elicit a range of emotions and behaviors from parents and their children. At Time 1, the five episodes (i.e., tasks) were: (1) Book reading: parents were instructed to read a picture book to their children (2) Wheels: assisted their children in naming as many objects with wheels as possible (3) Maze: parents guided their children through completing an Etch A Sketch® maze without touching any of the lines (4) Story: with the aid of their parents, children arranged cards depicting an action sequence in the correct temporal order and (5) Tangoes: children positioned geometric puzzle pieces to match a predetermined shape. At Time 2, the episodes were: (1) Guessing game: parents guide their children in guessing an image on an unseen card (2) Traffic: with their parents' help, children are required to shift cars up/down and left/right on a board to clear a path (3) Maze: parent and child are required to both collaboratively and competitively to direct a marble into holes on a wooden labyrinth board and (4) Block Buddies: parents and children work together to put together plastic shapes to match designs shown on cards.

Each episode was coded on the following five measures: (1) *Maternal Support*, a measure of the mother's expression of positive regard and emotional support towards the child; (2) *Maternal Intrusiveness*, characterized by parenting behaviors that interfere with a child's autonomy. Mothers scoring high on this measure demonstrate pervasive intrusions which challenge the child's self-directed efforts. (3) *Maternal Hostility* is characterized by expressions of anger, frustration, annoyance, or rejection. (4) *Maternal Positive Affectivity* and (5) *Maternal Negative Affectivity* are measures of the frequency and intensity of facial, bodily, and vocal displays of positive and negative affect, respectively. All measures were coded on a 5-point scale with the exception of Maternal

Positive and Negative Affectivity, which were scored on 3-point scales (Table 3). Each measure was averaged across tasks and z-scored.

To account for possible divergent effects of the dimensions of deprivation and threat on outcome measures, present analyses used two constructs at Time 1 and Time 2 to measure parenting behaviors (Table 3). A Negative Parenting Composite was created by averaging the above measures of Maternal Intrusiveness, Maternal Hostility, and Maternal Negative Affectivity. A Positive Parenting Composite was created by averaging z-scored measures of Maternal Support and Maternal Positive Affectivity. Internal consistencies (α) and intraclass correlation coefficients (ICC) for composite and subscale measures can be found in Table 3. Resulting values for each measure were z-scored according to the larger sample that successfully completed this task with their mother (*n*=161 at Time 1, *n*=97 at Time 2).

Table 3

Descriptive statistics for primary study variables.

	n	Mean[a]	*SD*[a]	Min[a]	Max[a]	ZMin[a]	ZMax[a]	α[b]	ICC[b]
Independent Variables									
T1 Negative Parenting	60	0.10	0.94	-0.66	3.75	-0.80	4.38	0.75	0.97
Maternal Intrusiveness		1.68	0.55	1.00	3.00	-	-	0.66	0.91
Maternal Hostility		1.19	0.36	1.00	2.60	-	-	0.76	0.89
Maternal Negative Affect		1.05	0.15	1.00	1.80	-	-	0.67	0.85
T1 Positive Parenting	60	-0.03	0.94	-2.44	1.57	-2.62	1.67	0.88	0.96
Maternal Support		4.00	0.87	1.40	5.00	-	-	0.88	0.96
Maternal Positive Affect		1.86	0.28	1.00	2.40	-	-	0.74	0.81
T2 Negative Parenting	59	-0.01	0.79	-0.58	2.50	-0.69	2.85	0.73	0.96
Maternal Intrusiveness		1.42	0.45	1.00	2.75	-	-	0.49	0.91
Maternal Hostility		1.18	0.37	1.00	3.00	-	-	0.84	0.96
Maternal Negative Affect		1.05	0.14	1.00	1.75	-	-	0.76	0.97
T2 Positive Parenting	59	-0.11	0.97	-4.46	1.39	-5.28	1.66	0.85	0.91
Maternal Support		4.32	0.75	1.50	5.00	-	-	0.81	0.92
Maternal Positive Affect		1.96	0.18	1.25	2.50	-	-	0.18	0.85
T1 AUC_g (log_{10})	59	1.08	0.28	0.60	2.30	-1.70	4.47	-	-
T1 AUC_i (log_{10})	59	1.88	0.08	1.52	1.97	-1.87	0.50	-	-
T2 AUC_g (log_{10})	62	1.07	0.28	0.52	2.36	-2.03	4.87	-	-
T2 AUC_i (log_{10})	62	1.31	0.10	1.07	1.66	-1.94	2.96	-	-
Dependent Measures [c]									
Right Hippocampal Total	63	4269.87	308.68	3522.63	4960.80	-	-	-	-
Right Hippocampal Head		2121.41	276.61	1574.82	2771.44	-	-	-	.97
Right Hippocampal Body		1455.43	173.56	1055.44	1892.07	-	-	-	.78
Right Hippocampal Tail		693.03	119.72	377.36	980.84	-	-	-	.87
Left Hippocampal Total	63	4180.49	314.87	3511.95	5154.20	-	-	-	-
Left Hippocampal Head		1970.35	292.45	1431.12	2842.79	-	-	-	.97
Left Hippocampal Body		1551.78	214.72	1001.79	2019.07	-	-	-	.87
Left Hippocampal Tail		658.37	125.58	297.70	973.72	-	-	-	.86

[a]Means, standard deviations, and ranges are reported for the subsample included in the present analyses. [b] T1 parenting internal consistencies (α) and intraclass correlation coefficients (ICC) for inter-rater reliability were based on *n*=174 and *n*=38,

respectively. T2 parenting α and ICC were based on *n*=103 and *n*=28, respectively. Hippocampal volume intraclass correlation coefficients were derived from the full sample, *n*=63. [c] Volume, measured in mm^3.

Cortisol Reactivity.

During the second visit at Time 1, 156 children provided salivary cortisol samples before and after a stressful task. Of the 156 children, 59 children also participated in the neuroimaging assessment at Time 2. Salivary cortisol samples were collected by dipping a cotton roll in a small amount of Kool Aid and placing it in the child's mouth until saturated with saliva. This method, which does not influence cortisol assays if used sparingly and consistently, stimulates saliva production and makes the sampling procedure more pleasant for children (Talge, Donzella, Kryzer, Gierens, & Gunnar, 2005). The baseline saliva sample was collected after a 30-minute period of quiet play (e.g., coloring, watching movies). The laboratory stress paradigm used a task developed by Kryski, Smith, Sheikh, Singh, and Hayden (2011), which was an adapted version of Lewis and Ramsay's (2002) paradigm. The task is a developmentally-appropriate laboratory stressor, which required children to pair animal pictures with colored chips within 3 minutes. The experimenter manipulated a timer so the child failed to complete the task three times. After the third failed trial, the experimenter informed the child that the timer was broken, praised the child's performance, and presented the child with a desired prize (for a complete description of the task, see Dougherty, Tolep, et al., 2013; Tolep & Dougherty, 2014). This task has been successful in eliciting a cortisol response in preschool-aged children (Kryski et al., 2011).

At Time 2, children completed a modified version of the Trier Social Stress Task for Children (TSST-C; Buske-Kirschbaum et al., 1997) followed by a puzzle. During the task, children were instructed to tell a 4.5-minute story about an unfamiliar picture book after 30 seconds of preparation. After completion of the task, children were instructed to

complete an unsolvable puzzle within 3 minutes (for a complete description of the tasks, see Leppert, Kushner, Smith, Lemay, & Dougherty, 2016).

At Time 1 and Time 2, children were told that the tasks they were completing were very easy for young children and that they would receive a prize based on their performance. Additionally, to elicit feelings of social evaluation, the experimenter pretended to take notes on the child's performance.

At both Time 1 and Time 2, salivary cortisol samples were collected at baseline and 20-, 30-, 40-, and 50-minutes post-stressor, frozen at -20°C, and assayed in duplicate using a time-resolved fluorescence immunoassay with fluorometric end-point detection (DELFIA) at the Biochemical Laboratory at the University of Trier, Germany. Inter- and intra- assay coefficients of variation ranged between 7.1-9.0% and 4.0-6.7%, respectively. Measures of cortisol reactivity were derived from the trapezoid formula from the 5 individual cortisol samples at each timepoint (Pruessner, Kirschbaum, Meinlschmid, & Hellhammer, 2003). The area under the curve with respect to ground (AUC_g), a measure of the magnitude of total cortisol secretion across the 5 samples, as well as the area under the curve with respect to increase (AUC_i), a measure of total cortisol change, are included in analyses (Table 3). Two participants had one sample exceeding 44nmol/L so these extreme values were discarded and the missing data points were interpolated using the average of five multiple imputations.

Neuroimaging Assessment.

Sixty-four children from the original sample completed the neuroimaging session at Time 2, of which, 63 provided scan data for analysis (1 child did not complete any scans due to claustrophobia). During the session, children completed a 30-60 minute

mock scanner training to become acclimated to the scanner environment and receive feedback regarding motion. Participants were scanned in a Siemens 3.0-T scanner (MAGNETOM Trio Tim System, Siemens Medical Solutions, Erlangen, Germany) using a 12-channel coil.

Hippocampal Structure. Children watched a video of their choosing while structural data were collected using a high-resolution T1 magnetization-prepared rapid gradient-echo (MPRAGE) sequence consisting of 176 contiguous sagittal slices (1.0 × 1.0 × 1.0 mm voxel dimensions; 1900 ms TR; 2.52ms TE; 900ms inversion time; 9° flip angle; pixel matrix= 256 x 256). T1 images were analyzed in Freesurfer (Version 5.1.0), an automatized segmentation package (surfer.nmr.mgh.harvard.edu). Resulting hippocampal segmentations were visually checked and manual edits were performed (*n*=7), as necessary, to correct for gross over- or under-inclusions.

Given evidence that subregions of the hippocampus (i.e., head, body, tail) may be differentially susceptible to early insults and specific hippocampal subfields (e.g., dentate gyrus and the cornu ammonis areas 1-4) are differentially distributed along the longitudinal axis of the hippocampus, the Freesurfer hippocampal volumes were segmented into head, body, and tail subregions. This was achieved by aligning Freesurfer volumes to the anterior commissure-posterior commissure to eliminate distortions introduced by reorientation (Poppenk & Moscovitch, 2011). The anterior boundary of the hippocampal head was identified using the most anterior slice of the hippocampus identified by Freesurfer. The posterior boundary of the hippocampal head was identified as the last coronal slice in which the uncal apex is visible (Riggins, Blankenship, Mulligan, Rice, & Redcay, 2015; Weiss, Dewitt, Goff, Ditman, & Heckers, 2005). The

anterior boundary of the hippocampal tail was identified as the slice at which the fornix separates from the hippocampus and becomes clearly visible (Riggins et al., 2015; Watson et al., 1992). The posterior boundary of the hippocampal tail was identified by Freesurfer. The hippocampal body was identified as the area between these regions. These divisions were identified twice for each participant (n=63) by independent raters with a high degree of consistency between raters (intraclass correlation coefficients (ICCs) for the posterior boundary of the right and left head and the anterior boundary of the right and left tail were .92, .94, .90, and .88, respectively). Final unilateral hippocampal total, head, body, and tail volumes were adjusted for total intracranial volume (ICV) to ensure all observed associations were not confounded by differences in total brain volume (Raz et al., 2005), and are used as dependent measures in structural analyses (Table 3).

Hippocampal Functional Connectivity. Metrics of hippocampal connectivity were derived from a 6-minute resting-state scan during which children viewed abstract shapes (similar to screen savers). Use of abstract shapes has become a common methodological choice in pediatric neuroimaging because it reduces participant motion while not significantly compromising patterns of resting-state network activity (Blankenship et al., 2016; Riggins, Geng, Blankenship, & Redcay, 2016; Vanderwal, Kelly, Eilbott, Mayes, & Castellanos, 2015). Data were collected with the following scan parameters: 180 EPI volumes consisting of 36 oblique interleaved slices with a 3.0 x 3.0 x 3.0 mm voxel size; 2s TR; 24 ms TE; 3mm slice thickness; 90° flip angle; 64x64 pixel matrix.

Functional images were slice-time corrected in the Analysis of Functional Neuroimages (AFNI; Version 16.0.00) software package (Cox, 1996). All functional images were aligned to the first volume using rigid-body motion-correction and registered to both the T1 structural images and the Freesurfer subcortical segmentations (i.e., asegs) using the Advanced Normalization Tools (ANTs; version 1.9.v4) software (http://stnava.github.io/ANTs/). The data were then bandpass filtered at .009<f<.08 and nuisance regressed. Nuisance regression included 21 regressors: 6 motion parameters and their 6 temporal derivatives, baseline, linear, quadratic, and cubic drift, as well as separate timeseries for left and right hemisphere white matter, left and right hemisphere lateral ventricles, and the corpus callosum[2]. Timepoints where the framewise displacement exceeded 1mm were excluded, along with the previous volume, using censor files. Participants who had more than 10% of their total volumes censored were excluded from group analyses (*n*=9). Average unilateral anterior and posterior hippocampal timeseries were extracted from the nuisance-regressed and filtered data.

Functional volumes were then normalized to a 4.5-8.5 year symmetrical MNI Child Template (Fonov et al., 2011) with an multivariate transformation in ANTS. Data were smoothed using a 6mm Gaussian kernel within a whole brain mask. Whole brain connectivity analyses were run for unilateral hippocampal anterior and posterior seeds using the 3dDeconvolve t command in AFNI. The resulting R^2 values were converted to Pearson's r and then to z-scores using a Fisher's r-to-z transformation. Individual

[2] Two participants' lateral ventricles were too small to generate lateral ventricle masks that did not intersect with surrounding neural tissue. Nuisance regression for these two participants did not include CSF regressors.

subjects' z-scored connectivity maps were entered into the group analysis. To control for multiple comparisons, 10,000 Monte Carlo simulations were be run on the residual timeseries of each analysis using AFNI's 3dClustSim for analysis-specific cluster-corrected *p*-values of $p<.05$ (Table 4).

Table 4
Minimum cluster size (k) for $p_{corrected} <.05$ at $p_{uncorrected} < .005$.

Independent Variables	Anterior Hippocampus (k)	Posterior Hippocampus (k)
Negative Parenting	68	68
Positive Parenting	68	69
AUCg	70	70
AUCi	69	69
Maternal Lifetime Depressive Disorder	69	68
Cumulative Exposure to Maternal Depression	68	69
Cumulative Exposure x Negative Parenting	67	66
Cumulative Exposure x Positive Parenting	70	69
Cumulative Exposure x AUCg	70	69
Cumulative Exposure x AUCi	69	68
Maternal Lifetime Depressive Disorder x Negative Parenting	68	67
Maternal Lifetime Depressive Disorder x Positive Parenting	68	70
Maternal Lifetime Depressive Disorder x AUCg	70	70
Maternal Lifetime Depressive Disorder x AUCi	70	71

Masks. Freesurfer segmentation files (described above) were used to generate subject-specific masks for hippocampal and nuisance signal timeseries extraction. Given the small volume of the hippocampal tail and lack of evidence for differential connectivity in the posterior regions of the hippocampus (i.e., between the body and tail; Poppenk, Evensmoen, Moscovitch, & Nadel, 2013), left and right hippocampal bodies and tails were collapsed to create a functional seed for bilateral posterior hippocampus. The bilateral anterior seed corresponds to the left and right hippocampal heads used in structural analyses. Bilateral seeds are a common methodological choice when no

differences in functional lateralization are hypothesized and limit the number of analyses run in under-powered samples. Additional masks were created for left and right hemisphere white matter, corpus callosum, and left and right lateral ventricles. Each mask was resampled to functional resolution and clipped at 100%, 50%, 80%, and 90%, respectively, for cerebral white matter, corpus callosum, lateral ventricles, and all hippocampal seeds.

Motion. Motion has been shown to have significant deleterious effects on resting-state analyses, especially in young children who may be susceptible to more frequent and larger movements than adults (Power et al., 2013, 2014; Power, Schlaggar, & Petersen, 2015; Satterthwaite et al., 2012; Van Dijk, Sabuncu, & Buckner, 2012). To mitigate any possible effects of motion on our results, a number of precautions were taken: (1) Only participants who showed < 3mm of movement from a reference volume throughout the entire scan were included[3]. (2) Volumes demonstrating >1mm of framewise displacement (FD), calculated as the Euclidean distance from the previous volume, along with the previous volume, were censored. (3) Participants were excluded if >10% of volumes were censored (4) Mean (FD) was calculated for each individual and included in all analyses as a covariate. (5) We ensured that mean FD did not correlate with age, independent variables of interest, including parenting (positive and negative dimensions) and cortisol reactivity (AUCg, AUCi), or either measure of maternal depression status (i.e., maternal lifetime history of depressive disorders, cumulative lifetime exposure to maternal depression (Table 5).

[3] One participant had a mean FD value of 3.02 and was included in present analyses.

Table 5
Correlations between mean FD and independent variables of interest.

	r	*p*
Scan Age	-.10	.519
T1 Negative Parenting	.01	.970
T1 Positive Parenting	.07	.668
T2 Negative Parenting	-.09	.580
T2 Positive Parenting	.13	.408
T1 AUCg	-.13	.395
T1 AUCi	<.01	.977
T2 AUCg	.07	.663
T2 AUCi	-.13	.393
Maternal Lifetime History of Depressive Disorders	.17	.249
Cumulative Lifetime Exposure to Maternal Depressive Disorders	-.03	.851

Data Analytic Methods

The overarching aim of the present investigation is to examine timing-dependent differences in the associations between early and concurrent parenting and cortisol reactivity with hippocampal volume and functional connectivity. To make claims about the relative significance of the timing of experience, both T1 and T2 measures of parenting or cortisol reactivity were entered into each model. For results of analyses investigating T1 or T2 parenting and cortisol reactivity (i.e., without controlling for shared variance), please refer to the Supplementary Material.

Aim 1: Examine the timing-dependent associations between early (ages 3-5 years) and concurrent (5-10 years) parenting behaviors with hippocampal structure and functional connectivity at 5-10 years.

Structure. To examine associations between early and concurrent parenting and hippocampal structure at follow-up, separate multiple regression analyses were run for each unilateral hippocampal whole and subregion volume with negative or positive T1

and T2 parenting composite scores and covariates (see *Covariates*, below) entered as independent variables.

Function. To examine associations between early and concurrent parenting and hippocampal functional connectivity, individual subjects' z-scored whole-brain hippocampal functional connectivity maps were entered into AFNI's 3dttest++ with T1 and T2 negative or positive parenting as the predictors, controlling for appropriate covariates (see *Covariates*, below). Separate analyses were run for positive and negative parenting dimensions.

Aim 2: Examine the timing-dependent associations between early (ages 3-6 years) and concurrent (5-10 years) cortisol reactivity3-6 with hippocampal volume and functional connectivity (5-10 years).

Structure. As above, to examine associations between early and concurrent cortisol reactivity with hippocampal structure, separate multiple regression analyses were run for each unilateral hippocampal whole and subregion volume with T1 and T2 measures of each measure of cortisol reactivity (AUCg or AUCi) and covariates (see *Covariates* below) entered as independent variables.

Function. To examine associations between early and concurrent cortisol reactivity with whole-brain hippocampal functional connectivity, analyses were conducted as above, with T1 and T2 AUCg or AUCi as independent variables in separate models.

Aim 3: Determine whether cortisol reactivity mediates the association between parenting and hippocampal volume and functional connectivity (5-10 years).

Structure. Mediation analyses will be conducted within a regression framework using the Hayes' SPSS PROCESS macro for mediation (Hayes, 2013). In contrast to the traditional Baron and Kenny (1986) step-wise method of mediation, Hayes' approach uses a regression approach to examine the magnitude difference between the effect of the independent measure (T1 or T2 positive or negative parenting) on the dependent measure (hippocampal volume) when the mediator (T1 or T2 cortisol reactivity) is or is not controlled. Use of the Hayes' method enables investigation of indirect effects in the absence of statistical significance in the association between parenting behavior and hippocampal volume (Aim 1) while controlling for other factors (see *Covariates*, below). As recommended by Hayes (2013), significance of the indirect effect will be tested using bias-corrected bootstrapped confidence intervals determined by 10,000 samples with replacements. This method of significance testing does not require assumptions about the underlying distribution and is recommended for use in small samples (Hayes, 2013).

Function. To test the partial mediation model, average connectivity z-scores were extracted from regions with a significant main effect of T1 or T2 Positive or Negative Parenting (from Aim 1). For each significant region, mediation was tested using the Hayes PROCESS macro in SPSS with the appropriate z-scores entered as the dependent variable in separate regression models.

Exploratory Aim: Explore the role of maternal depression on observed associations.

The present proposal investigated the effects of the early parenting environment on subsequent cortisol reactivity and hippocampal structure and functional connectivity in a sample of children over-selected for maternal depression. Although over-selection

equipped the present analyses with a more distributed range of parenting behaviors, maternal depression may confound observed effects. The goal of this exploratory aim was to examine the role maternal depression status may play in observed associations in Aims 1-3 (see Figure 3). Follow-up analyses were run to determine significant main effects of maternal depression on hippocampal structure and function as well as whether maternal depression (i.e., maternal lifetime history of depression or cumulative lifetime exposure to maternal depression) significantly moderated the associations between independent variables of interest (i.e., parenting and cortisol reactivity) and hippocampal structure and function.

Moderation was tested for both maternal lifetime history of depression and cumulative lifetime exposure to maternal depression as each of these indices may capture distinct risk factors associated with maternal depressive disorders, despite high correlations (Table 5). In particular, maternal lifetime history of depression may reflect genetic, environmental, or a combination of genetic and environmental factors associated with maternal depression. In contrast, cumulative exposure to maternal depression captures the additive consequence of long-term or repeated exposure to a depressed mother, reflecting, to some degree, an environmental risk that may or may not be compounded by a genetic risk.

Significant interactions were probed using simple slopes analyses (±1 SD), outlined by Aiken and West (1991). For structural analyses using a continuous moderator (i.e., cumulative lifetime exposure to maternal depression), the Johnson-Neyman procedure (Johnson & Fay, 1950) was run to determine at which levels of the moderator the effects were significant. Significant interactions in the functional analyses were

probed as above by limiting probe analyses (i.e., masking) to regions where the interaction was significant. Probed results were thresholded at $p<.005$, and considered significant at ± 1 SD above the mean if k>20.

Independent Variables.

T1 and T2 Positive and Negative Parenting as well as T1 and T2 AUCg and AUCi are the predictors of interest in both functional and structural analyses. In all analyses reported below, independent variables are z-scored values from the larger available sample (sample sizes vary, see Figure 4).

Covariates.

Hypothesized associations in the current models may be confounded by other factors. To account for this possibility, variables that were considered as potentially confounding factors included: child's gender, parent education (at least one parent with a four-year college degree or not), child's age at T2 scan, maternal lifetime history of depressive disorders (present or not), and proportion of the child's life from birth until present (i.e., mid- to late-childhood) exposed to maternal depression (in months) (Table 5). Where appropriate, independent samples *t*-tests, One-Way ANOVAs, or Pearson's correlations were run to determine significant differences among levels of possible covariates. Determination of inclusion in final structural analyses was established based on a significant difference between levels of potential covariates on the dependent measures (i.e., hippocampal volumes). Consistent with previous research standards, child age at the time of the T2 scan as well as mean FD displacement (see Motion, above) were entered as covariates in all functional connectivity analyses.

Outliers.

Limiting analyses to participants who provided imaging data resulted in reduced variability and non-normal distributions within some predictor variables. In all cases, the data from the imaging subsample reflected the distributions of the larger sample (Figure 4). Because potential outliers were not data measurement errors and reflected true variations in parenting or cortisol reactivity, it was not justified to remove outliers from any analysis. Where it appears that a result was driven by an outlier, we advise caution in interpreting the results, analyses were re-run without the outlier included, and the results of these follow-up analyses are included within the text or in a footnote.

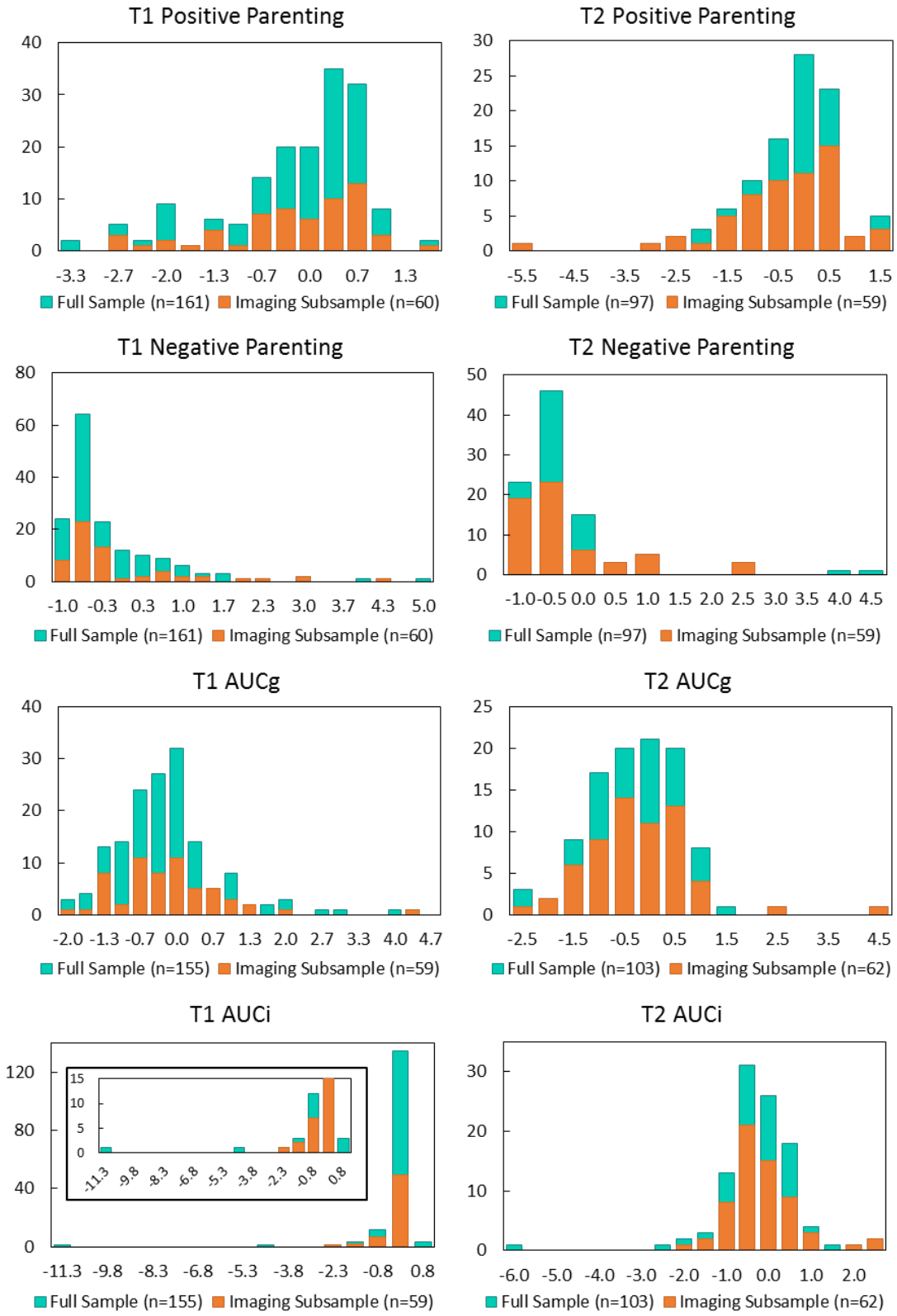


Figure 4. Histograms to display the distribution of independent variables of interest in the imaging subsample and the larger sample.

Chapter 5: Structural Results

Covariates

Bilateral hippocampal head volume differed between genders (Table 6), with males having larger right (male: *M*=2197.82, *SD*=276.13, range = 1649.32-2771.44 mm^3; female: *M*=2047.39, *SD*=260.27, range=1574.82-2649.33 mm^3) and left (male: *M*=2058.50, *SD*=318.17, range= 1431.12-2842.79 mm^3; female: *M*=1884.96, *SD*=240.39; range=1455.03-2527.68 mm^3) hippocampal heads. As such, gender was entered as a covariate in all analyses of left or right hippocampal head.

Scan age predicted right hippocampal body (Table 6), with older age predicting larger volume, and is included as a covariate in all subsequent analyses of right hippocampal body.

Table 6

Correlation table for all dependent, independent, and covariate variables.

		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	20	21
Dependent Variables																					
1.	Right Hippocampal Head																				
2.	Right Hippocampal Body	**-.45*****																			
3.	Right Hippocampal Tail	.21^{+}	.05																		
4.	Right Hippocampal Total	**.74*****	.16	**.60*****																	
5.	Left Hippocampal Head	**.78*****	**-.39****	.14	**.54*****																
6.	Left Hippocampal Body	**-.28***	**.62*****	-.03	.09	**-.45*****															
7.	Left Hippocampal Tail	.09	.17	**.54*****	**.39****	.17	-.09														
8.	Left Hippocampal Total	**.54*****	.16	**.32***	**.68*****	**.67*****	.23^{+}	**.50*****													
Independent Variables																					
9.	T1 Negative Parenting[a]	-.13	.10	.05	-.07	-.14	.01	.05	-.03												
10.	T1 Positive Parenting[a]	**.30***	-.01	-.16	.22	**.28***	.04	<.01	.25^{+}	**-.50*****											
11.	T2 Negative Parenting[a]	-.18	**.31***	-.02	<.01	-.17	.13	.04	-.01	**.68*****	-.25^{+}										
12.	T2 Positive Parenting[a]	.18	**-.29***	-.20	-.06	.17	-.26^{+}	-.23^{+}	-.15	**-.49*****	**.34****	**-.64*****									
13.	T1 AUC_g (log_{10})[a]	.13	**.26***	**.33***	**.38****	.05	.25^{+}	.17	.27^{+}	-.01	.13	-.14	-.10								
14.	T1 AUC_i (log_{10})[a]	.11	**-.45*****	-.16	-.21	.12	**-.36****	-.16	-.19	.07	-.13	.08	.13	**-.57*****							
15.	T2 AUC_g (log_{10})[a]	.05	-.15	-.20	-.12	-.08	.07	**-.26***	-.11	**.27***	-.18	.08	-.07	-.10	.11						
16.	T2 AUC_i (log_{10})[a]	-.07	.03	-.19	-.17	-.17	.13	**-.35****	-.17	**.28***	-.03	.12	.01	.05	.12	**.53*****					
Potential Covariates																					
17.	Maternal Lifetime DD	.04	-.01	-.16	-.04	.20	-.11	-.04	.11	.02	-.03	.17	.05	-.02	.02	-.09	-.16				
18.	Percent exposure to DD	-.12	.14	-.04	-.05	-.03	-.07	.06	-.04	.24^{+}	-.17	**.41****	-.19	<-.01	-.08	-.01	-.12	**.51*****			
19.	Child gender	**-.27***	.21	.01	-.16	**-.30***	.21	<.01	-.06	-.03	-.05	-.17	-.09	.15	.07	-.14	.06	-.15	.07		
20.	Child's age at scan	-.14	**.27***	-.14	-.02	-.01	.04	-.06	-.05	-.24^{+}	-.21	.06	.08	-.16	.13	-.02	-.05	.02	.04	-.06	
21.	Parent Education	.15	-.04	.10	.18	.14	-.04	.14	.10	**-.43****	**.28***	**-.43****	.21	.13	-.09	-.21^{+}	-.21^{+}	-.11	-.11	.15	.17

Aim 1: Associations between Parenting and Children's Hippocampal Volume

T1 Negative Parenting, controlling for T2 Negative Parenting, did not predict any whole or segmented hippocampal volume at T2 (Table 7). T2 Negative Parenting, controlling for T1 Negative Parenting, did not significantly predict any whole or segmented hippocampal volume at T2 (Table 7).

Greater T1 Positive Parenting, controlling for T2 Positive Parenting, significantly predicted larger right head and left total hippocampus volume and marginally predicted larger left hippocampal head at T2 (Table 8, Figure 5). Greater T2 Positive Parenting, controlling for T1 Positive Parenting, predicted smaller bilateral body and left total hippocampus volumes at T2 (Table 8, Figure 6)[4].

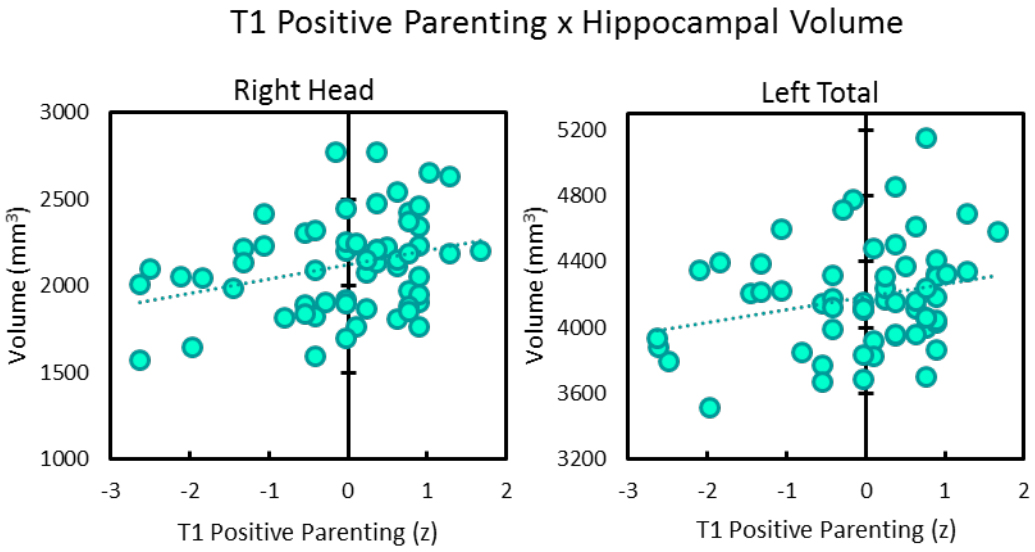


Figure 5. Associations between T1 Positive Parenting and right head and left total hippocampal head volumes. Note: Scatterplots depict bivariate correlations between the predictor and dependent variable and are not adjusted for additional factors included in the statistical models.

[4] No effects between T2 Positive Parenting and bilateral body or left total volumes remained significant when the one individual with extremely low Positive Parenting was removed from the analysis.

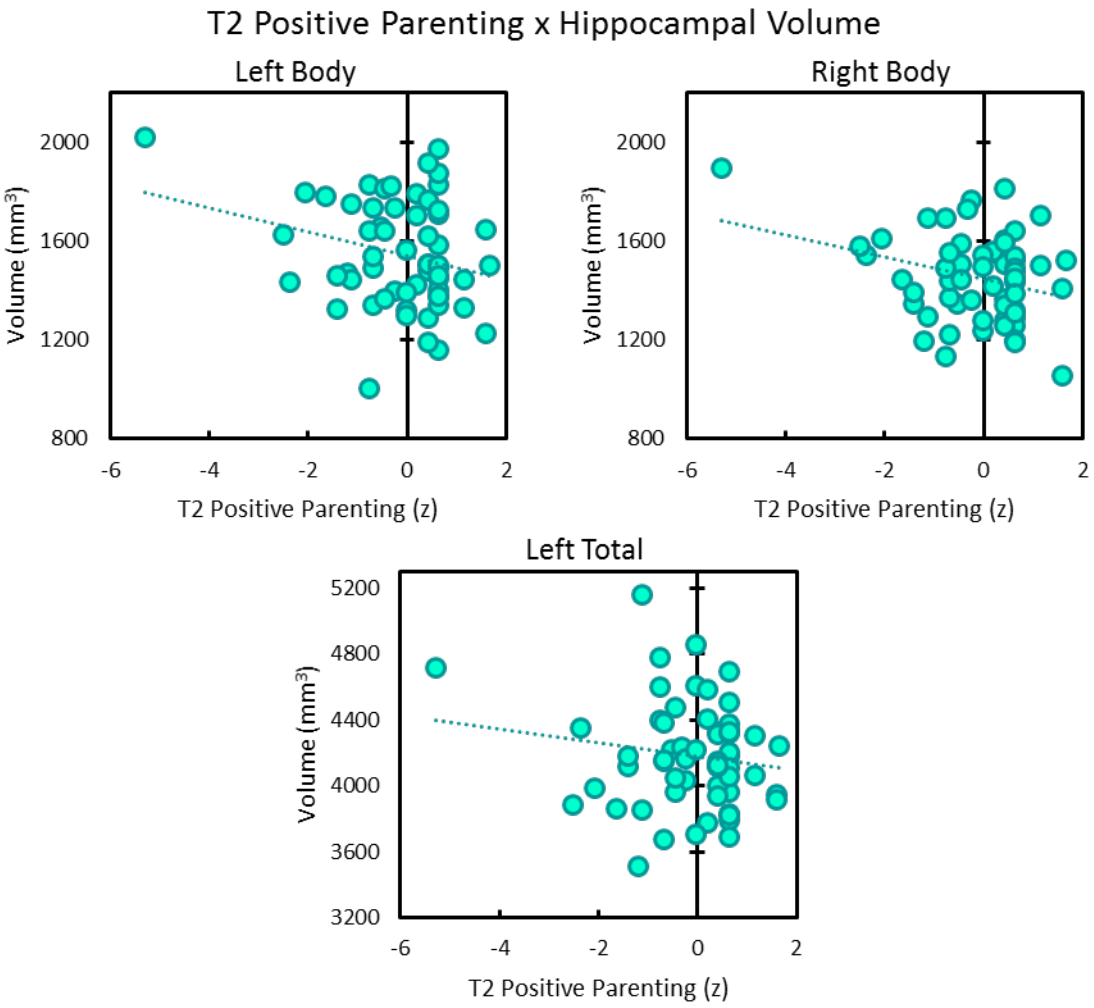


Figure 6. Association between T2 Positive Parenting and left and right hippocampal body volume. Note: Scatterplots depict bivariate correlations between the predictor and dependent variable and are not adjusted for additional factors included in the statistical models.

Aim 2: Associations between Children's Cortisol Reactivity and Hippocampal Volume

The magnitude of the cortisol response to stress at T1 (AUCg), controlling for AUCg at T2, predicted larger T2 bilateral hippocampal body and bilateral total volumes (Table 9, Figure 7)[5]. In contrast, greater change in cortisol (AUCi) at T1, controlling for AUCi at T2, predicted smaller T2 bilateral bodies (Table 10, Figure 8).

Greater T2 change in cortisol (AUCi), controlling for T1 AUCi, significantly predicted smaller left hippocampal tail volume (Table 10, Figure 9). The association between the magnitude of the cortisol response (AUCg) at T2, controlling for T1 AUCg, and left tail was marginally significant, with greater T2 AUCg predicting smaller left tail volume (Table 9).

[5] The effects between T1 AUCg and bilateral body volumes remained significant when the one participant with high T1 AUCg was removed from analyses. The effects between T1 AUCg and bilateral total volumes were no longer significant when this individual was excluded.

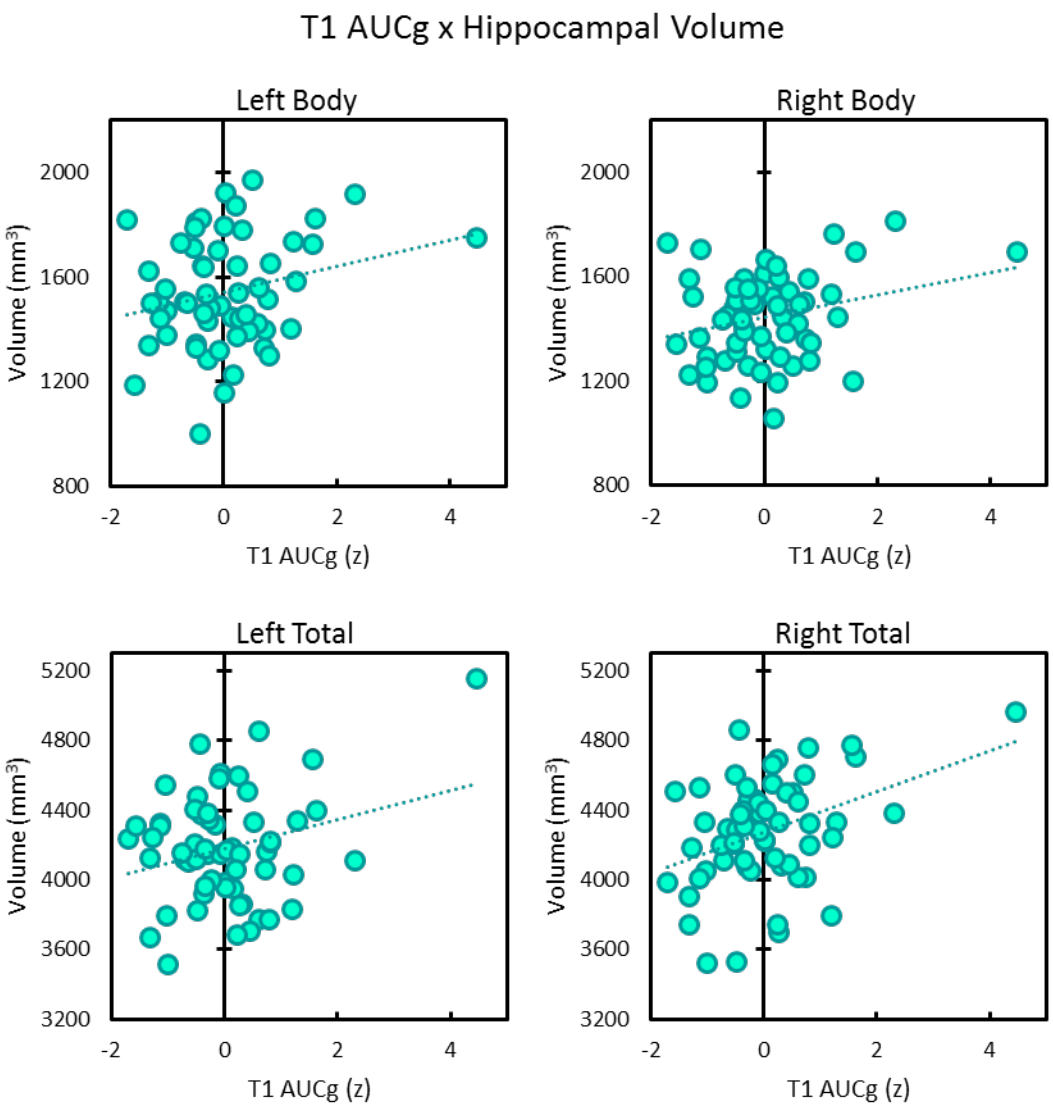


Figure 7. Associations between T1 AUCg and right and left body and total hippocampal volumes. Note: Scatterplots depict bivariate correlations between the predictor and dependent variable and are not adjusted for additional factors included in the statistical models.

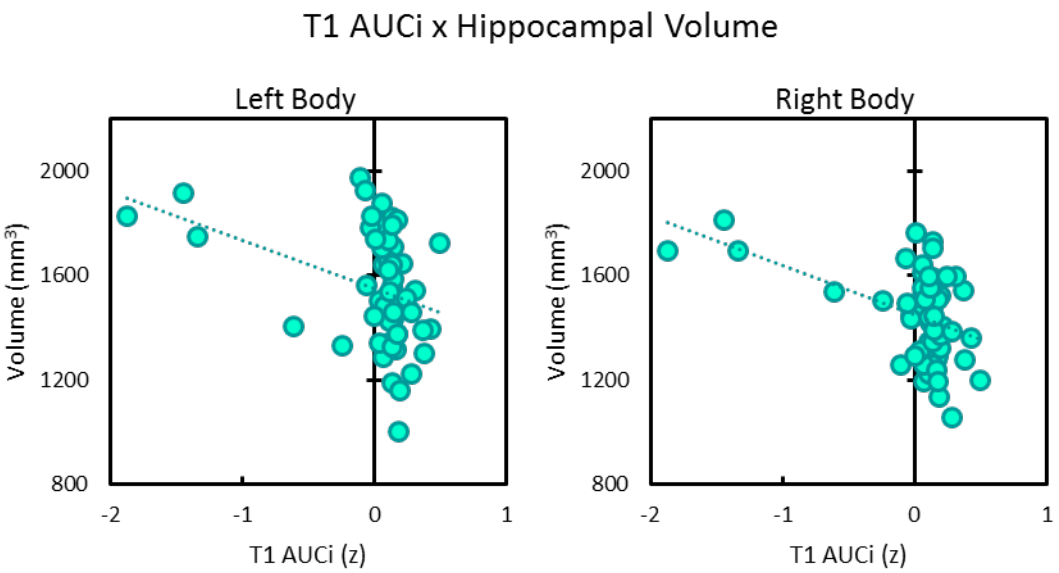


Figure 8. Associations between T1 AUCi and left and right hippocampal body volumes. Note: Scatterplots depict bivariate correlations between the predictor and dependent variable and are not adjusted for additional factors included in the statistical models.

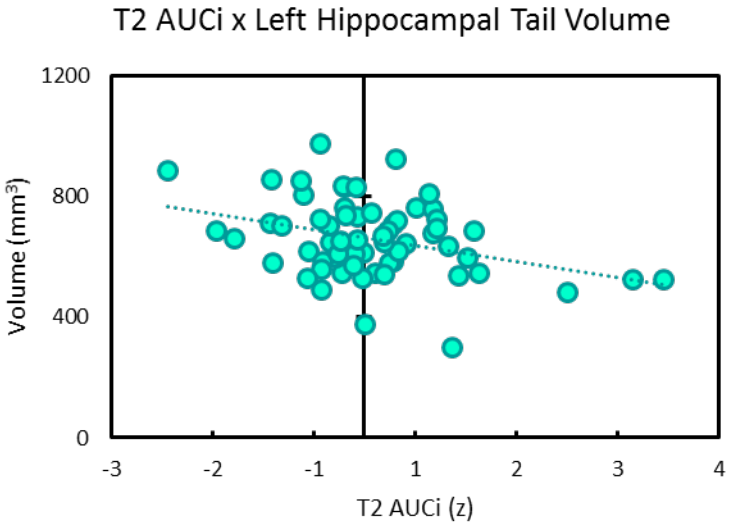


Figure 9. Association between T2 AUCi and left hippocampal tail volume. Note: Scatterplot depicts bivariate correlation between the predictor and dependent variable and is not adjusted for additional factors included in the statistical model.

Aim 3: Mediation of Association between Parenting and Hippocampal Volume by Cortisol Reactivity

As seen in Table 3, parenting did not significantly predict children's cortisol reactivity. Nevertheless, using Preacher and Hayes' bootstrap method (Hayes, 2013), we tested whether cortisol reactivity (T1 or T2; AUCg or AUCi) mediated associations between any parenting composite (T1 or T2; Positive or Negative) and hippocampal subregion volume.

There was a significant indirect effect of T1 Negative Parenting on T2 left hippocampal tail through T2 AUCi (Table 27). As Figure 10 illustrates, greater T1 Negative Parenting significantly predicted greater T2 total change in cortisol (*a*=0.20, *p*=.038), and greater T2 change in cortisol significantly predicted smaller left hippocampal tail volume *(b*=-55.89, *p*=.009). The bootstrapping method (Hayes, 2013) indicated that the indirect effect (*ab* = (.20)(-55.89) = -11.18) was significant, with a boot-strapped confidence interval range of (-34.49, -0.35), indicating that greater T1 Negative Parenting predicts increased T2 AUCi which, in turn, predicts smaller left hippocampal tail volumes. T1 Negative Parenting did not significantly predict left hippocampal tail volume independent of its effects on T2 AUCi (*c'* = 18.37, *p*=.372, CI = -22.57, 59.32).

No other mediation models were statistically significant.

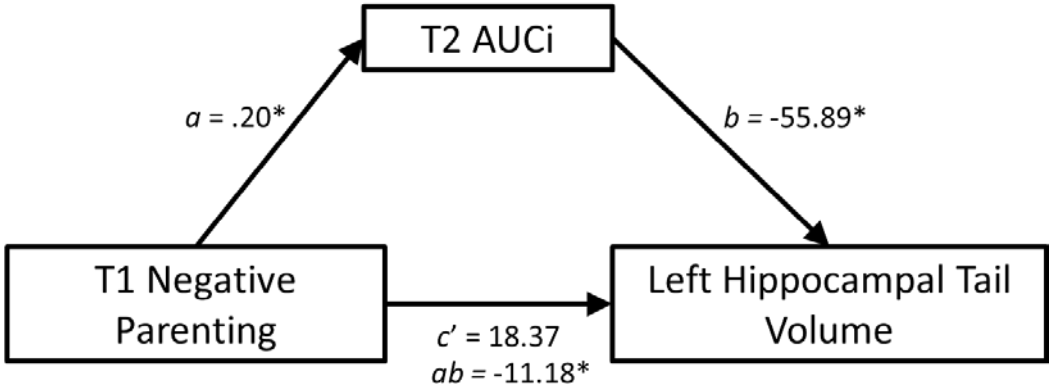


Figure 10. Standardized regression coefficients for the association between T1 Negative Parenting and left hippocampus tail volume, as mediated by T2 AUCi. * p <.05

Exploratory Aim: Role of Maternal Depression

Main Effects of Maternal Depression.

Neither lifetime history of maternal depression or lifetime exposure to maternal depression significantly predicted any hippocampal subregion volume (Table 6).

Interactions with Maternal Depression.

Exploratory analyses were run to assess the potential moderating role of maternal lifetime history of depression or cumulative exposure to maternal depression on the associations between T1 and T2 parenting or cortisol reactivity and hippocampus subregion volume. All models tested included: both T1 and T2 measures of the independent variable of interest (positive or negative parenting, AUCg or AUCi), the maternal depression index (cumulative lifetime exposure to maternal depression or maternal lifetime history of depressive disorders), two interaction terms (between each measure of the independent variable and the maternal depression index), and any additional covariates as determined above.

Interactions between Parenting and Maternal Depression.

Neither maternal lifetime depression status nor cumulative exposure to maternal depression significantly moderated the associations between T1 Positive Parenting, controlling for T2 Positive Parenting, and any whole or segmented hippocampal volume at T2 (Table 11-Table 18).

Maternal lifetime history of depressive disorders interacted with T2 Positive Parenting, while controlling for T1 Positive Parenting, to predict bilateral hippocampal head volumes at T2 (Table 11, Table 15, Figure 11)[6]. Specifically, in offspring without a maternal lifetime history of depression, greater T2 Positive Parenting, controlling for T1 Positive Parenting, predicted larger left (β =.63 b=159.71, SE=65.28, *pr*=.32, *p*=.018) and right (β = .57 b = 139.28, SE = 63.80, *pr* = .29, *p*=.034) hippocampal head volumes. This association was not significant in offspring with a lifetime history of maternal depression for left (β =-.14 b=-34.83, SE=37.27, *pr*=-.13, *p*=.354) or right (β =-.09 b=-22.46, SE=36.43, *pr*=-.09, *p*=.540) head.

T1 Negative Parenting, controlling for T2 Negative Parenting, interacted with cumulative exposure to maternal depression in predicting right total hippocampal volume (Table 14, Figure 12). In offspring with high exposure to maternal depression, greater T1 Negative Parenting predicted smaller right total hippocampal volumes (β =-.70 b=-192.27, SE=89.83, *pr*=-.29, *p*=.037), significant at standardized exposure values greater than .61 (25.86% of the sample). This association was not significant in offspring with low exposure to maternal depression (β = .26 b=69.62, SE=73.78, *pr*=.13, *p*=.350).

[6] The interaction between T2 Positive Parenting and maternal lifetime history of depressive disorders in predicting bilateral hippocampal head volumes remained significant when the one individual with extremely low T2 Positive Parenting was excluded from analysis.

Moreover, controlling for the effects of T1 Negative Parenting, greater T2 Negative Parenting interacted with cumulative exposure to maternal depression in predicting right total (Table 14) and left tail volumes (Table 17, Figure 13). In offspring with values of cumulative exposure to maternal depression one standard deviation above the mean, greater T2 Negative Parenting marginally predicted larger right total volumes (β = .57 b=192.76, SE=100.30, *pr*=.26, *p*=.060). The effect was significant at standardized exposure levels greater than 1.20 (17.24% of the sample), and there was no association in offspring with low exposure to maternal depression (β =-.22 b=-75.54, SE=98.65, *pr*=-.11, *p*=.447). The interaction for the left tail was not significant when probed at ± 1 SD above the mean of cumulative exposure (β = .39 b=53.63, SE=41.37, *pr*=.18, *p*=.201 and β = -.43 b=-59.64, SE=40.69, *pr*=-.20, *p*=.149, respectively). To further explore this interaction, T2 Negative Parenting was probed as the moderator between cumulative lifetime exposure and left tail volume. This analysis revealed that high (+1 SD above the mean) T2 Negative Parenting marginally predicted greater left tail volume (β = .46 b=55.71, SE=30.28, *pr*=.25, *p*=.071). This effect was significant at standardized values of T2 Negative Parenting greater than 1.55 (5.17% of the sample). There was no effect in offspring with low T2 Negative Parenting (β = -.48 b=-57.56, SE=34.51, *pr*=-.23, *p*=.101).

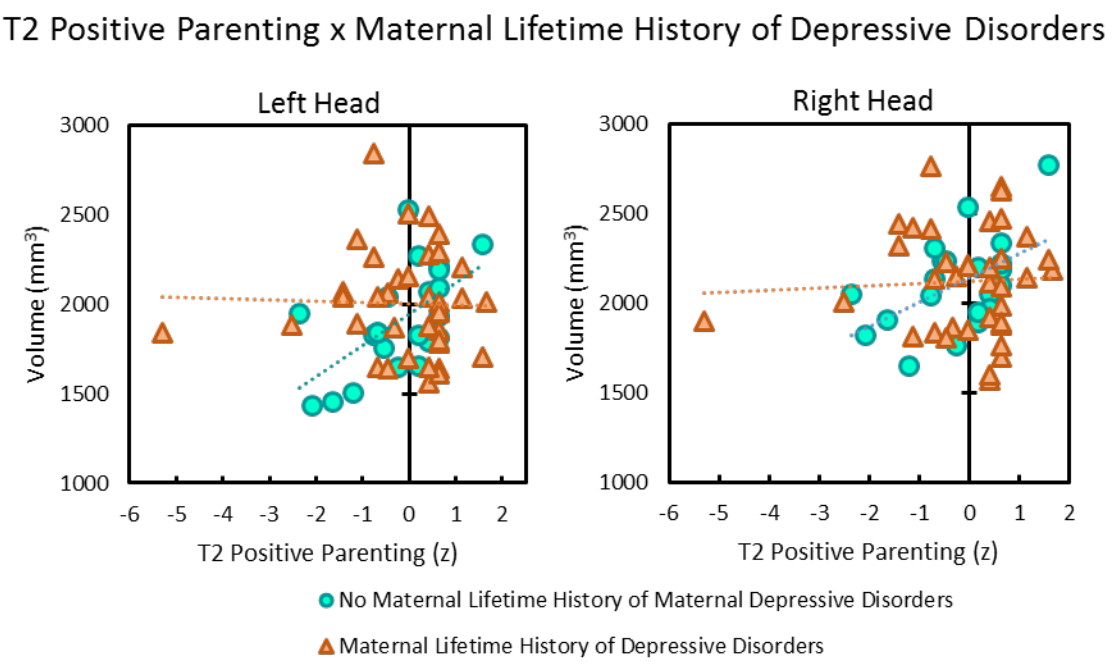


Figure 11. Interactions between T2 Positive Parenting and maternal lifetime history of depressive disorders on left and right hippocampal head volumes. Note: Scatterplots depict bivariate correlations between the predictor and dependent variable and are not adjusted for additional factors included in the statistical models.

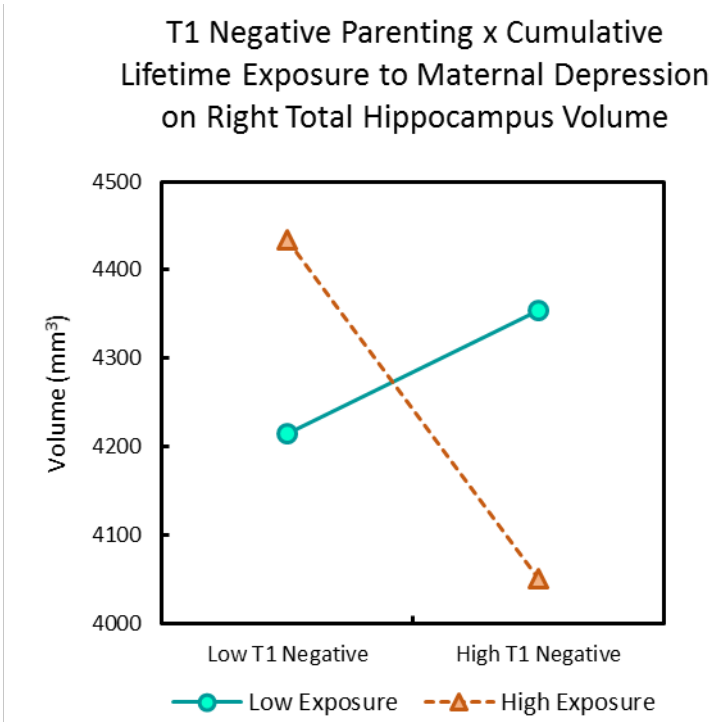


Figure 12. Interaction between T1 Negative Parenting and cumulative exposure to maternal depression on right total hippocampus volume. Note: Scatterplot depicts bivariate correlation between the predictor and dependent variable and is not adjusted for additional factors included in the statistical model.

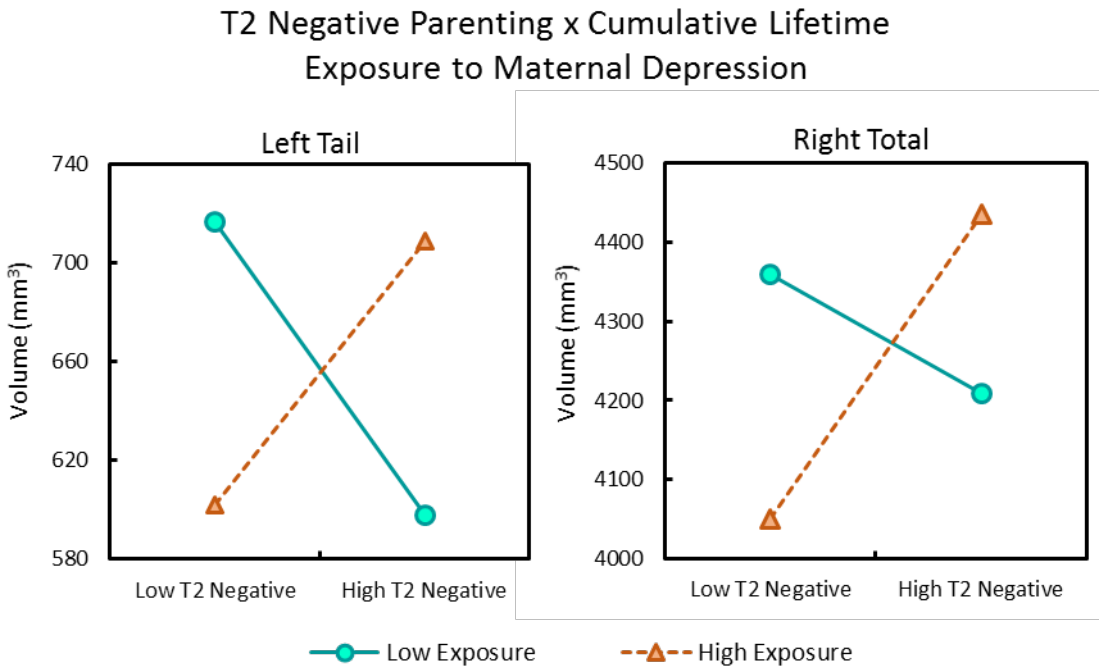


Figure 13. Interactions between T2 Negative Parenting and cumulative exposure to maternal depression on left tail and right total hippocampus volumes. Note: Scatterplots depict bivariate correlations between the predictor and dependent variable and are not adjusted for additional factors included in the statistical models.

Interactions between Cortisol Reactivity and Maternal Depression.

Neither maternal lifetime history of depression nor cumulative exposure to maternal depression significantly interacted with either measure of T1 cortisol reactivity to predict any whole or segmented hippocampal volume (Table 19-Table 26). There were significant interactions between lifetime exposure to maternal depression and T2 total change in cortisol (AUCi), controlling for T1 AUCi, in predicting right hippocampal head (Table 19), tail (Table 21), and total (Table 22) volumes (Figure 14). Specifically, in offspring with high exposure to maternal depression, greater T2 AUCi significantly predicted smaller right tail (β = -.53 b=-70.62, SE=24.41, *pr*=-.38, *p*=.006; significant at standardized values of exposure greater than .36, 22.81% of the sample), and total volumes (β = -.57 b=-202.10, SE=64.54, *pr*=-.40, *p*=.003; significant at standardized

values of exposure greater than .38, 22.81% of the sample) and marginally predicted smaller right hippocampal head (β = -.36 b=-114.99, SE=62.82, *pr*=-.25, *p*=.073; this effect was significant at standardized values of exposure greater than 2.79, 1.75% of the sample). In offspring with low lifetime exposure to maternal depression, T2 AUCi did not significantly predict right head (β = .28, b=90.95, SE=71.55, *pr*=.18, *p*=.210), tail (β = .30, b=39.74, SE=27.72, *pr*=.20, *p*=.158), or total volumes (β = .41 b = 144.76, SE = 73.28, *pr* = .27, *p* = .054).

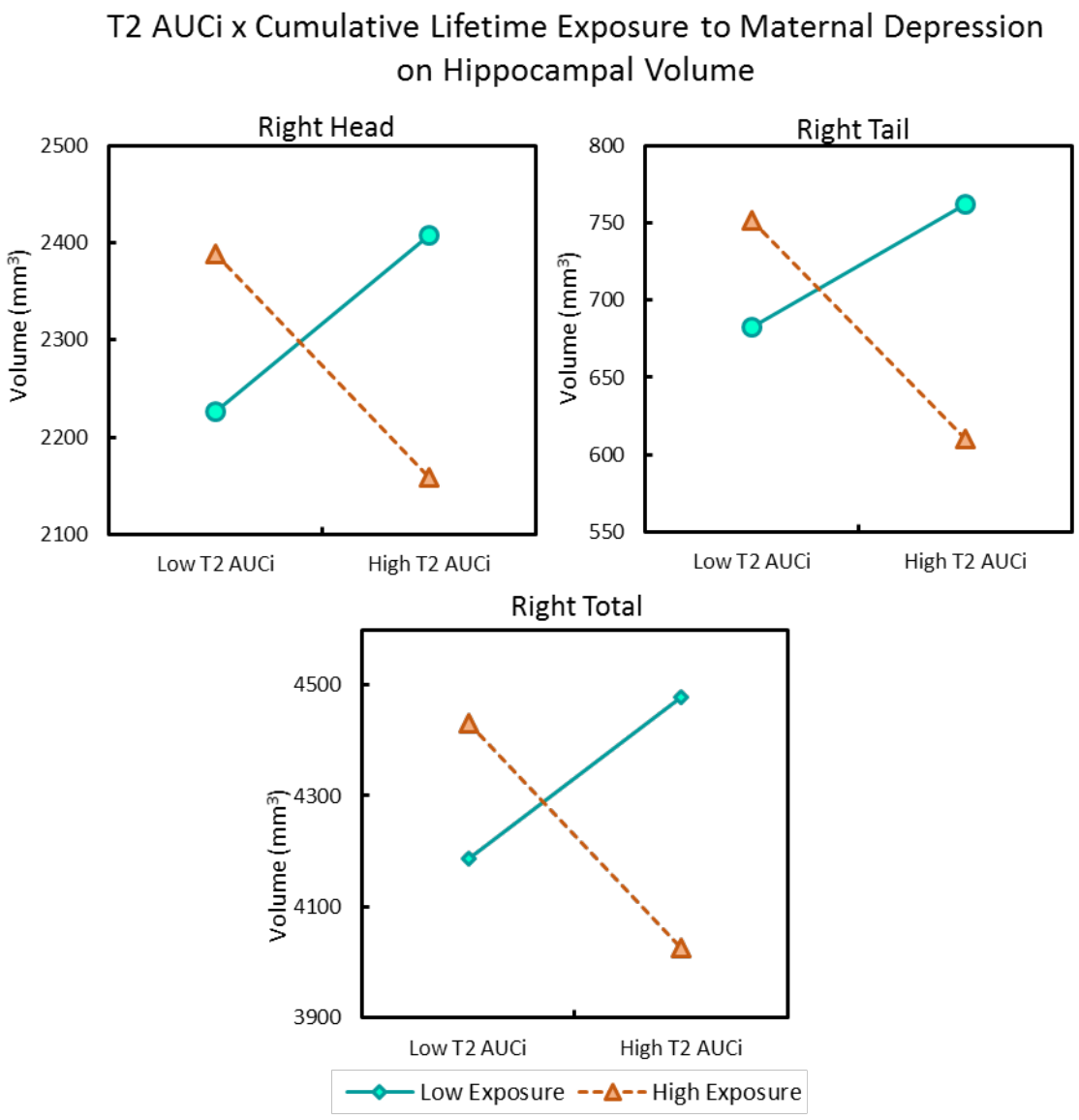


Figure 14. Interaction between T2 AUCi and proportion lifetime exposure to maternal depression on right head, tail, and total hippocampal volumes. Note: Scatterplots depict bivariate correlations between the predictor and dependent variable and are not adjusted for additional factors included in the statistical models.

Table 7
Associations between negative parenting and hippocampal volume.

Model	IV β	IV b(SE)	IV *pr*	IV *p*
DV: Right Hippocampus Head				
T1 Negative Parenting	.02	5.45(43.99)	.02	.902
T2 Negative Parenting	-.24	-73.52(55.26)	-.18	.189
Gender	-.28	-153.58(72.06)	-.28	.038
DV: Right Hippocampus Body				
T1 Negative Parenting	-.09	-13.65(28.55)	-.06	.634
T2 Negative Parenting	.35	68.29(34.46)	.26	.052
Scan Age	.20	39.23(26.14)	.20	.139
DV: Right Hippocampus Tail				
T1 Negative Parenting	.07	7.54(19.16)	.05	.695
T2 Negative Parenting	-.03	-3.81(23.74)	-.02	.873
DV: Right Hippocampus Total				
T1 Negative Parenting	-.13	-37.04(50.91)	-.10	.470
T2 Negative Parenting	.09	31.94(63.09)	.07	.615
DV: Left Hippocampus Head				
T1 Negative Parenting	-.02	-3.99(45.55)	-.01	.930
T2 Negative Parenting	-.21	-68.84(57.21)	-.16	.234
Gender	-.31	-177.64(74.60)	-.31	.021
DV: Left Hippocampus Body				
T1 Negative Parenting	-.12	-23.61(35.05)	-.09	.503
T2 Negative Parenting	.22	52.10(43.44)	.16	.235
DV: Left Hippocampus Tail				
T1 Negative Parenting	.04	4.60(20.67)	.03	.825
T2 Negative Parenting	.01	1.81(25.62)	.01	.944
DV: Left Hippocampus Total				
T1 Negative Parenting	-.05	-13.87(52.03)	-.04	.791
T2 Negative Parenting	.02	8.19(64.48)	.02	.899

Table 8

Associations between positive parenting and hippocampal volume.

Model	IV *β*	IV b(SE)	IV *pr*	IV *p*
DV: Right Hippocampus Head				
T1 Positive Parenting	.27	73.04 (36.19)	.26	**.048**
T2 Positive Parenting	.07	18.02 (32.28)	.08	.579
Gender	-.22	-120.40 (69.18)	-.23	.087
DV: Right Hippocampus Body				
T1 Positive Parenting	.05	8.06 (22.78)	.05	.725
T2 Positive Parenting	-.33	-49.73 (19.89)	-.32	**.015**
Scan Age	.26	49.96 (24.63)	.26	.047
DV: Right Hippocampus Tail				
T1 Positive Parenting	-.10	-11.83 (15.88)	-.10	.459
T2 Positive Parenting	-.16	-16.34 (14.14)	-.15	.253
DV: Right Hippocampus Total				
T1 Positive Parenting	.27	82.44 (41.89)	.25	.054
T2 Positive Parenting	-.15	-40.17 (37.29)	-.14	.286
DV: Left Hippocampus Head				
T1 Positive Parenting	.25	72.23 (37.75)	.25	.061
T2 Positive Parenting	.06	14.70 (33.67)	.06	.664
Gender	-.25	-146.00 (72.17)	-.26	.048
DV: Left Hippocampus Body				
T1 Positive Parenting	.13	27.69 (28.87)	.13	.342
T2 Positive Parenting	-.30	-56.80 (25.70)	-.28	**.031**
DV: Left Hippocampus Tail				
T1 Positive Parenting	.09	10.70 (17.04)	.08	.533
T2 Positive Parenting	-.26	-28.16 (15.17)	-.24	.069
DV: Left Hippocampus Total				
T1 Positive Parenting	.35	107.31 (41.24)	.33	.012
T2 Positive Parenting	-.27	-73.96 (36.71)	-.26	**.049**

Table 9

Main effects of total cortisol release, AUCg, on hippocampal volume.

Model	IV β	IV b(SE)	IV *pr*	IV *p*
DV: Right Hippocampus Head				
T1 AUCg	.15	41.88(36.67)	.15	.258
T2 AUCg	.05	11.63(33.24)	.05	.728
Gender	-.26	-139.63(72.89)	-.25	.061
DV: Right Hippocampus Body				
T1 AUCg	.37	61.09(19.84)	.39	**.003**
T2 AUCg	-.13	-18.88(27.87)	.14	.295
Scan Age	.36	66.30(22.11)	.38	.004
DV: Right Hippocampus Tail				
T1 AUCg	.26	28.99(14.54)	.26	.051
T2 AUCg	-.17	-17.61(13.25)	-.18	.189
DV: Right Hippocampus Total				
T1 AUCg	.36	112.02(39.19)	.36	**.006**
T2 AUCg	-.07	-20.11(35.71)	-.08	.576
DV: Left Hippocampus Head				
T1 AUCg	.08	24.88(39.50)	.09	.531
T2 AUCg	-.11	-30.29(35.81)	-.11	.401
Gender	-.31	-184.92(78.53)	-.31	.022
DV: Left Hippocampus Body				
T1 AUCg	.31	64.13(26.90)	.31	**.021**
T2 AUCg	.10	18.90(24.52)	.10	.444
DV: Left Hippocampus Tail				
T1 AUCg	.13	15.65(15.73)	.13	.324
T2 AUCg	-25	-27.37(14.33)	-.25	.061
DV: Left Hippocampus Total				
T1 AUCg	.27	86.64(41.14)	.27	**.040**
T2 AUCg	-.07	-21.22(37.49)	-.08	.574

Table 10
Main effects of total change in cortisol, AUCi, on hippocampal volume.

Model	IV *β*	IV b(SE)	IV *pr*	IV *p*
DV: Right Hippocampus Head				
T1 AUCi	.11	70.43(88.93)	.11	.432
T2 AUCi	-.08	-24.28(42.56)	-.08	.571
Gender	-.23	-127.29(71.75)	-.24	.082
DV: Right Hippocampus Body				
T1 AUCi	-.53	-211.90(44.69)	-.54	**<.001**
T2 AUCi	.04	8.13(21.22)	.05	.703
Scan Age	.37	69.29(20.40)	.42	.001
DV: Right Hippocampus Tail				
T1 AUCi	-.14	-37.42(36.44)	-.14	.309
T2 AUCi	-.18	-23.75(17.44)	-.18	.179
DV: Right Hippocampus Total				
T1 AUCi	-.19	-144.60(100.23)	-.19	.155
T2 AUCi	-.12	-44.01(47.97)	-.12	.363
DV: Left Hippocampus Head				
T1 AUCi	.12	90.14(94.06)	.13	.342
T2 AUCi	-.19	-65.03(45.02)	-.19	.154
Gender	-.29	169.12(75.89)	-.29	.030
DV: Left Hippocampus Body				
T1 AUCi	-.39	-198.91(63.14)	-.39	**.003**
T2 AUCi	.18	43.62(30.22)	.19	.155
DV: Left Hippocampus Tail				
T1 AUCi	-.11	-33.59(37.16)	-.12	.370
T2 AUCi	-.35	-49.17(17.78)	-.35	**.008**
DV: Left Hippocampus Total				
T1 AUCi	-.17	-134.12(102.09)	-.17	.194
T2 AUCi	-.14	-51.12(48.86)	-.14	.300

Table 11

Interactions between parenting and maternal depression on right hippocampal head volume.

	β	**b (SE)**	***pr***	***p***
Model 1				
Gender	-.31	-171.43 (74.83)	-.30	.026
T1 Negative Parenting	.21	52.67 (59.66)	.12	.381
T2 Negative Parenting	-.51	-157.79 (114.04)	-.19	.172
Maternal Lifetime Depressive Disorder	.05	29.92 (79.07)	.05	.707
T1 Negative Parenting x Maternal DD	-.34	-108.05 (92.35)	-.16	.247
T2 Negative Parenting x Maternal DD	.41	142.17 (136.10)	.14	.301
Model 2				
Gender	-.29	-162.46 (74.18)	-.29	.033
T1 Negative Parenting	-.05	-13.52 (45.10)	-.04	.766
T2 Negative Parenting	-.19	-57.04 (67.78)	-.12	.404
Percent Exposure to Maternal DD	-.04	-9.33 (38.55)	-.03	.810
T1 Negative Parenting x Exposure to Maternal DD	-.57	-106.16 (57.16)	-.25	.069
T2 Negative Parenting x Exposure to Maternal DD	.58	109.91 (58.48)	-.26	.066
Model 3				
Gender	-.24	-131.15 (68.36)	-.26	.061
T1 Positive Parenting	<-.01	-0.18 (52.32)	<.01	.997
T2 Positive Parenting	.57	139.28 (63.80)	.29	.034
Maternal Lifetime Depressive Disorder	-.06	-33.99 (71.44)	-.07	.636
T1 Positive Parenting x Maternal DD	.31	119.25 (71.71)	.23	.102
T2 Positive Parenting x Maternal DD	-.57	-161.74 (73.58)	-.29	**.032**
Model 4				
Gender	-.21	-115.81 (71.94)	-.22	.114
T1 Positive Parenting	.24	64.75 (38.12)	.23	.095
T2 Positive Parenting	.16	38.18 (40.96)	.13	.356
Percent Exposure to Maternal DD	-.07	-18.42 (37.64)	-.07	.627
T1 Positive Parenting x Exposure to Maternal DD	.03	8.72 (37.66)	.03	.818
T2 Positive Parenting x Exposure to Maternal DD	-.14	-18.70 (22.14)	-.12	.402

Note. DD = Depressive Disorder, including Major Depressive Disorder or Dysthymic Disorder

Table 12

Interactions between parenting and maternal depression on right hippocampal body volume.

	β	**b (SE)**	***pr***	***p***
Model 1				
Scan Age	.19	37.40(26.97)	.19	.171
T1 Negative Parenting	-.07	-11.46(37.06)	-.04	.758
T2 Negative Parenting	.52	99.52(69.78)	.19	.160
Maternal Lifetime Depressive Disorder	-.03	-9.92(48.48)	-.03	.839
T1 Negative Parenting x Maternal DD	-.05	-9.14(55.85)	-.02	.871
T2 Negative Parenting x Maternal DD	-.15	-31.78(82.18)	-.05	.701
Model 2				
Scan Age	.19	36.59(26.67)	.19	.176
T1 Negative Parenting	-.12	-18.18(29.62)	-.09	.542
T2 Negative Parenting	.39	73.44(42.37)	.24	.089
Percent Exposure to Maternal DD	.02	3.92(23.51)	.02	.868
T1 Negative Parenting x Exposure to Maternal DD	-.22	-25.73(35.12)	-.10	.467
T2 Negative Parenting x Exposure to Maternal DD	.19	22.08(35.76)	.09	.540
Model 3				
Scan Age	.25	48.23(25.00)	.26	.059
T1 Positive Parenting	.23	38.70(33.90)	-.15	.267
T2 Positive Parenting	-.58	-88.14(40.71)	-.29	.035
Maternal Lifetime Depressive Disorder	.08	28.87(45.28)	.09	.527
T1 Positive Parenting x Maternal DD	-.22	-51.43(45.85)	-.15	.267
T2 Positive Parenting x Maternal DD	.29	50.66(46.83)	.15	.284
Model 4				
Scan Age	.25	47.23(25.25)	.25	.067
T1 Positive Parenting	.07	10.75(23.75)	.06	.653
T2 Positive Parenting	-.31	-45.63(25.06)	-.25	.075
Percent Exposure to Maternal DD	.08	13.74(23.16)	.08	.556
T1 Positive Parenting x Exposure to Maternal DD	-.06	-10.55(23.09)	-.06	.650
T2 Positive Parenting x Exposure to Maternal DD	.02	1.18(13.52)	.01	.931

Note. DD = Depressive Disorder, including Major Depressive Disorder or Dysthymic Disorder

Table 13

Interactions between parenting and maternal depression on right hippocampal tail volume.

	β	**b (SE)**	***pr***	***p***
Model 1				
T1 Negative Parenting	.06	6.04(25.80)	.03	.816
T2 Negative Parenting	.16	20.90(49.12)	.06	.672
Maternal Lifetime Depressive Disorder	-.12	-28.20(34.88)	-.11	.422
T1 Negative Parenting x Maternal DD	-.02	-1.99(40.09)	-.01	.961
T2 Negative Parenting x Maternal DD	-.17	-24.07(59.10)	-.06	.685
Model 2				
T1 Negative Parenting	.04	4.40(20.33)	.03	.829
T2 Negative Parenting	-.04	-5.32(29.85)	-.03	.859
Percent Exposure to Maternal DD	-.05	-5.01(17.29)	-.04	.773
T1 Negative Parenting x Exposure to Maternal DD	-.14	-11.03(25.83)	-.06	.671
T2 Negative Parenting x Exposure to Maternal DD	.22	17.35(26.30)	.09	.512
Model 3				
T1 Positive Parenting	-.25	-28.95(23.79)	-.17	.229
T2 Positive Parenting	-.16	-16.42(29.00)	-.08	.574
Maternal Lifetime Depressive Disorder	-.09	-20.80(32.18)	-.09	.521
T1 Positive Parenting x Maternal DD	.21	33.29(32.61)	.14	.312
T2 Positive Parenting x Maternal DD	<.01	0.29(33.36)	<.01	.993
Model 4				
T1 Positive Parenting	-.13	-14.47(16.84)	-.12	.394
T2 Positive Parenting	-.12	-12.05(18.10)	-.09	.509
Percent Exposure to Maternal DD	-.08	-9.31(16.63)	-.08	.578
T1 Positive Parenting x Exposure to Maternal DD	.02	2.55(16.64)	.02	.879
T2 Positive Parenting x Exposure to Maternal DD	-.09	-4.87(9.77)	-.07	.620

Note. DD = Depressive Disorder, including Major Depressive Disorder or Dysthymic Disorder

Table 14

Interactions between parenting and maternal depression on right total hippocampal volume.

	β	**b (SE)**	***pr***	***p***
Model 1				
T1 Negative Parenting	-.03	-7.73(68.73)	-.02	.911
T2 Negative Parenting	.11	36.35(130.85)	.04	.782
Maternal Lifetime Depressive Disorder	-.01	-3.50(92.91)	-.01	.970
T1 Negative Parenting x Maternal DD	-.20	-73.29(106.78)	-.09	.495
T2 Negative Parenting x Maternal DD	.07	27.27(157.41)	.02	.863
Model 2				
T1 Negative Parenting	-.23	-61.33(50.85)	-.17	.233
T2 Negative Parenting	.17	58.61(74.63)	.11	.436
Percent Exposure to Maternal DD	-.07	-21.12(43.23)	-.07	.627
T1 Negative Parenting x Exposure to Maternal DD	-.64	-130.94(64.59)	-.27	**.048**
T2 Negative Parenting x Exposure to Maternal DD	.65	134.15(65.77)	.27	**.046**
Model 3				
T1 Positive Parenting	.08	24.11(62.57)	.05	.701
T2 Positive Parenting	.14	37.06(76.27)	.07	.629
Maternal Lifetime Depressive Disorder	-.01	-3.24(84.65)	-.01	.970
T1 Positive Parenting x Maternal DD	.23	100.08(85.78)	.16	.249
T2 Positive Parenting x Maternal DD	-.33	-103.84(87.75)	-.16	.242
Model 4				
T1 Positive Parenting	.25	72.89(43.26)	.23	.098
T2 Positive Parenting	-.04	-10.41(46.49)	-.03	.824
Percent Exposure to Maternal DD	-.04	-11.43(42.71)	-.04	.790
T1 Positive Parenting x Exposure to Maternal DD	.02	6.34(42.73)	.02	.883
T2 Positive Parenting x Exposure to Maternal DD	-.16	-23.14(25.09))	-.13	.361

Note. DD = Depressive Disorder, including Major Depressive Disorder or Dysthymic Disorder

Table 15

Interactions between parenting and maternal depression on left hippocampal head volume.

	β	**b (SE)**	***pr***	***p***
Model 1				
Gender	-0.30	-173.29(76.79)	-.30	.028
T1 Negative Parenting	-.01	-2.65(61.21)	-.01	.966
T2 Negative Parenting	-.51	-165.85(117.02)	-.19	.162
Maternal Lifetime Depressive Disorder	.19	112.38(81.13)	.19	.172
T1 Negative Parenting x Maternal DD	.06	18.56(94.76)	.03	.846
T2 Negative Parenting x Maternal DD	.25	90.30(139.66)	.09	.521
Model 2				
Gender	-.34	-197.09(78.08)	-.33	.015
T1 Negative Parenting	-.05	-14.21(47.47)	-.04	.766
T2 Negative Parenting	-.30	-98.21(71.34)	-.19	.175
Percent Exposure to Maternal DD	.07	20.52(40.58)	.07	.615
T1 Negative Parenting x Exposure to Maternal DD	-.27	-53.71(60.16)	-.12	.376
T2 Negative Parenting x Exposure to Maternal DD	.40	79.73(61.55)	.18	.201
Model 3				
Gender	-.26	-152.20(69.94)	-.29	.034
T1 Positive Parenting	.12	34.95(53.54)	.09	.517
T2 Positive Parenting	.63	159.71(65.28)	.32	.018
Maternal Lifetime Depressive Disorder	.07	42.41(73.09)	.08	.564
T1 Positive Parenting x Maternal DD	.11	45.85(73.37)	.09	.535
T2 Positive Parenting x Maternal DD	-.66	-194.54(75.29)	-.34	**.013**
Model 4				
Gender	-.26	-150.52(74.71)	-.27	.049
T1 Positive Parenting	.24	67.54(39.59)	.23	.094
T2 Positive Parenting	.17	44.07(42.54)	.14	.305
Percent Exposure to Maternal DD	-.02	-4.58(39.08)	-.02	.907
T1 Positive Parenting x Exposure to Maternal DD	-.07	-19.16(39.11)	-.07	.626
T2 Positive Parenting x Exposure to Maternal DD	-.17	-23.39(23.00)	-.14	.314

Note. DD = Depressive Disorder, including Major Depressive Disorder or Dysthymic Disorder

Table 16

Interactions between parenting and maternal depression on left hippocampal body volume.

	β	**b (SE)**	***pr***	***p***
Model 1				
T1 Negative Parenting	-.21	-39.91(46.68)	-.12	.396
T2 Negative Parenting	.60	143.54(88.86)	.22	.112
Maternal Lifetime Depressive Disorder	-.17	-76.44(63.09)	-.16	.231
T1 Negative Parenting x Maternal DD	.10	25.09(72.52)	.05	.731
T2 Negative Parenting x Maternal DD	-.41	-108.87(106.90)	-.14	.313
Model 2				
T1 Negative Parenting	-.14	-27.01(36.75)	-.10	.466
T2 Negative Parenting	.21	50.12(53.94)	.13	.358
Percent Exposure to Maternal DD	-.15	-31.92(31.25)	-.14	.312
T1 Negative Parenting x Exposure to Maternal DD	.05	7.17(46.68)	.02	.879
T2 Negative Parenting x Exposure to Maternal DD	.08	11.49(47.54)	.03	.810
Model 3				
T1 Positive Parenting	.31	66.41(42.91)	.21	.128
T2 Positive Parenting	-.62	-117.51(52.31)	-.30	.029
Maternal Lifetime Depressive Disorder	-.05	-19.98(58.05)	-.05	.732
T1 Positive Parenting x Maternal DD	-.22	-65.29(58.83)	-.15	.272
T2 Positive Parenting x Maternal DD	.37	82.24(60.18)	.18	.178
Model 4				
T1 Positive Parenting	.12	24.93(29.91)	.12	.408
T2 Positive Parenting	-.24	-45.79(32.14)	-.19	.160
Percent Exposure to Maternal DD	-.17	-34.93(29.53)	-.16	.242
T1 Positive Parenting x Exposure to Maternal DD	-.18	-37.07(29.54)	-.17	.215
T2 Positive Parenting x Exposure to Maternal DD	-.09	-9.00(17.34)	-.07	.606

Note. DD = Depressive Disorder, including Major Depressive Disorder or Dysthymic Disorder

Table 17

Interactions between parenting and maternal depression on left hippocampal tail volume.

	β	**b (SE)**	***pr***	***p***
Model 1				
T1 Negative Parenting	.15	16.93(27.77)	.08	.545
T2 Negative Parenting	.11	15.06(52.86)	.04	.777
Maternal Lifetime Depressive Disorder	-.06	-16.36(37.53)	-.06	.665
T1 Negative Parenting x Maternal DD	-.23	-33.83(43.14)	-.11	.436
T2 Negative Parenting x Maternal DD	.01	1.65(63.59)	<.01	.979
Model 2				
T1 Negative Parenting	-.04	-4.82(20.97)	-.03	.819
T2 Negative Parenting	-.02	-3.00(30.78)	-.01	.923
Percent Exposure to Maternal DD	-.01	-0.93(17.83)	-.01	.959
T1 Negative Parenting x Exposure to Maternal DD	-.52	-43.83(26.64)	-.22	.106
T2 Negative Parenting x Exposure to Maternal DD	.66	56.64(27.13)	.28	**.042**
Model 3				
T1 Positive Parenting	-.03	-3.82(25.20)	-.02	.880
T2 Positive Parenting	-.49	-54.08(30.72)	-.24	.084
Maternal Lifetime Depressive Disorder	-.01	-3.21(34.10)	-.01	.925
T1 Positive Parenting x Maternal DD	.20	34.01(34.55)	.13	.330
T2 Positive Parenting x Maternal DD	.26	33.80(35.35)	.13	.343
Model 4				
T1 Positive Parenting	.08	9.39(17.97)	.07	.604
T2 Positive Parenting	-.24	-26.18(19.32)	-.19	.181
Percent Exposure to Maternal DD	.03	3.66(17.75)	.03	.837
T1 Positive Parenting x Exposure to Maternal DD	.08	9.60(17.76)	.08	.591
T2 Positive Parenting x Exposure to Maternal DD	-.02	-1.07(10.42)	-.01	.918

Note. DD = Depressive Disorder, including Major Depressive Disorder or Dysthymic Disorder

Table 18

Interactions between parenting and maternal depression on left total hippocampal volume.

	β	**b (SE)**	***pr***	***p***
Model 1				
T1 Negative Parenting	-.07	-18.71(70.32)	-.04	.791
T2 Negative Parenting	.17	58.17(133.86)	.06	.666
Maternal Lifetime Depressive Disorder	.05	29.91(95.05)	.04	.754
T1 Negative Parenting x Maternal DD	.05	18.46(109.24)	.02	.866
T2 Negative Parenting x Maternal DD	-.19	-75.95(161.04)	-.07	.639
Model 2				
T1 Negative Parenting	-.23	-35.88(52.55)	-.09	.498
T2 Negative Parenting	.01	1.60(77.13)	<.01	.984
Percent Exposure to Maternal DD	-.09	-28.04(44.68)	-.09	.533
T1 Negative Parenting x Exposure to Maternal DD	-.42	-88.27(66.76)	-.18	.192
T2 Negative Parenting x Exposure to Maternal DD	.59	124.57(67.98)	.25	.073
Model 3				
T1 Positive Parenting	.32	99.78(62.19)	.22	.115
T2 Positive Parenting	-.11	-29.62(75.81)	-.05	.698
Maternal Lifetime Depressive Disorder	.07	46.49(84.13)	.08	.583
T1 Positive Parenting x Maternal DD	.02	7.59(85.26)	.01	.929
T2 Positive Parenting x Maternal DD	-.19	-60.56(87.21)	-.10	.490
Model 4				
T1 Positive Parenting	.33	100.13(41.96)	.31	.021
T2 Positive Parenting	-.15	-40.56(45.10)	-.12	.373
Percent Exposure to Maternal DD	-.12	-36.10(41.43)	-.12	.388
T1 Positive Parenting x Exposure to Maternal DD	-.15	-44.62(41.45)	-.15	.287
T2 Positive Parenting x Exposure to Maternal DD	-.17	-24.82(24.34)	-.14	.313

Note. DD = Depressive Disorder, including Major Depressive Disorder or Dysthymic Disorder

Table 19

Interactions between cortisol reactivity and maternal depression on right hippocampal head volume.

	β	**b (SE)**	***pr***	***p***
Model 1				
Gender	-.24	-128.58(76.14)	-.23	.097
T1 AUCg	.09	23.61(29.21)	.04	.767
T2 AUCg	.19	46.89(58.24)	.11	.424
Maternal Lifetime Depressive Disorder	.07	37.31(75.42)	.07	.623
T1 AUCg x Maternal DD	.05	19.63(89.31)	.03	.827
T2 AUCg x Maternal DD	-.16	-49.73(71.39)	-.10	.489
Model 2				
Gender	-.23	-127.41(75.29)	-.23	.097
T1 AUCg	.15	40.77(37.52)	.15	.282
T2 AUCg	.07	16.97(34.79)	.07	.628
Percent Exposure to Maternal DD	-.05	-14.83(39.31)	-.05	.708
T1 AUCg x Exposure to Maternal DD	-.12	-37.75(43.42)	-.12	.389
T2 AUCg x Exposure to Maternal DD	-.12	-35.45(41.16)	-.12	.393
Model 3				
Gender	-.23	-22.25(77.00)	-.22	.119
T1 AUCi	.14	91.54(142.80)	.09	.524
T2 AUCi	.12	37.46(65.80)	.08	.572
Maternal Lifetime Depressive Disorder	.08	40.95(75.86)	.08	.592
T1 AUCi x Maternal DD	-.06	-55.53(190.60)	-.04	.772
T2 AUCi x Maternal DD	-.25	-112.27(88.41)	-.18	.210
Model 4				
Gender	-.20	-109.55(72.04)	-.21	.135
T1 AUCi	.06	37.59(90.70)	.06	.680
T2 AUCi	-.04	12.02(44.16)	-.04	.787
Percent Exposure to Maternal DD	-.08	-22.17(38.40)	-.08	.566
T1 AUCi x Exposure to Maternal DD	.03	28.24(121.22)	.03	.817
T2 AUCi x Exposure to Maternal DD	-.28	-102.97(50.83)	-.28	**.048**

Note. DD = Depressive Disorder, including Major Depressive Disorder or Dysthymic Disorder

Table 20

Interactions between cortisol reactivity and maternal depression on right hippocampal body volume.

	β	**b (SE)**	***pr***	***p***
Model 1				
Scan Age	.36	65.72(22.05)	.39	.004
T1 AUCg	.60	99.45(41.68)	.32	.021
T2 AUCg	.04	6.41(30.44)	.03	.834
Maternal Lifetime Depressive Disorder	-.10	-33.76(39.08)	-.12	.392
T1 AUCg x Maternal DD	-.28	-51.75(47.26)	-.15	.279
T2 AUCg x Maternal DD	-.23	-43.33(37.64)	-.16	.255
Model 2				
Scan Age	.35	63.60(22.68)	.37	.007
T1 AUCg	.38	61.63(20.03)	.40	.003
T2 AUCg	-.14	-20.37(18.46)	-.15	.275
Percent Exposure to Maternal DD	-.03	-4.96(21.11)	-.03	.815
T1 AUCg x Exposure to Maternal DD	.03	5.67(23.48)	.03	.810
T2 AUCg x Exposure to Maternal DD	-.03	-5.29(22.00)	-.03	.811
Model 3				
Scan Age	.38	69.8(21.11)	.42	.002
T1 AUCi	-.40	-161.90(70.21)	-.31	.025
T2 AUCi	.01	1.26(32.64)	.01	.969
Maternal Lifetime Depressive Disorder	-.11	-34.76(37.19)	-.13	.354
T1 AUCi x Maternal DD	-.16	-86.00(91.58)	-.13	.352
T2 AUCi x Maternal DD	.01	1.43(44.95)	<.01	.975
Model 4				
Scan Age	.38	68.49(21.04)	.42	.002
T1 AUCi	-.53	-209.06(46.67)	-.54	<.001
T2 AUCi	.02	3.00(22.58)	.02	.895
Percent Exposure to Maternal DD	-.06	-10.68(19.71)	-.08	.590
T1 AUCi x Exposure to Maternal DD	<-.01	-0.96(62.09)	<-.01	.988
T2 AUCi x Exposure to Maternal DD	<.01	0.91(26.18)	.01	.972

Note. DD = Depressive Disorder, including Major Depressive Disorder or Dysthymic Disorder

Table 21

Interactions between cortisol reactivity and maternal depression on right hippocampal tail volume.

	β	**b (SE)**	***pr***	***p***
Model 1				
T1 AUCg	.67	75.70(30.74)	.32	.017
T2 AUCg	-.13	-13.41(22.44)	-.08	.553
Maternal Lifetime Depressive Disorder	-.11	-24.46(28.83)	-.12	.400
T1 AUCg x Maternal DD	-.47	-60.55(34.82)	-.23	.088
T2 AUCg x Maternal DD	-.08	-10.63(27.76)	-.05	.703
Model 2				
T1 AUCg	.25	27.93(14.46)	.26	.059
T2 AUCg	-.16	-16.60(13.46)	-.17	.223
Percent Exposure to Maternal DD	-.10	-11.51(15.36)	-.10	.457
T1 AUCg x Exposure to Maternal DD	-.26	-33.67(16.96)	-.27	.053
T2 AUCg x Exposure to Maternal DD	-.07	-8.38(16.04)	-.07	.604
Model 3				
T1 AUCi	-.33	-91.26(57.15)	-.22	.116
T2 AUCi	-.06	-7.68(26.38)	.16	.250
Maternal Lifetime Depressive Disorder	-.14	-31.89(30.28)	-.15	.297
T1 AUCi x Maternal DD	.24	86.63(74.41)	.16	.250
T2 AUCi x Maternal DD	-.17	-31.79(35.76)	-.12	.378
Model 4				
T1 AUCi	-.21	-56.68(35.17)	-.22	.113
T2 AUCi	-.12	-15.44(17.11)	-.13	.371
Percent Exposure to Maternal DD	-.18	-20.73(14.93)	-.19	.171
T1 AUCi x Exposure to Maternal DD	.14	51.95(46.95)	.15	.274
T2 AUCi x Exposure to Maternal DD	-.37	-55.18(19.73)	-.37	**.007**

Note. DD = Depressive Disorder, including Major Depressive Disorder or Dysthymic Disorder

Table 22

Interactions between cortisol reactivity and maternal depression on right total hippocampal volume.

	β	**b (SE)**	***pr***	***p***
Model 1				
T1 AUCg	.61	188.72(83.72)	.30	.028
T2 AUCg	.15	42.52(61.12)	.10	.490
Maternal Lifetime Depressive Disorder	<.01	0.95(78.54)	<.01	.990
T1 AUCg x Maternal DD	-.30	-103.81(94.85)	-.15	.279
T2 AUCg x Maternal DD	-.29	-100.39(75.62)	-.18	.190
Model 2				
T1 AUCg	.37	112.75(38.16)	.38	.005
T2 AUCg	-.06	-15.14(35.53)	-.17	.229
Percent Exposure to Maternal DD	-.10	-30.46(40.54)	-.11	.456
T1 AUCg x Exposure to Maternal DD	-.16	-54.53(44.77)	-.17	.229
T2 AUCg x Exposure to Maternal DD	-.18	-58.40(42.34)	-.19	.174
Model 3				
T1 AUCi	-.27	-202.34(156.34)	-.18	.201
T2 AUCi	.15	54.93(72.16)	.11	.450
Maternal Lifetime Depressive Disorder	-.01	-5.71(82.84)	-.01	.945
T1 AUCi x Maternal DD	.07	65.76(203.58)	.05	.748
T2 AUCi x Maternal DD	-.37	-185.55(97.83)	-.25	.063
Model 4				
T1 AUCi	-.27	-200.11(92.97)	-.29	.036
T2 AUCi	-.08	-28.67(45.23)	-.09	.529
Percent Exposure to Maternal DD	-.17	-52.03(39.46)	-.18	.193
T1 AUCi x Exposure to Maternal DD	.07	66.16(124.11)	.07	.596
T2 AUCi x Exposure to Maternal DD	-.43	-173.43(52.17)	-.42	**.002**

Note. DD = Depressive Disorder, including Major Depressive Disorder or Dysthymic Disorder

Table 23

Interactions between cortisol reactivity and maternal depression on left hippocampal head volume.

	β	**b (SE)**	***pr***	***p***
Model 1				
Gender	-.27	-159.78(80.84)	-.27	.054
T1 AUCg	-.02	-6.78(84.09)	-.01	.936
T2 AUCg	<.01	0.67(61.82)	<.01	.991
Maternal Lifetime Depressive Disorder	.19	111.33(80.07)	.19	.170
T1 AUCg x Maternal DD	.11	36.23(94.81)	.05	.704
T2 AUCg x Maternal DD	-.11	-35.94(75.79)	-.07	.637
Model 2				
Gender	-.31	-186.13(81.52)	-.31	.027
T1 AUCg	.08	23.52(40.62)	.08	.565
T2 AUCg	-.14	-37.33(37.67)	-.14	.326
Percent Exposure to Maternal DD	.07	20.40(42.56)	.07	.634
T1 AUCg x Exposure to Maternal DD	-.05	-17.02(47.01)	-.05	.719
T2 AUCg x Exposure to Maternal DD	.12	38.03(44.57)	.12	.398
Model 3				
Gender	-.27	-159.06(80.77)	-.27	.05
T1 AUCi	.21	153.89(149.78)	.14	.309
T2 AUCi	-.05	-17.96(69.02)	-.04	.796
Maternal Lifetime Depressive Disorder	.19	112.22(79.56)	.19	.164
T1 AUCi x Maternal DD	-.13	-120.84(199.91)	-.08	.548
T2 AUCi x Maternal DD	-.15	-73.86(92.73)	-.11	.429
Model 4				
Gender	-.26	-155.42(78.48)	-.27	.053
T1 AUCi	.10	73.73(98.81)	.11	.459
T2 AUCi	-.15	-53.27(48.11)	-.16	.273
Percent Exposure to Maternal DD	-.01	-1.82(41.84)	-.01	.966
T1 AUCi x Exposure to Maternal DD	.06	54.38(132.05)	.06	.682
T2 AUCi x Exposure to Maternal DD	-.16	-62.81(55.37)	-.16	.262

Note. DD = Depressive Disorder, including Major Depressive Disorder or Dysthymic Disorder

Table 24

Interactions between cortisol reactivity and maternal depression on left hippocampal body volume.

	β	**b (SE)**	***pr***	***p***
Model 1				
T1 AUCg	.21	42.99(57.85)	.10	.461
T2 AUCg	.14	25.39(42.24)	.09	.535
Maternal Lifetime Depressive Disorder	-.18	-75.41(54.27)	-.19	.171
T1 AUCg x Maternal DD	.11	26.03(65.54)	.06	.693
T2 AUCg x Maternal DD	-.07	-15.69(52.26)	-.04	.765
Model 2				
T1 AUCg	.31	64.08(26.99)	.32	.021
T2 AUCg	.09	16.72(25.13)	.09	.509
Percent Exposure to Maternal DD	-.23	-48.92(28.67)	-.23	.094
T1 AUCg x Exposure to Maternal DD	.03	7.25(31.66)	.03	.820
T2 AUCg x Exposure to Maternal DD	<.01	0.60(29.94)	<.01	.984
Model 3				
T1 AUCi	-.38	-195.09(99.65)	-.26	.056
T2 AUCi	.05	11.82(45.99)	.04	.798
Maternal Lifetime Depressive Disorder	-.18	-75.38(52.80)	-.19	.159
T1 AUCi x Maternal DD	<.01	1.42(129.76)	<.01	.991
T2 AUCi x Maternal DD	.14	45.92(62.36)	.10	.465
Model 4				
T1 AUCi	-.42	-213.01(64.65)	-.42	.002
T2 AUCi	.16	37.76(31.46)	.17	.236
Percent Exposure to Maternal DD	-.26	-55.51(27.44)	-.27	.048
T1 AUCi x Exposure to Maternal DD	.01	8.62(86.31)	.01	.921
T2 AUCi x Exposure to Maternal DD	-.09	-25.67(36.28)	-.10	.482

Note. DD = Depressive Disorder, including Major Depressive Disorder or Dysthymic Disorder

Table 25

Interactions between cortisol reactivity and maternal depression on left hippocampal tail volume.

	β	**b (SE)**	***pr***	***p***
Model 1				
T1 AUCg	.12	14.49(34.52)	.06	.676
T2 AUCg	-.26	-28.22(25.20)	-.15	.268
Maternal Lifetime Depressive Disorder	-.01	-3.11(32.38)	-.01	.924
T1 AUCg x Maternal DD	.01	1.55(39.11)	.01	.969
T2 AUCg x Maternal DD	.01	1.16(31.18)	.01	.970
Model 2				
T1 AUCg	.12	14.89(15.66)	.13	.346
T2 AUCg	-.26	-28.74(14.58)	-.27	.054
Percent Exposure to Maternal DD	.06	7.11(16.63)	.06	.671
T1 AUCg x Exposure to Maternal DD	-.21	-28.89(18.37)	-.22	.122
T2 AUCg x Exposure to Maternal DD	.02	2.06(17.37)	.02	.906
Model 3				
T1 AUCi	-.17	-49.26(59.29)	-.11	.410
T2 AUCi	-.21	-29.71(27.36)	-.15	.283
Maternal Lifetime Depressive Disorder	-.04	-9.36(31.41)	-.04	.767
T1 AUCi x Maternal DD	.05	20.09(77.20)	.04	.796
T2 AUCi x Maternal DD	-.19	-37.67(37.10)	-.14	.315
Model 4				
T1 AUCi	-.13	-37.99(38.15)	-.14	.324
T2 AUCi	-.33	-45.81(18.56)	-.33	.017
Percent Exposure to Maternal DD	-.03	-3.37(16.20)	-.03	.836
T1 AUCi x Exposure to Maternal DD	.10	38.26(50.93)	.11	.456
T2 AUCi x Exposure to Maternal DD	-.15	-24.20(21.41)	-.16	.264

Note. DD = Depressive Disorder, including Major Depressive Disorder or Dysthymic Disorder

Table 26

Interactions between cortisol reactivity and maternal depression on left total hippocampal volume.

	β	**b (SE)**	***pr***	***p***
Model 1				
T1 AUCg	.06	18.14(88.19)	.03	.838
T2 AUCg	.13	38.54(64.38)	.08	.552
Maternal Lifetime Depressive Disorder	.11	70.83(82.73)	.12	.396
T1 AUCg x Maternal DD	.23	85.52(99.91)	.12	.407
T2 AUCg x Maternal DD	-.23	-83.47(79.66)	-.14	.300
Model 2				
T1 AUCg	.27	84.16(40.52)	.28	.043
T2 AUCg	-.11	-31.84(37.73)	-.12	.403
Percent Exposure to Maternal DD	-.07	-21.55(43.05)	-.07	.619
T1 AUCg x Exposure to Maternal DD	-.15	-52.44(47.54)	-.15	.275
T2 AUCg x Exposure to Maternal DD	.11	37.05(44.96)	.12	.414
Model 3				
T1 AUCi	-.17	-127.89(162.67)	-.11	.435
T2 AUCi	.01	3.55(75.08)	.01	.962
Maternal Lifetime Depressive Disorder	.11	67.75(86.19)	.11	.435
T1 AUCi x Maternal DD	-.03	-27.05(211.82)	-.02	.259
T2 AUCi x Maternal DD	-.18	-92.39(101.79)	-.13	.368
Model 4				
T1 AUCi	-.22	-165.12(99.64)	-.23	.104
T2 AUCi	-.11	-39.72(48.48)	-.11	.416
Percent Exposure to Maternal DD	-.17	-55.41(52.30)	-.18	.196
T1 AUCi x Exposure to Maternal DD	.15	151.83(133.02)	.16	.259
T2 AUCi x Exposure to Maternal DD	-.27	-110.31(55.92)	-.27	.054

Note. DD = Depressive Disorder, including Major Depressive Disorder or Dysthymic Disorder

Table 27

Mediation of the association between parenting and hippocampal volume by cortisol reactivity.

Dependent Measure	Predictor	Covariate	Mediator	Total Effect	Direct Effect	Indirect Effect	SE	Lower CI	Upper CI
Right Head	T1 Positive Parenting	Gender, T2 Positive Parenting	T1 AUCg	56.01	45.55	6.87	10.83	-5.47	37.59
		Gender, T2 Positive Parenting	T1 AUCi	56.01	54.07	2.73	8.32	-5.59	33.35
		Gender, T2 Positive Parenting	T2 AUCg	74.57	77.98	-3.37	7.88	-23.04	9.74
		Gender, T2 Positive Parenting	T2 AUCi	74.57	73.78	0.78	5.61	-7.62	19.51
	T1 Negative Parenting	Gender, T2 Negative Parenting	T1 AUCg	25.07	25.56	-0.33	5.66	-11.67	11.31
		Gender, T2 Negative Parenting	T1 AUCi	25.07	23.95	2.05	3.78	-2.13	15.42
		Gender, T2 Negative Parenting	T2 AUCg	2.87	0.74	1.33	11.63	-22.10	29.44
		Gender, T2 Negative Parenting	T2 AUCi	2.87	11.47	-6.59	12.81	-46.05	10.03
	T2 Positive Parenting	Gender, T1 Positive Parenting	T2 AUCg	17.28	17.62	-1.17	5.21	-24.18	3.03
		Gender, T1 Positive Parenting	T2 AUCi	17.28	17.26	0.24	4.77	-6.41	11.38
	T2 Negative Parenting	Gender, T1 Negative Parenting	T2 AUCg	-73.88	-72.41	0.47	7.80	-7.77	32.05
		Gender, T1 Negative Parenting	T2 AUCi	-73.88	-77.57	-3.65	9.03	-39.12	5.92
Right Body	T1 Positive Parenting	Scan Age, T2 Positive Parenting	T1 AUCg	21.24	9.53	6.83	8.88	-6.09	33.30
		Scan Age, T2 Positive Parenting	T1 AUCi	21.24	28.71	-12.07	17.47	-55.62	14.51
		Scan Age, T2 Positive Parenting	T2 AUCg	6.72	0.75	6.24	5.39	-0.44	21.38
		Scan Age, T2 Positive Parenting	T2 AUCi	6.72	6.71	0.07	2.86	-5.29	7.69
	T1 Negative Parenting	Scan Age, T2 Negative Parenting	T1 AUCg	-17.80	-20.26	-0.43	6.30	-13.02	12.68
		Scan Age, T2 Negative Parenting	T1 AUCi	-17.80	-10.12	-5.67	4.88	-15.02	4.50
		Scan Age, T2 Negative Parenting	T2 AUCg	-11.71	2.92	-9.15	9.72	-38.42	0.20
		Scan Age, T2 Negative Parenting	T2 AUCi	-11.71	-9.12	-2.08	7.11	-20.39	8.35

	T2 Positive Parenting	Scan Age, T1 Positive Parenting	T2 AUCg	-48.59	-48.89	2.17	4.16	-2.71	14.30
		Scan Age, T1 Positive Parenting	T2 AUCi	-48.59	-48.59	0.02	2.49	-4.91	3.53
	T2 Negative Parenting	Scan Age, T1 Negative Parenting	T2 AUCg	71.01	61.82	-3.25	7.32	-25.15	6.09
		Scan Age, T1 Negative Parenting	T2 AUCi	71.01	70.00	-1.15	5.05	-17.75	4.07
Right Tail	T1 Positive Parenting	T2 Positive Parenting	T1 AUCg	-23.66	-32.13	5.63	6.54	-4.73	21.66
		T2 Positive Parenting	T1 AUCi	-23.66	-21.81	-2.58	5.79	-23.41	14.09
		T2 Positive Parenting	T2 AUCg	-9.79	-14.36	4.66	3.70	-0.12	15.08
		T2 Positive Parenting	T2 AUCi	-9.79	-10.55	0.76	3.54	-6.04	9.71
	T1 Negative Parenting	T2 Negative Parenting	T1 AUCg	12.89	8.27	-0.30	3.81	-7.73	8.76
		T2 Negative Parenting	T1 AUCi	12.89	13.58	-1.63	2.16	-7.09	1.51
		T2 Negative Parenting	T2 AUCg	4.76	14.25	-6.35	6.58	-29.74	0.23
		T2 Negative Parenting	T2 AUCi	4.76	14.83	-7.79	7.07	-30.58	0.21
	T2 Positive Parenting	T1 Positive Parenting	T2 AUCg	-17.75	-17.98	1.62	3.11	-2.29	10.99
		T1 Positive Parenting	T2 AUCi	-17.75	-17.75	0.23	3.21	-5.52	7.66
	T2 Negative Parenting	T1 Negative Parenting	T2 AUCg	-5.86	-11.59	-2.25	4.99	-16.25	3.55
		T1 Negative Parenting	T2 AUCi	-5.86	-10.02	-4.32	6.00	-23.85	1.71
Left Head	T1 Positive Parenting	Gender, T2 Positive Parenting	T1 AUCg	62.90	55.62	4.78	9.73	-4.21	38.44
		Gender, T2 Positive Parenting	T1 AUCi	62.90	60.83	2.91	9.65	-7.94	34.08
		Gender, T2 Positive Parenting	T2 AUCg	72.56	70.89	1.65	7.17	-9.11	21.10
		Gender, T2 Positive Parenting	T2 AUCi	72.56	71.13	1.41	7.86	-9.24	25.57

	T1 Negative Parenting	Gender, T2 Negative Parenting	T1 AUCg	10.98	7.90	-0.23	4.62	-10.71	8.11
		Gender, T2 Negative Parenting	T1 AUCi	10.98	9.73	2.27	4.32	-3.26	15.16
		Gender, T2 Negative Parenting	T2 AUCg	-4.71	4.03	-5.47	11.05	-35.47	9.15
		Gender, T2 Negative Parenting	T2 AUCi	-4.71	11.52	-12.43	15.71	-60.00	6.97
	T2 Positive Parenting	Gender, T1 Positive Parenting	T2 AUCg	14.53	14.37	0.57	4.09	-4.71	15.35
		Gender, T1 Positive Parenting	T2 AUCi	14.53	14.50	0.43	6.92	-8.67	16.69
	T2 Negative Parenting	Gender, T1 Negative Parenting	T2 AUCg	-68.94	-75.01	-1.94	8.04	-29.40	6.65
		Gender, T1 Negative Parenting	T2 AUCi	-68.94	-75.90	-6.89	11.31	-57.45	5.26
Left Body	T1 Positive Parenting	T2 Positive Parenting	T1 AUCg	48.81	38.72	6.71	8.18	-4.82	29.47
		T2 Positive Parenting	T1 AUCi	48.81	56.57	-10.82	17.31	-59.13	11.14
		T2 Positive Parenting	T2 AUCg	26.01	28.30	-2.33	5.15	-14.06	6.97
		T2 Positive Parenting	T2 AUCi	26.01	26.95	-0.94	5.39	-17.47	6.52
	T1 Negative Parenting	T2 Negative Parenting	T1 AUCg	-32.47	-39.55	-0.45	7.11	-13.33	16.14
		T2 Negative Parenting	T1 AUCi	-32.47	-30.43	-4.85	4.48	-14.01	3.62
		T2 Negative Parenting	T2 AUCg	-21.01	-27.14	4.10	8.26	-9.60	26.83
		T2 Negative Parenting	T2 AUCi	-21.01	-33.37	9.57	11.86	-6.15	44.85
	T2 Positive Parenting	T1 Positive Parenting	T2 AUCg	-55.64	-55.53	-0.81	3.57	-14.86	2.94
		T1 Positive Parenting	T2 AUCi	-55.64	-55.64	-0.28	4.93	-13.97	6.19
	T2 Negative Parenting	T1 Negative Parenting	T2 AUCg	54.02	57.73	1.46	6.04	-5.03	23.73
		T1 Negative Parenting	T2 AUCi	54.02	59.12	5.30	9.78	-3.75	46.29
Left Tail	T1 Positive Parenting	T2 Positive Parenting	T1 AUCg	-6.25	-10.60	2.90	5.62	-2.72	20.54

	T2 Positive Parenting	T1 AUCi	-6.25	-4.82	-1.98	5.29	-21.39	3.47
	T2 Positive Parenting	T2 AUCg	11.28	5.86	5.52	4.81	-0.38	20.52
	T2 Positive Parenting	T2 AUCi	11.28	10.21	1.07	4.67	-8.41	10.68
T1 Negative Parenting	T2 Negative Parenting	T1 AUCg	15.94	13.18	-0.18	2.86	-6.13	6.19
	T2 Negative Parenting	T1 AUCi	15.94	16.49	-1.31	2.13	-7.28	1.73
	T2 Negative Parenting	T2 AUCg	3.92	16.68	-8.54	7.97	-34.90	0.35
	T2 Negative Parenting	T2 AUCi	3.92	18.37	-11.18	8.62	**-34.49**	**-0.35**
T2 Positive Parenting	T1 Positive Parenting	T2 AUCg	-28.56	-28.83	1.92	3.80	-2.19	15.03
	T1 Positive Parenting	T2 AUCi	-28.56	-28.56	0.32	4.29	-7.57	10.10
T2 Negative Parenting	T1 Negative Parenting	T2 AUCg	1.30	-6.41	-3.03	6.59	-24.56	4.39
	T1 Negative Parenting	T2 AUCi	1.30	-4.66	-6.20	8.04	-32.03	3.20

Chapter 6: Structural Discussion

The present study sought to investigate the longitudinal associations between early (3-6 years) and concurrent (5-10 years) parenting and cortisol reactivity with hippocampal volumes at 5-10 years. Results revealed timing- and region-dependent associations between parenting and the cortisol response to stress on hippocampal subregion volume that were, in some cases, moderated by a maternal history of depressive disorders. The discussion below will focus on significant effects identified in hippocampal subregions; effects of whole hippocampal volumes will be omitted because they did not prove informative over the results from subregion analyses.

Parenting

Results revealed timing and region-dependent associations between parenting and hippocampal volume with greater early (T1) positive parenting predicting larger right hippocampal head volume and greater later (T2) positive parenting predicting smaller bilateral hippocampal body volumes. Not only does this pattern of results imply that hippocampal subregions have different developmental sensitivities to the parenting environment, but they may be affected in different ways.

Maternal lifetime history of depressive disorders moderated the association between T2 Positive Parenting and bilateral hippocampal head volumes. Specifically, in offspring without a maternal lifetime history of depression, greater T2 Positive Parenting predicted larger left head volumes. There was no association in offspring with a maternal lifetime history of depression. Coupled with the main effects described above, this pattern of results suggests that during the preschool years, children, regardless of maternal depression status, are sensitive to the effects of positive parenting; however, the

sensitivity of the hippocampal head to positive parenting behaviors decreases over time in offspring of depressed mothers. Considered differently, the left hippocampal heads of offspring of non-depressed mothers may remain sensitive to the parenting environment longer than those of offspring with a maternal history of depression. No associations between T1 or T2 Negative Parenting and hippocampal subregion volume were significantly moderated by maternal depression status. However, in the left tail, high T2 Negative Parenting moderated the association between cumulative lifetime exposure to maternal depression and left hippocampal tail volume. This association was only significant at extreme high values of T2 Negative Parenting and should be interpreted with caution.

In contrast to what may be hypothesized based on research in maltreatment and neglect (e.g., Andersen et al., 2008; Belsky & de Haan, 2011), in the present study, the effects of parenting on hippocampal volume appeared to be largely driven by positive, and not negative, parenting behaviors. This suggests that during the early to middle childhood period, the hippocampus is more sensitive to the mother's positive supportive presence versus the presence of negative behaviors such as hostility and intrusiveness. This is largely consistent with what has been reported in the rodent literature and in previous human studies. For instance, both studies which found significant effects between hippocampal volume and variations in parenting behaviors used measures of parental nurturance (Rao et al., 2010) or support (Luby et al., 2012). Moreover, the licking and grooming paradigm frequently used to test caregiving behaviors in rodent models may more closely mirror the construct of positive parenting as low licking and grooming represents the absence of developmentally-appropriate (i.e., positive) inputs

and not the presence of harsh or developmentally-stressful (i.e., negative) inputs. Despite these consistencies with the established parenting literature, it should be noted that 1) no previous study investigating the effects of parenting on brain development in human children has investigated a measure of negative parenting and 2) the current measure of Negative Parenting does not tap extreme forms of negative parenting and lacks considerable variability. There was only one significant interaction between Negative Parenting and cumulative lifetime exposure to maternal depression in predicting hippocampal subregion volume, and it was driven by the most extreme cases (top %5, approximately 3 children) of observed Negative Parenting. Therefore, effects of negative parenting on hippocampal volume during childhood may only emerge in in more extreme cases and in the presence of multiple risk factors (e.g., exposure to maternal depression). This possibility should be addressed by future research with greater variability in observed negative parenting.

These findings lend important insights into existing contradictions in the literature regarding associations between parenting behaviors and hippocampal volumes. Specifically, of the three studies which have examined positive parenting and whole hippocampal volume, one found a positive association between maternal support at 3-6 years and volume at 7-13 years (Luby et al., 2012), one found a negative association between maternal nurturance at age 4 and volume at 14 years (Rao et al., 2010), and one failed to find a significant association between warm and supportive parenting at 12 years and volume at 16 years (Whittle et al., 2014). The present results indicate that the effects of parenting on hippocampal volume are regionally-specific and may be obscured by use of whole hippocampal volumes. In many of the present analyses, we fail to find

significant main effects of parenting on whole hippocampal volume despite significant subregion associations. This highlights the utility of incorporating hippocampal subregion metrics into analyses of hippocampal structural development as use of the full hippocampal volume may obscure more nuanced, regionally-specific differences. By using measure of hippocampus head, body, and tail, we were better able to identify regionally-specific changes in hippocampal volume that previous studies failed to explore (Luby et al., 2012; Rao et al., 2010; Whittle et al., 2014). Additionally, the present results add to a growing body of literature which suggests that the hippocampus may be particularly sensitive to the parenting environment during childhood (Luby et al., 2012; Rao et al., 2010) versus adolescence (Whittle et al., 2014). The exact timing and significance of this developmental sensitivity should be addressed by future research.

Moreover, to our knowledge, this is the first study to find that the hippocampus may be sensitive to later, concurrent parenting behaviors and not only behavior during the preschool and early childhood periods. Only one previous study to our knowledge assessed developmentally-specific differences in parenting on hippocampal volume, and found that early (4 years), but not later (8 years), maternal nurturance predicted smaller hippocampal volumes (Rao et al., 2010). This is in contrast to the present results which show that early positive parenting predicted larger head volumes and later positive parenting predicted smaller body volumes. This suggests that hippocampal sensitivity to the parenting environment may last longer than previously expected. The timing and specificity of this sensitivity should be explored by future work as previous research suggests this sensitivity may end by age 12 years (Whittle et al., 2014).

Cortisol Reactivity

Similar timing- and region-dependent patterns of effects were observed between cortisol reactivity and hippocampal volume. Early (T1) cortisol reactivity was associated with left and right body volumes whereas later (T2) cortisol reactivity predicted left tail volumes. Total amount of cortisol released in response to a stressor (AUCg) at T1 and total change in cortisol (AUCi) at T1 had inverse associations with hippocampal body volumes: greater T1 cortisol volume release (AUCg) predicted larger body volumes whereas greater T1 change in cortisol (AUCi) predicted smaller body volumes. At face value, this suggests that different metrics of the cortisol response to stress may be differentially associated with hippocampal volumes. However, upon closer inspection, it appears that the association between T1 AUCi and bilateral body volumes appears to be driven by three individuals with high baseline cortisol levels which declined over time (i.e., a blunted cortisol response; Fairchild et al., 2008; Figure 15). Therefore, taken together, these effects may indicate that hippocampal body volume is affected by high T1 cortisol levels (at baseline or in response to stress). This is in contrast to what would be predicted from the glucocorticoid neurotoxicity hypothesis (Conrad, 2009; Sapolsky et al., 1990; Sapolsky, 1988; Uno et al., 1994) and should be explored in greater detail. Greater change in cortisol in response to a stressor (AUCi) at T2 was associated with reduced left hippocampal tail volume. Mirroring the effects found with parenting, in addition to T1 and T2 cortisol reactivity predicting different hippocampal subregion volumes, the direction of these associations were also different: while early (T1) cortisol reactivity predicted larger body volumes, later (T2) cortisol reactivity predicted smaller tail volumes.

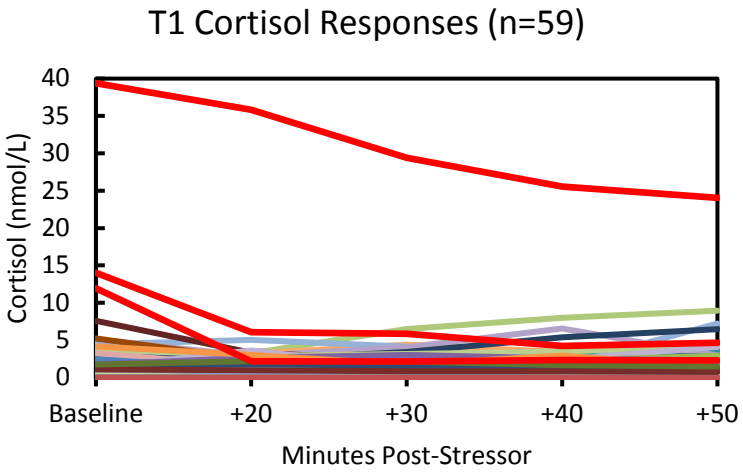


Figure 15. T1 cortisol levels at baseline, 20-, 30-, 40-, and 50-minutes post-stressor. Individuals driving T1 AUCi findings are highlighted in red.

Cumulative lifetime exposure to maternal depression significantly moderated associations between cortisol reactivity and hippocampal volume.

In offspring with high exposure to maternal depression, greater cortisol change in in response to a stressor (AUCi) at T2 predicted reduced right hippocampal head and tail volumes at T2. There was no significant effect of T2 AUCi (total change in cortisol) on right head or right tail volume in offspring without exposure to maternal depression. This suggests that offspring exposed to high degrees of maternal depression during their lifetime have greater right head and tail susceptibility to T2 AUCi. This may indicate that high lifetime exposure to a depressed mother may make a child more susceptible to the damaging effects of high cortisol reactivity during later childhood.

To our knowledge, no existing work has examined the possible timing-dependent effects of cortisol on hippocampal volume. Evidence of increased T1 cortisol reactivity predicting increased hippocampal body volume aligns with evidence of associations

between cortisol and hippocampal structure in young adults (Narita et al., 2012; Pruessner et al., 2007), but fails to integrate well with evidence in children (Pagliaccio et al., 2015; Wiedenmayer et al., 2006), older adults (Knoops et al., 2010; Sudheimer et al., 2014), or a considerable body of literature in rodents (Conrad, 2009, for review) and non-human primates (Uno et al., 1994). Consistent with the vast body of literature supporting the neurotoxicity hypothesis, T2 total change in cortisol in response to a stressor (AUCi) predicted reduced tail volumes at T2. Therefore, this may reflect a developmental trend that has yet to be explored whereby cortisol reactivity interacts with different developmental mechanisms to predict unique hippocampal subregion volumes. Additional research is needed to explore these potential timing and regionally-dependent effects.

Mediation

This was the first study to examine whether cortisol reactivity mediates the association between parenting and hippocampal volume in a young human population. Results indicated that T2 total change in cortisol, AUCi, significantly mediated the association between T1 Negative Parenting and left hippocampal tail volume. Consistent with the original hypothesis derived from the rodent literature, greater T1 Negative Parenting predicted increased T2 AUCi, which, in turn, predicted smaller left hippocampal tail volumes. This is the first evidence that this pathway exists in human children. Significant mediation highlights the utility of rodent model systems for the investigation of risk transmission, and provides support for the assumption that similar cellular mechanisms may be driving these cross-species effects.

General Discussion

This is the first study to investigate the longitudinal associations between hippocampal subregion (i.e., head, body, tail) volume and early parenting or cortisol reactivity in a young human population. Using this methodology has provided many benefits, but produced many challenges in relating the present results to the extant literature.

All previous human literature examining the associations between parenting or cortisol reactivity and hippocampal volume have used whole hippocampal volume as the dependent measure of interest (Luby et al., 2012; Narita et al., 2012; Pagliaccio et al., 2014; Pruessner et al., 2007; Rao et al., 2010; Whittle et al., 2014) . While these studies have provided important first passes at identifying important effects, this method disregards the internal functional organization of the hippocampus and may have driven many inconsistencies between studies. For instance, Rao et al. (2010) found that greater maternal nurturance at 4 years-old predicted smaller hippocampal volumes at age 14 whereas Luby and colleagues (2012) found that greater maternal support at 3-6 years-old predicted increased hippocampal volumes at 7-13 years of age. It is possible that these inconsistencies may reflect subtle regionally-specific changes within the hippocampus that may or may not be specific to sample demographics.

The hippocampus, in both rodents and humans, is composed of five subfields (i.e., the cornu ammonis regions CA1-3, dentate gyrus, and subiculum) that have distinct cytoarchitectures and are integrated into unique circuits that perform specific neural computations. In the human hippocampus, these subfields are distributed along the longitudinal axis – the very axis which is sliced coronally to designate head, body, and

tail subregions - resulting in varied proportions of each subfield within each subregion (i.e., head, body, tail). In order to link the current findings to the established rodent literature, it is necessary to consider the relative distributions of subfields within the hippocampal subregions included in the present findings. One study in adults found that the greatest proportion of the dentate gyrus was located within the hippocampal body and tail, the greatest proportion of regions CA1-3 were in the head and tail, and the largest portions of the subiculum were found in the hippocampal head and body (Malykhin et al., 2010). Therefore, in the present results, individual differences in hippocampal head volume may reflect underlying changes in CA1-3 or the subiculum whereas differences in hippocampal body volume may reflect changes in dentate gyrus or subiculum, and differences in hippocampal tail volume may reflect changes in CA1-3 or the dentate gyrus. Unfortunately, these subregion-subfield mappings must be applied with caution to the present results as they were generated from adults and may not accurately reflect hippocampal subfield distributions in the developing brain.

Given that the hippocampus undergoes known developmental change, the present results must be considered in light of typical developmental trajectories and the mechanisms which shape them. While there is some disagreement between sources (Giedd et al., 1996; Hu, Pruessner, Coupé, & Collins, 2013; Uematsu et al., 2012; Wierenga et al., 2014; Yang, Goh, Chen, & Qiu, 2013), there is evidence that, throughout the lifespan, the anterior hippocampus (i.e., head) decreases in volume while the posterior hippocampus (i.e., body and tail) increases in volume (Gogtay et al., 2006). The exact timing or the mechanisms driving these changes are not currently well understood; however, this typical developmental trajectory highlights the possible pitfalls of buying

into a blanket “bigger is better” interpretation of brain development: at a given point in time, larger volumes may be indicative of better outcomes while at a later point in development, larger volumes may be associated with poorer cognitive or affective outcomes. The interpretability of whether an increase or decrease in volume is beneficial will be dependent on the region and the period of development in which it is measured.

It is a common theme in developmental neuroscience that regions undergoing developmental change are more susceptible to the effects of environmental perturbations – for better or for worse – coincidentally or by design (Pechtel & Pizzagalli, 2011). In the current dataset, the hippocampal head appears preferentially sensitive to the early parenting environment, the hippocampal body is sensitive to the later parenting environment and early cortisol reactivity, and the hippocampal tail is sensitive to later cortisol reactivity. Differences in the trajectories of hippocampal subregion development are likely interacting with early or late parenting and cortisol reactivity to drive the region-, timing-, and input-specific effects observed in the present report. The findings that greater T1 positive parenting predicts increased hippocampal head volumes and greater T2 cortisol reactivity (AUCg, AUCi) predicts reduced hippocampal tail volumes are consistent with what would be hypothesized from the glucocorticoid neurotoxicity hypothesis. The unexpected findings that larger hippocampal body volumes are predicted by lower T2 positive parenting and higher T1 cortisol reactivity may indicate that the hippocampal body, or its likely subregions, the subiculum and the dentate gyrus, respond differently to these inputs than other regions. Moreover, this differential sensitivity may be activating distinct mechanisms that drive unique intra- or extra-cellular forces. Structural MRI has the ability to measure global changes in brain volume; however, it

lacks the resolution to precisely measure specific brain tissues. In fact, observed volumetric associations could be attributed to changes in the number, size, or complexity of neurons, synapses, and/or glia (Willard, Hemby, Register, McIntosh, & Shively, 2014). While this is a limitation of the current method, it provides impetus for future research to examine these questions using technologies better suited for measuring cellular changes.

Individual differences in hippocampal subregion volumes may be linked to differences in cognitive abilities. In 6-, but not 4-year-olds, larger hippocampal heads are associated with greater episodic memory performance (Riggins et al., 2015); however, this trend appears to reverse with age: smaller hippocampal head volumes are associated with improved statistical learning and associative inferences in adolescence (Schlichting, Guarino, Schapiro, Turk-Browne, & Preston, 2016) and with better episodic memory performance in adults (Demaster et al., 2014). This reflects a timing-dependent change that is consistent with the expected developmental trajectory of the hippocampal head, as described above. Specifically, in childhood, a larger anterior hippocampus, presumably with more connections, is beneficial to memory (Lee, Ekstrom, & Ghetti, 2014; Riggins et al., 2015), but, with age, unnecessary connections are pruned away, at which point a smaller, but more efficient anterior hippocampus is associated with better memory performance (Demaster et al., 2014; cf Van Petten, 2004). Therefore, the current pattern of results may suggest that early positive parenting facilitates improved memory performance in later childhood. In adults, a larger hippocampal body predicts better episodic memory performance (Demaster et al., 2014), suggesting that, at least in adulthood, larger body volumes are associated with better cognitive outcomes. The

association in the present dataset which implicates greater early cortisol reactivity with increased hippocampal body volume during mid- to late-childhood may suggest that early stress reactivity accelerates the development of the hippocampal body (Bath, Manzano-Nieves, & Goodwill, 2016; for evidence of developmental acceleration due to stress in the amygdala, see Gee et al., 2013 and Gee & Casey, 2015), that acute stress reactivity during early childhood facilitates increased neurogenesis within the dentate gyrus (Kirby et al., 2013), or, possibly, that early stress disrupts normative pruning processes (Andersen & Teicher, 2004; Liu et al., 2016; Wei, Simen, Mane, & Kaffman, 2012). It is possible that, like adults, in children, an enlarged hippocampal body is associated with improved memory performance or, alternatively, the association between the hippocampal body and memory performance may mirror the developmental changes identified in the hippocampal head with greater body volume during childhood associated with reduced memory performance during childhood. Finally, the hippocampal tail has been linked to spatial navigation in older adults (Chen, Chuah, Sim, & Chee, 2010) and, in children, larger hippocampal tail volume is associated with increased episodic memory performance (Demaster et al., 2014). Therefore, in the present report, reduced left hippocampal tail volumes with greater T2 cortisol reactivity may predict poorer episodic memory performance or spatial navigation skills.

Hippocampal volume has also been linked to affective functioning and the pathophysiology of many psychological disorders, including depression (Bremner et al., 2000; Videbech, Ravnkilde, & Ph, 2004). Hippocampal volume was found to be approximately 54% genetically inherited (Lyons, Yang, Sawyer-Glover, Moseley, & Schatzberg, 2001) and offspring with a familial risk for depression demonstrate reduced

volumes (Chen et al., 2010). Smaller hippocampal volumes partially mediate the association between early life adversity and depression in later life (Rao et al., 2010), predicts poorer long-term outcomes in depressed adults (MacQueen & Frodl, 2011), and increases an individual's risk for developing a stress-related psychopathology (Gilbertson et al., 2002). A large meta-analysis of 726 depressed adults and 795 healthy controls found that reduced episodic memory functioning was the most consistent cognitive deficit in depression (Zakzanis, Leach, & Kaplan, 1998). Investigations directly testing hippocampal volume in these disorders and specific non-memory cognitive and affective outcomes are sparse and inconsistent.

Some research suggests that smaller hippocampal volumes are associated with increased depressive symptoms (Brown et al., 2014), greater apathy (Lavretsky et al., 2008), and reduced cognitive functioning across domains (O'Brien, Lloyd, McKeith, Gholkar, & Ferrier, 2004; Sawyer, Corsentino, Sachs-Ericsson, & Steffens, 2012), including poorer executive functioning (Frodl et al., 2006). Reduced hippocampal volume has also been linked to greater functional activations during viewing of negative (versus neutral) faces (Suzuki et al., 2013). However, many other investigations have found the opposite pattern of effects, with greater hippocampal volumes predicting poorer outcomes, such as increased trait anxiety (Rusch, Abercrombie, Oakes, Schaefer, & Davidson, 2001), higher behavioral inhibition (Cherbuin et al., 2008), and reduced emotional memory (Matsuoka et al., 2007).

Many of these inconsistencies may be attributed to universal use of a whole hippocampal seed that may obscure regionally-specific changes or differences in the age of studied populations. As reviewed above, hippocampal volume – function associations

may change throughout development (Demaster et al., 2014). Additionally, it is possible that changes in hippocampal volume do not have direct effects on other (i.e., non-memory) cognitive systems, but rather, changes in hippocampal volume may simply reflect a history of HPA axis function. Therefore, associations between hippocampal volume and the symptomatology of psychological disorders may be indirect, acting through the functions of cortisol. Future research is needed to explore these possibilities and identify the non-memory cognitive processes that changes in hippocampal volume may impact.

Chapter 7: Functional Connectivity Results

Covariates

Mean framewise displacement (FD) and scan age were entered as covariates in all functional analyses to mitigate the effects of individual differences in motion on connectivity metrics and to control for known differences in network connectivity across age.

Aim 1: Associations between Parenting and Children's Hippocampal Connectivity

There were no significant associations between T1 Negative or T1 Positive Parenting and bilateral anterior or posterior hippocampal connectivity when controlling for T2 Negative and T2 Positive Parenting, respectively.

Controlling for T1 Negative Parenting, greater T2 Negative Parenting predicted reduced bilateral anterior (Figure 16A; Table 28) and posterior (Figure 16B; Table 28) hippocampal connectivity with regions of left and right cerebellum. Consistent with these results, when controlling for T1 Positive Parenting, greater T2 Positive Parenting predicted increased posterior hippocampal connectivity with a region of left cerebellum (k=142, [-22 -74 -45], t=3.64; Figure 17)[7]. There was no significant association between T2 Positive Parenting and anterior hippocampal connectivity when controlling for T1 Positive Parenting.

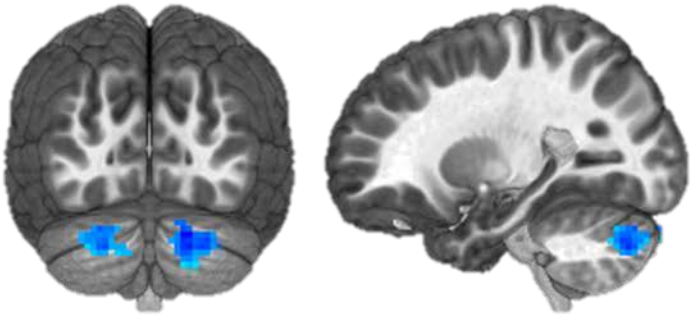
[7] This effect remained significant when the one individual with an extremely low T2 Positive Parenting score was excluded from analysis.

Table 28

Regions of hippocampal connectivity that vary as a function of T2 Negative Parenting, controlling for T1 Negative Parenting

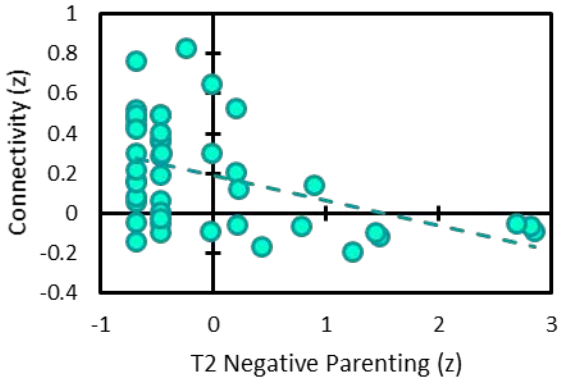
Region	k	x	y	z	*t*
Anterior Hippocampus					
Right Cerebellum	191	20	-83	-39	-3.55
Left Cerebellum	139	-25	-77	-39	-3.40
Posterior Hippocampus					
Left Cerebellum	249	-28	-71	-36	-3.50
Right Cerebellum	115	26	-71	-30	-3.44

A

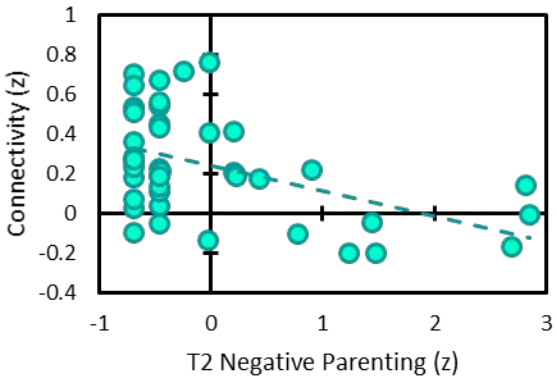


y = -80 x = -25

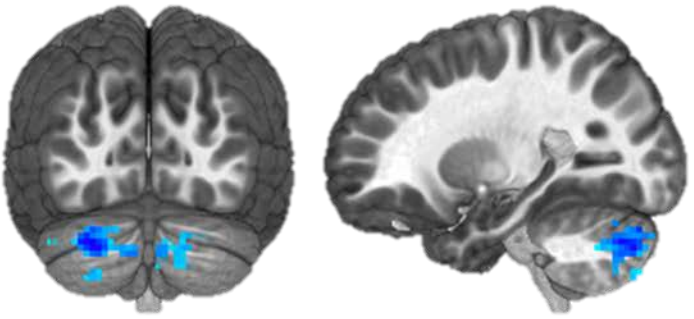
Bilateral Anterior Hippocampus Connectivity with Left Cerebellum



Bilateral Anterior Hippocampus Connectivity with Right Cerebellum

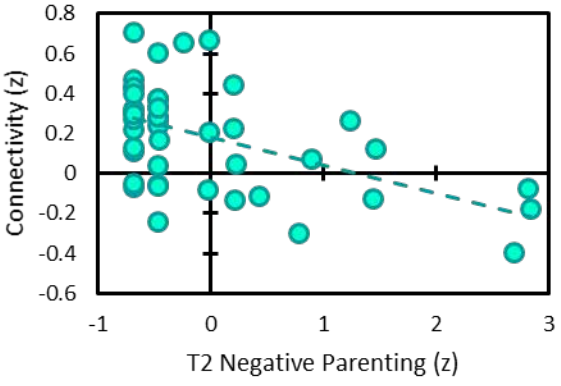


B



y = - 80 x = - 25

Bilateral Posterior Hippocampus Connectivity with Left Cerebellum



Bilateral Posterior Hippocampus Connectivity with Right Cerebellum

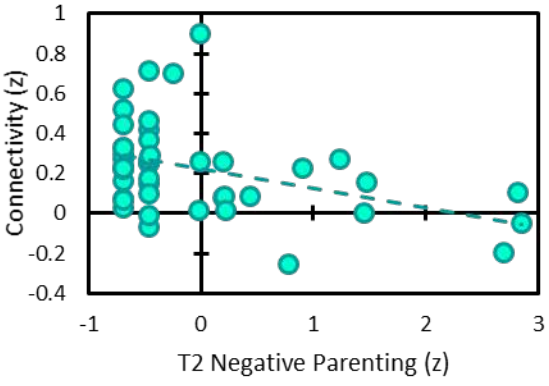


Figure 16. Regions demonstrating significant associations between T2 Negative Parenting (controlling for T1 Negative Parenting, age, and mean FD) and (A) anterior and (B) posterior hippocampus connectivity. Note: Scatterplots depict bivariate correlations between the predictor and connectivity and are not adjusted for covariates included in the statistical models.

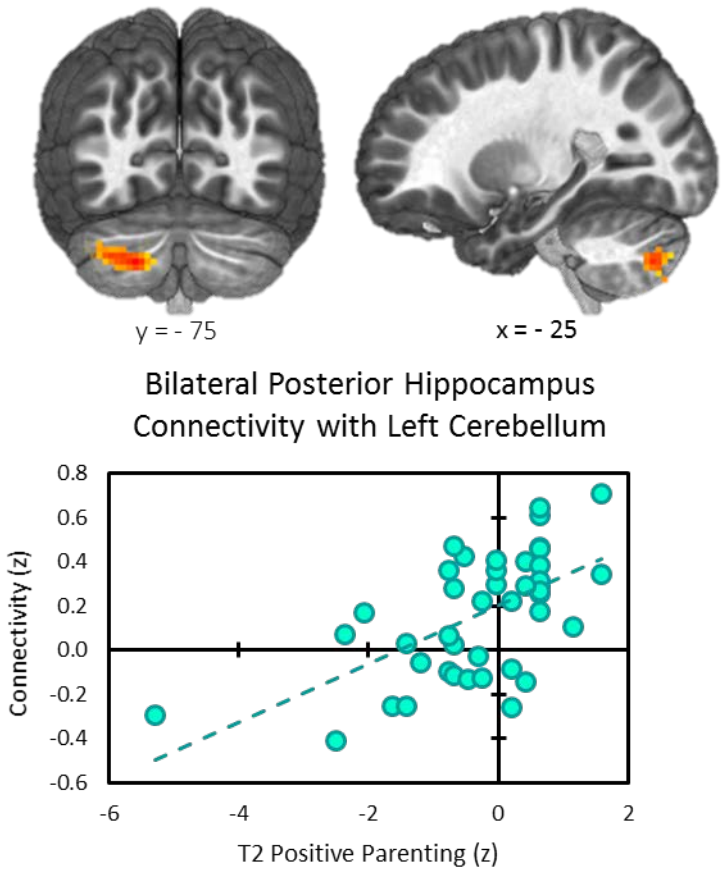


Figure 17. Regions demonstrating significant associations between T2 Positive Parenting (controlling for T1 Positive Parenting, age, and mean FD) and posterior hippocampus connectivity. Note: Scatterplot depicts the bivariate correlation between the predictor and connectivity and is not adjusted for covariates included in the statistical model.

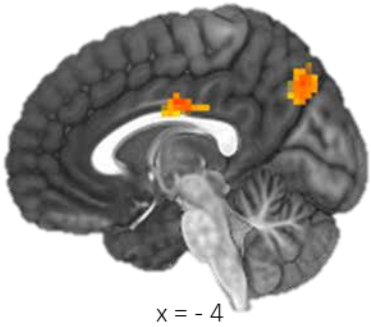
Aim 2: Associations between Children's Cortisol Reactivity and Hippocampal Connectivity

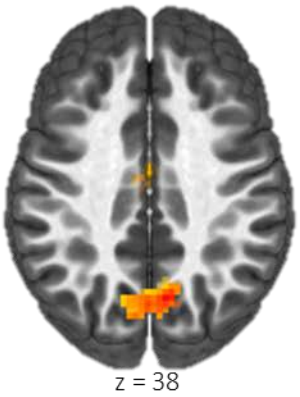
Controlling for T2 total cortisol volume (AUCg), greater T1 AUCg predicted increased anterior hippocampal connectivity with bilateral precuneus and bilateral middle cingulate cortex and increased posterior hippocampal connectivity with bilateral precuneus and posterior cingulate cortex (Table 29; Figure 18). T1 total change in cortisol (AUCi) was not significantly associated with either anterior or posterior hippocampal connectivity when controlling for T2 AUCi.

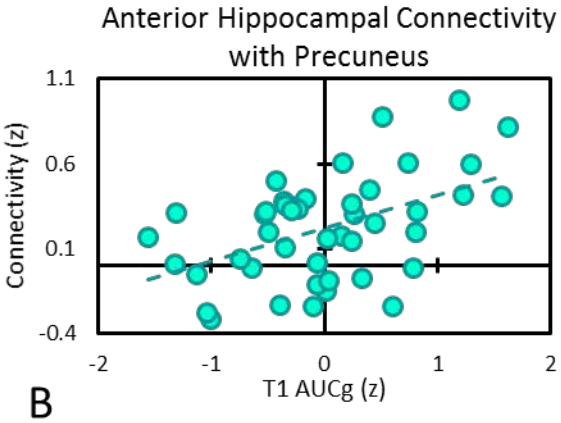
Table 29
Regions of hippocampal connectivity that vary as a function of T1 AUCg, controlling for T2 AUCg

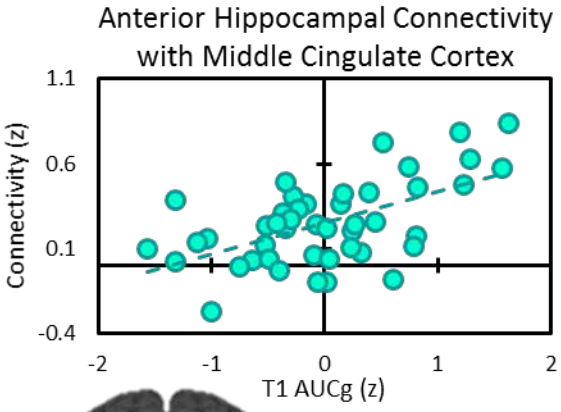
Region	k	x	y	z	*t*
Anterior Hippocampus					
Right Precuneus	141	8	-71	39	3.38
Left Precuneus					
Left Middle Cingulate Cortex	75	-7	-17	30	3.42
Right Middle Cingulate Cortex					
Posterior Hippocampus					
Right Precuneus	178	2	-80	45	3.53
Left Precuneus					
Left Posterior Cingulate Cortex	112	-13	-44	33	3.38
Right Posterior Cingulate Cortex					

A

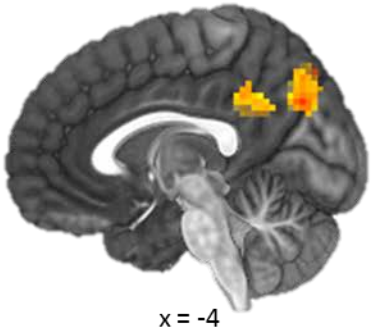

x = - 4

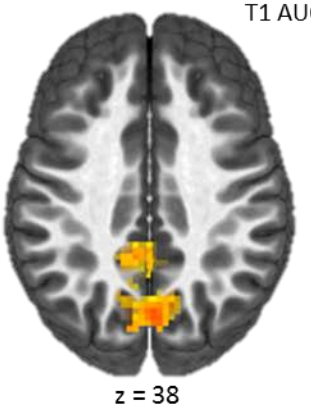

z = 38

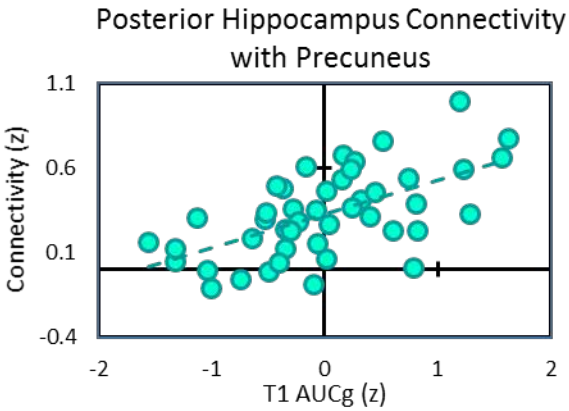

Anterior Hippocampal Connectivity with Precuneus
Connectivity (z)
1.1
0.6
0.1
-0.4
-2
-1
0
1
2
T1 AUCg (z)


Anterior Hippocampal Connectivity with Middle Cingulate Cortex
Connectivity (z)
1.1
0.6
0.1
-0.4
-2
-1
0
1
2
T1 AUCg (z)

B


x = -4


z = 38


Posterior Hippocampus Connectivity with Precuneus
Connectivity (z)
1.1
0.6
0.1
-0.4
-2
-1
0
1
2
T1 AUCg (z)

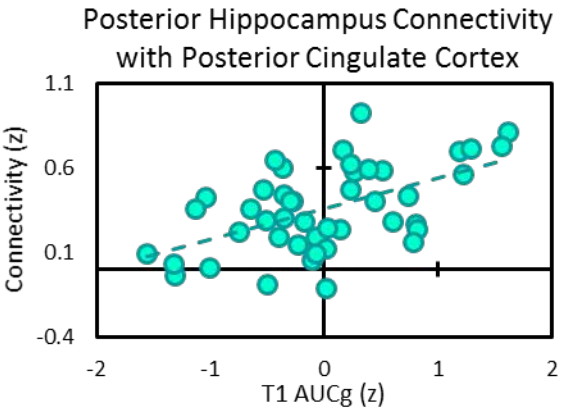

Posterior Hippocampus Connectivity with Posterior Cingulate Cortex
Connectivity (z)
1.1
0.6
0.1
-0.4
-2
-1
0
1
2
T1 AUCg (z)

Figure 18. Regions where T1 AUCg was significantly associated with (A) anterior and (B) posterior hippocampus connectivity after controlling for T2 AUCg, age, and mean FD. Note: Scatterplots depict bivariate correlations between the predictor and connectivity and are not adjusted for covariates included in the statistical models.

There were no significant associations between T2 change in cortisol (AUCi) or total cortisol response (AUCg) and bilateral anterior or posterior hippocampal connectivity after controlling for T1 AUCi and T1 AUCg, respectively.

Aim 3: Mediation Association between Parenting and Hippocampal Connectivity by Cortisol Reactivity

There were five regions for which parenting significantly predicted hippocampal connectivity. The raw connectivity scores of each these regions for each participant were entered as the dependent variables in separate mediation models with T2 AUCg and T2 AUCi entered as the mediator and T2 Positive Parenting or T2 Negative Parenting entered as the predictor. Significant mediation was not observed in any model (Table 30).

Table 30

Mediation of the association between parenting and hippocampal resting-state functional connectivity by cortisol reactivity.

Predictor	Dependent Variable	Mediator	Covariates	Total Effect	Direct Effect	Indirect Effect	SE	CI	*p*
T2 Positive Parenting	Posterior Connectivity with Left Cerebellum	T2 AUCg	Age, Mean FD, T1 Positive Parenting	-0.16	-0.16	<-0.01	0.05	[-0.11 0.09]	.980
		T2 AUCi	Age, Mean FD, T1 Positive Parenting	-0.16	-0.19	0.03	0.08	[-0.05 0.31]	.747
T2 Negative Parenting	Anterior Connectivity with Right Cerebellum	T2 AUCg	Age, Mean FD, T1 Negative Parenting	-0.69	-0.87	-0.10	0.15	[-0.04 0.64]	.502
		T2 AUCi	Age, Mean FD, T1 Negative Parenting	-0.69	-0.83	0.04	0.09	[-0.02 0.42]	.684
	Anterior Connectivity with Left Cerebellum	T2 AUCg	Age, Mean FD, T1 Negative Parenting	-2.28	-2.23	-0.09	0.21	[-0.77 0.20]	.639
		T2 AUCi	Age, Mean FD, T1 Negative Parenting	-2.38	-2.43	0.01	0.09	[-0.09 0.22]	.894
	Posterior Connectivity with Left Cerebellum	T2 AUCg	Age, Mean FD, T1 Negative Parenting	-0.02	-0.03	<0.01	0.14	[-0.31 0.31]	.989
		T2 AUCi	Age, Mean FD, T1 Negative Parenting	-0.02	-0.08	0.01	0.07	[-0.04 0.25]	.882
	Posterior Connectivity with Right Cerebellum	T2 AUCg	Age, Mean FD, T1 Negative Parenting	0.07	0.25	-0.10	0.21	[-0.80 0.17]	.596
		T2 AUCi	Age, Mean FD, T1 Negative Parenting	0.07	0.04	0.01	0.07	[-0.09 0.21]	.924

Note. CI = Confidence Interval; SE = Standard Error; FD = Framewise Displacement.

Exploratory Aim: Role of Maternal Depression

Main Effects of Maternal Depression. There was a significant main effect of maternal lifetime history of depressive disorders on anterior hippocampal connectivity (Table 31, Figure 19). Specifically, offspring with a maternal history of depressive disorders demonstrated increased anterior hippocampal connectivity with the left posterior hippocampus and parahippocampal gyrus. There was no significant main effect of proportion lifetime exposure to maternal depression on anterior or posterior hippocampal connectivity.

Table 31
Main effect of maternal lifetime history of depressive disorders on anterior hippocampus connectivity.

Region	k	x	y	z	*t*
Left Parahippocampal Gyrus	103	-25	-50	0	3.58
Left Posterior Hippocampus					

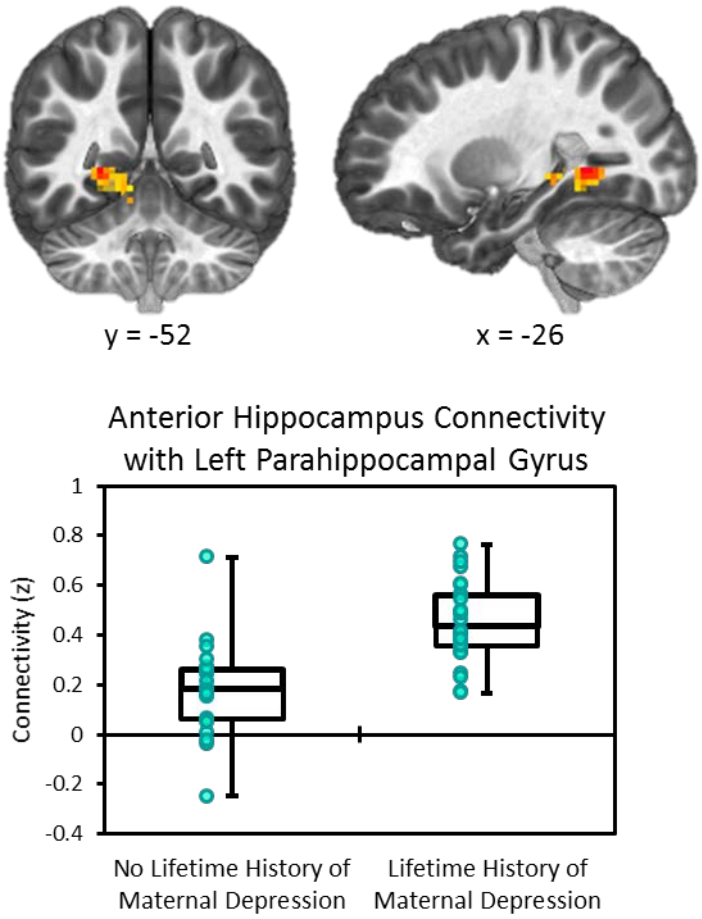


Figure 19. Main effect of maternal lifetime history of depressive disorders on anterior hippocampus connectivity. Note: Plots are not adjusted for covariates included in the statistical model (i.e., age, mean FD).

Interactions with Maternal Depression.

As an exploratory aim, the moderating influence of maternal depression on the associations between T1 and T2 parenting (positive or negative) or cortisol reactivity (AUCg or AUCi) and hippocampal functional connectivity (anterior or posterior) was tested. Each model tested includes Time 1 and Time 2 independent variables (positive or negative parenting, AUCg or AUCi), an index of maternal depression (maternal lifetime history of depressive disorders or cumulative lifetime exposure to maternal depression), two interaction terms (between T1 and T2 independent variables and the maternal depression index), and covariates (mean FD, scan age).

Interactions between Parenting and Maternal Depression. Cumulative lifetime exposure to maternal depression moderated the association between T1 Positive Parenting and bilateral posterior hippocampal connectivity with a region spanning left and right cuneus (Table 32, Figure 20). Specifically, in children with high exposure to maternal depression, greater T1 Positive Parenting was associated with increased connectivity between posterior hippocampus and bilateral cuneus. Offspring with low exposure to maternal depression demonstrated the opposite trend: greater T1 Positive Parenting predicted decreased posterior hippocampus connectivity with this region. The interaction between cumulative lifetime exposure to maternal depression and T2 Positive Parenting in predicting posterior hippocampus connectivity was not significant.

Table 32

Regions where proportion of lifetime exposure to maternal depression moderated the association between posterior hippocampus connectivity with T1 Positive Parenting, controlling for T2 Positive Parenting

Region	k	x	y	z	*t*
Left Cuneus*	130	-7	-92	36	3.22
Right Cuneus					

*Significant connectivity for offspring with high and low cumulative exposure to maternal depression.

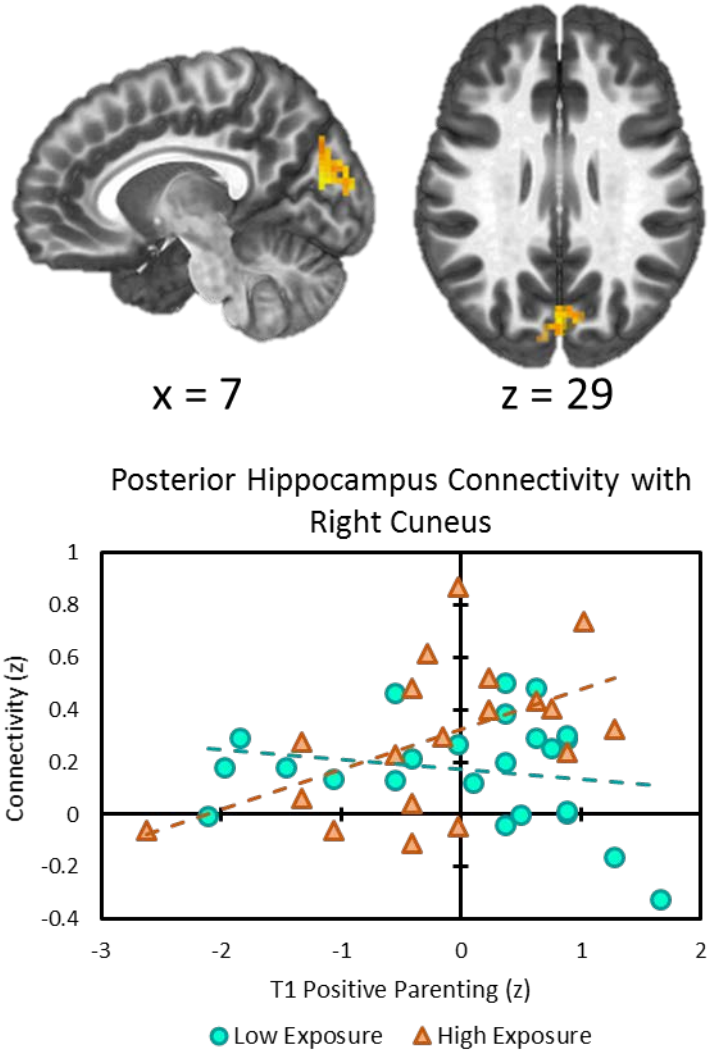


Figure 20. Regions where proportion lifetime exposure to maternal depression moderated the association between posterior hippocampus connectivity with T1 Positive Parenting, controlling for T2 Positive Parenting, age, and mean FD. Note: Scatterplot depicts bivariate correlations between the predictor and connectivity and is not adjusted for covariates included in the statistical model.

Maternal lifetime history of depression significantly moderated the associations between T1 and T2 Positive Parenting with posterior hippocampus connectivity. Maternal lifetime history of depression moderated the association between T1 Positive Parenting and bilateral posterior hippocampus connectivity with a large region of bilateral lingual gyri extending into bilateral fusiform gyri as well as regions of left and right middle occipital gyrus, left inferior temporal gyrus, right cerebellum, left inferior parietal lobule, and left precuneus (Table 33, Figure 21). In all regions, in offspring with a maternal history of depressive disorders, greater T1 Positive Parenting was associated with greater posterior hippocampal connectivity and in offspring without a maternal history of depressive disorders, greater T1 Positive Parenting was only associated with lower bilateral posterior hippocampal connectivity with the left and right middle occipital gyrus, left inferior temporal gyrus, and left precuneus. The association between T1 Positive Parenting and posterior hippocampus connectivity was not significant in offspring with a maternal history of depressive disorders in any other regions. Additionally, maternal lifetime history of depression moderated the association between T2 Positive Parenting and posterior hippocampus connectivity with a region of left lingual gyrus extending into bilateral calcarine gyri (Table 34, Figure 22). In offspring without a maternal history of depression, greater T2 Positive Parenting was associated with increased connectivity whereas offspring without a maternal history of depression do not demonstrate an association. This result should be interpreted with caution, as the interaction is driven by one child with a maternal history of depression with an extremely

low positive parenting score[8]. Inspection of the raw data suggests offspring with and without a maternal history of depressive disorders demonstrate increased connectivity with this region with greater T2 Positive Parenting.

Table 33
Regions where maternal lifetime history of depressive disorders moderated the association between T1 Positive Parenting, controlling for T2 Positive Parenting, and posterior hippocampus connectivity.

Region	k	x	y	z	*t*
Left Lingual Gyrus	448	-28	-53	-6	3.38
Left Fusiform Gyrus					
Right Lingual Gyrus					
Right Fusiform Gyrus					
Left Middle Occipital Gyrus*	248	-37	-77	24	3.67
Left Inferior Temporal Gyrus*	208	-49	-56	-9	3.45
Left Middle Temporal Gyrus					
Right Middle Occipital Gyrus*	134	38	-80	27	3.46
Right Cerebellum	116	32	-56	-21	3.30
Right Fusiform Gyrus					
Left Inferior Parietal Lobule	96	-43	-38	45	3.25
Left Precuneus*	77	-4	-59	-57	3.44

*Significant connectivity for offspring with and without maternal lifetime history of depressive disorders. Unmarked regions are only significant for offspring with a maternal lifetime history of depressive disorders.

[8] This effect did not remain significant when the one individual with an extremely low T2 Positive Parenting was excluded from analyses.

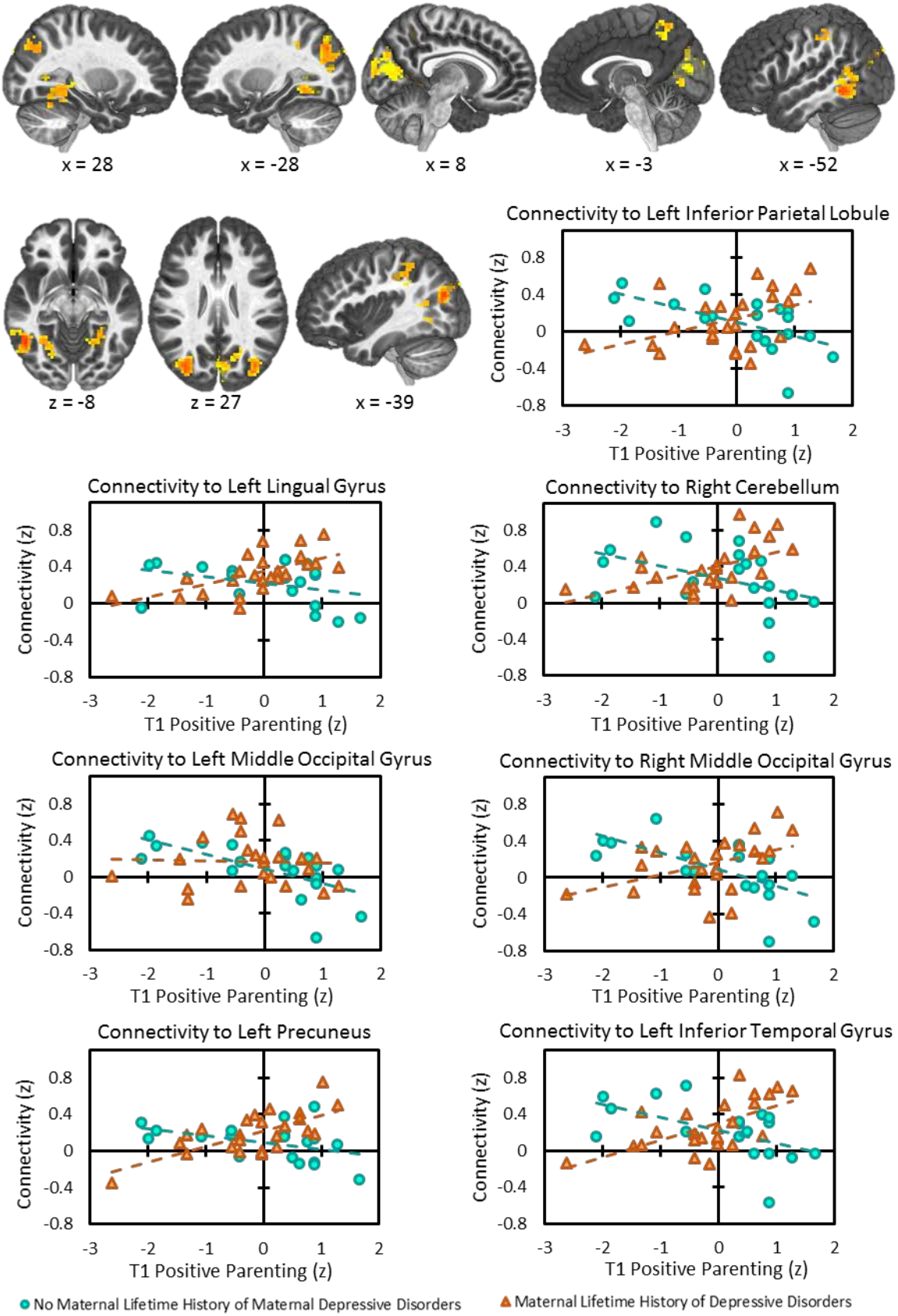

x = 28
x = -28
x = 8
x = -3
x = -52
z = -8
z = 27
x = -39
Connectivity to Left Inferior Parietal Lobule
Connectivity to Left Lingual Gyrus
Connectivity to Right Cerebellum
Connectivity to Left Middle Occipital Gyrus
Connectivity to Right Middle Occipital Gyrus
Connectivity to Left Precuneus
Connectivity to Left Inferior Temporal Gyrus
Connectivity (z)
T1 Positive Parenting (z)
No Maternal Lifetime History of Maternal Depressive Disorders
Maternal Lifetime History of Depressive Disorders

Figure 21. Regions where maternal lifetime history of depressive disorders moderated the association between T1 Positive Parenting (controlling for T2 Positive Parenting, age, and mean FD) and posterior hippocampus connectivity. Note: Scatterplots depict bivariate correlations between the predictor and connectivity and are not adjusted for covariates included in the statistical models.

Table 34

Regions where maternal lifetime history of depressive disorders significantly moderated the association between T2 Positive Parenting, controlling for T1 Positive Parenting, and posterior hippocampus connectivity

Region	k	x	y	z	*t*
Left Lingual Gyrus	135	-7	-68	6	-3.40
Left Calcarine Gyrus					
Right Calcarine Gyrus					
Left Cuneus					
Right Cuneus					

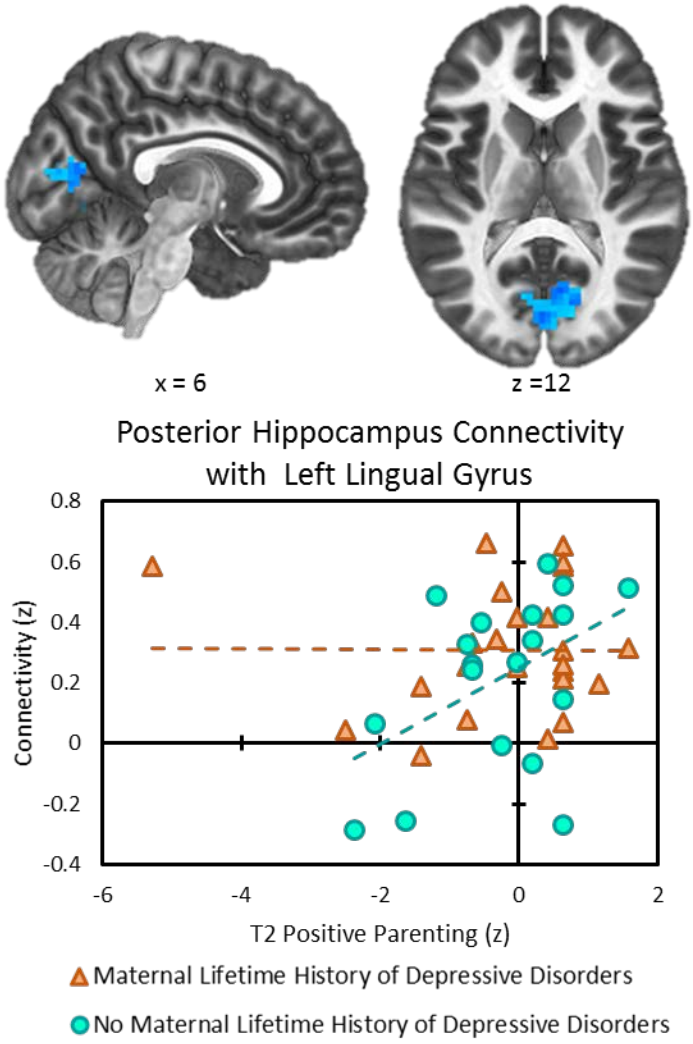


Figure 22. Regions where maternal lifetime history of depressive disorders significantly moderated the association between T2 Positive Parenting (controlling for T1 Positive Parenting, age, and mean FD) and posterior hippocampal connectivity. Note: Scatterplot depicts bivariate correlations between the predictor and connectivity and is not adjusted for covariates included in the statistical model.

No other interactions between T1 or T2 Positive or Negative Parenting and either index of maternal depression significantly predicted anterior or posterior hippocampus connectivity.

Interactions between Cortisol Reactivity and Maternal Depression. Exposure to early maternal depression moderated the association between T1 AUCi and bilateral anterior hippocampus connectivity with right superior orbital gyrus (k=83, [26 -55-6], *t*=-3.44; Figure 23), with greater exposure associated with decreased connectivity and lower exposure associated with increased connectivity in this region[9]. The interaction between cumulative lifetime exposure and T2 AUCi in predicting anterior hippocampus connectivity was not significant.

[9] This effect remained significant when one or both individuals with low T1 AUCi were removed from analyses.

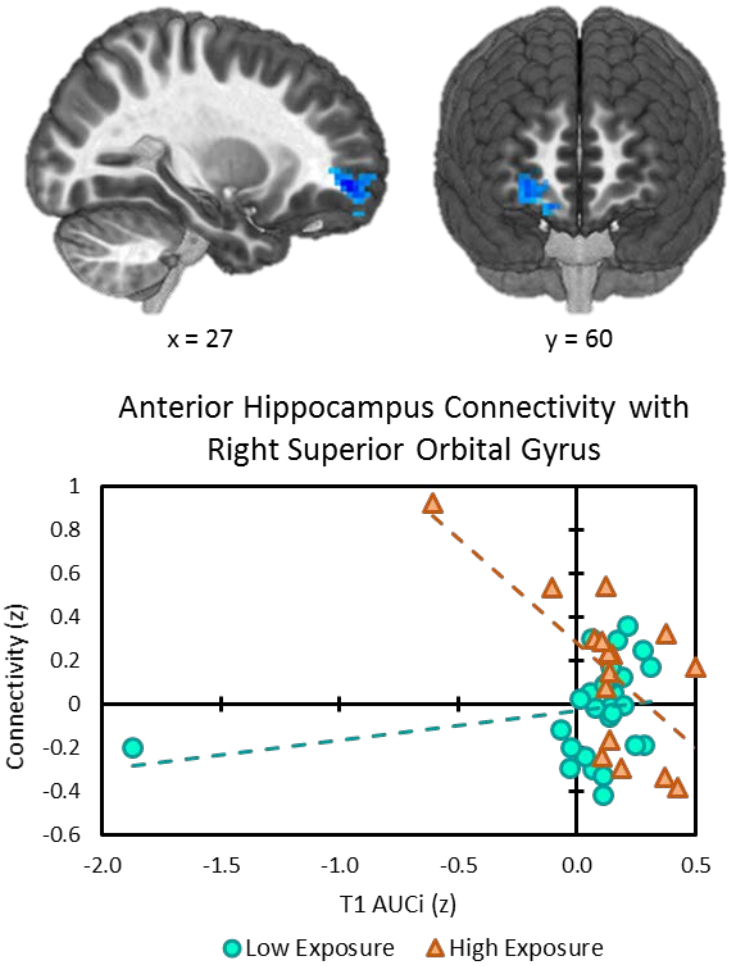


Figure 23. Regions where the association between T1 AUCi (controlling for T2 AUCi, age, and mean FD) and anterior hippocampus connectivity was significantly moderated by proportion lifetime exposure to maternal depression. Note: Scatterplot depicts bivariate correlation between the predictor and connectivity and is not adjusted for covariates included in the statistical model.

There was a significant interaction between maternal lifetime history of depression and T1 AUCg in predicting bilateral anterior hippocampus connectivity with the left middle frontal gyrus (k=80, [-28 37 21], *t*=3.46; Figure 24). In offspring with a maternal lifetime history, greater T1 AUCg was associated with greater bilateral head connectivity with the left middle frontal gyrus. In offspring without a lifetime history, greater T1 AUCg was associated with reduced connectivity in this region. The interaction between maternal lifetime history of depression and T2 AUCg in predicting anterior hippocampus connectivity was not significant.

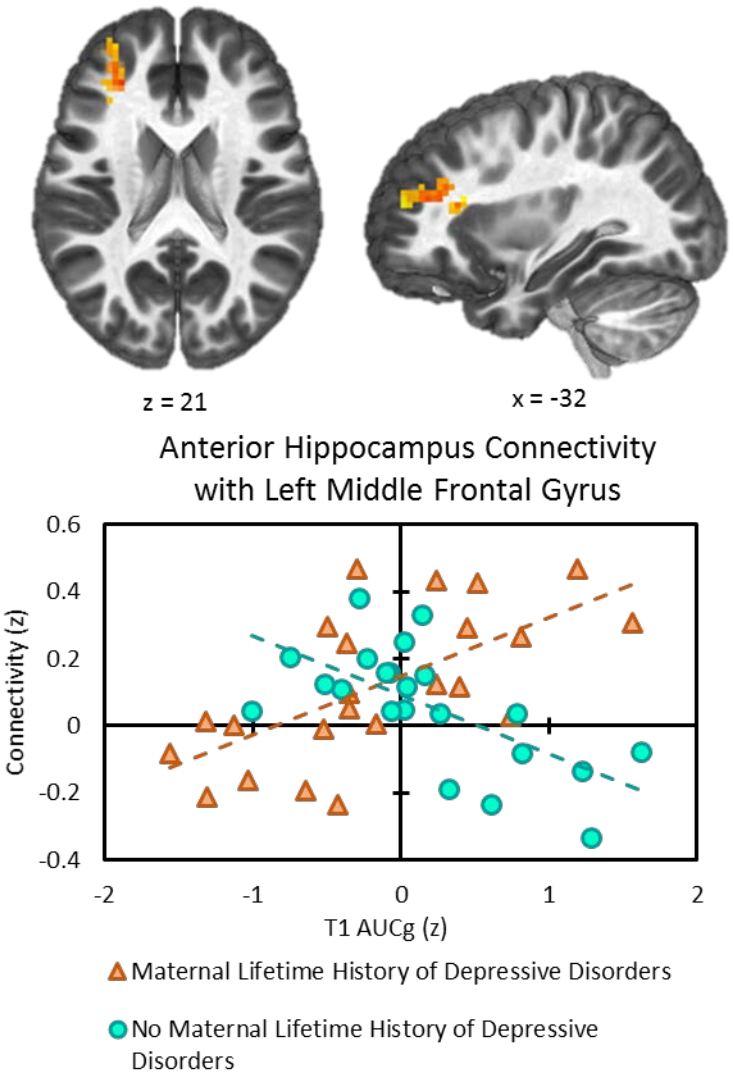


Figure 24. Regions where the association between T1 AUCg (controlling for T2 AUCg, age, and mean FD) and anterior hippocampus connectivity was significantly moderated by a maternal lifetime history of depressive disorders. Note: Scatterplot depicts bivariate correlation between the predictor and connectivity and is not adjusted for covariates included in the statistical model.

There was a significant interaction between maternal lifetime history of depression and T2 AUCi in predicting bilateral posterior hippocampus connectivity with the right inferior frontal gyrus, the right fusiform gyrus, and the right middle temporal gyrus (Table 35, Figure 25). In each of these regions, maternal history of depressive disorders was associated with greater T2 AUCi predicted increased connectivity while no maternal history was associated with a negative association between T2 AUCi and connectivity. The interaction between maternal lifetime history of depression and T2 AUCi in predicting posterior hippocampus connectivity was not significant.

Table 35
Regions where lifetime history of maternal depression significantly moderated the association between T2 AUCi, controlling for T1 AUCi, and bilateral posterior hippocampus connectivity.

Region	k	x	y	z	*t*
Right Inferior Frontal Gyrus (pars Triangularis)	101	47	16	18	3.47
Right Inferior Frontal Gyrus (pars Opercularis)					
Right Fusiform Gyrus	71	38	-74	-18	3.45
Right Inferior Temporal Gyrus					
Right Middle Temporal Gyrus	71	53	-41	-9	3.33
Right Inferior Temporal Gyrus					

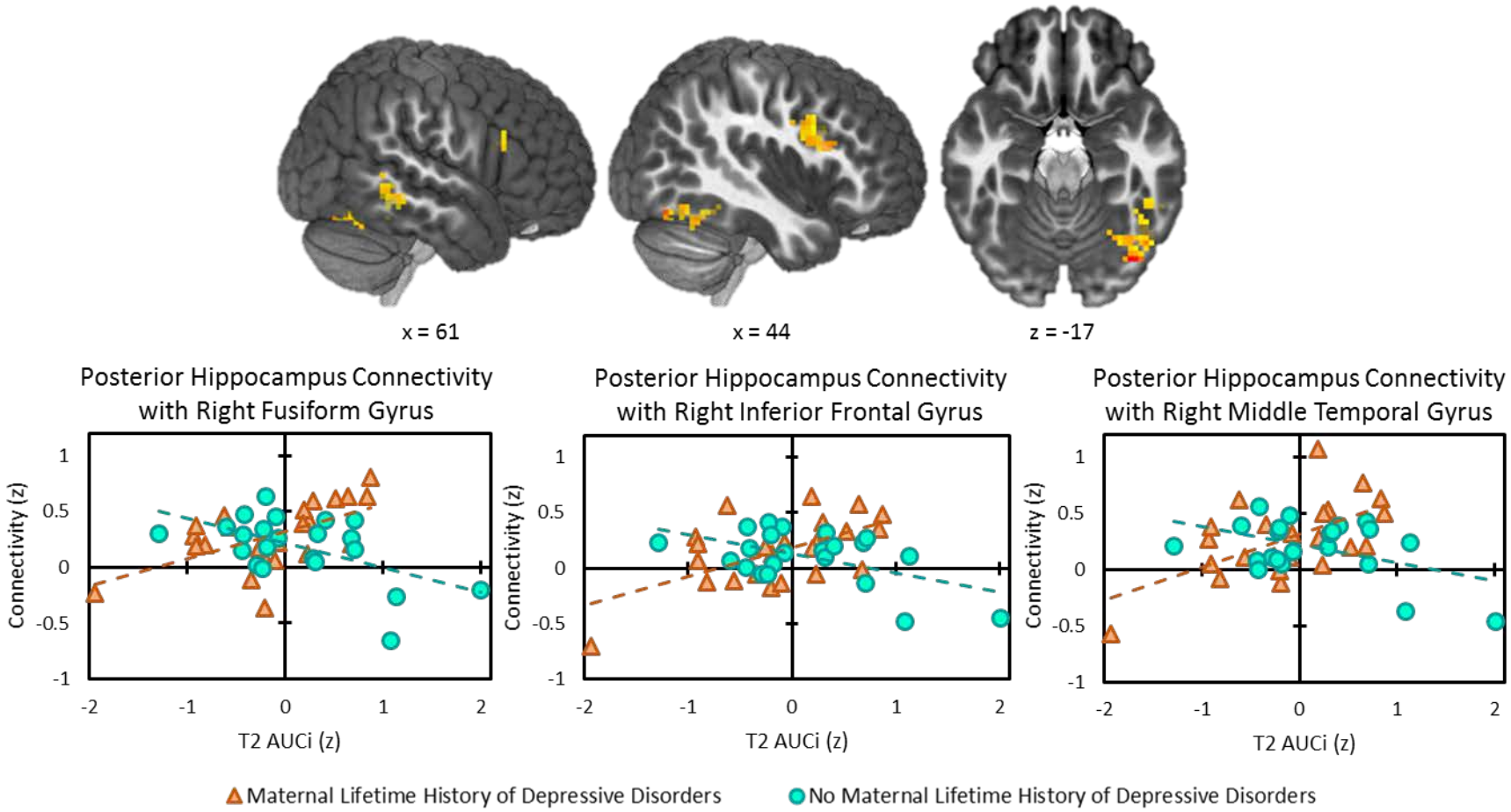


Figure 25. Regions where the association between T2 AUCi (controlling for T1 AUCi, age, and mean FD) and posterior hippocampus connectivity was significantly moderated by a maternal lifetime history of depressive disorders. Note: Scatterplots depict bivariate correlations between the predictor and connectivity and are not adjusted for covariates included in the statistical models.

Neither maternal lifetime history of depression nor cumulative lifetime exposure to maternal depression significantly moderated any other associations between T1 or T2 AUCg or AUCi and any region of anterior or posterior hippocampus connectivity.

Chapter 8: Functional Connectivity Discussion

This was the first study to investigate the longitudinal associations between early and concurrent parenting and cortisol reactivity on anterior and posterior hippocampal functional connectivity at rest in a young human population. Analyses revealed that later parenting (both positive and negative) predicted hippocampal connectivity with regions of the cerebellum whereas total cortisol released in response to a stressor (AUCg) during preschool (T1) predicted increased connectivity with the cuneus and regions of the cingulate gyrus. This suggests that hippocampal network architectures may be selectively sensitive to early stress and later parenting behaviors.

Both T2 negative and T2 positive parenting predicted hippocampal connectivity with regions of the cerebellum. As would be expected, positive and negative parenting were associated with inverse effects on hippocampal connectivity: greater T2 negative parenting predicted reduced anterior and posterior hippocampus connectivity with regions of left and right cerebellum whereas greater T2 positive parenting predicted increased posterior hippocampus connectivity with a region of left cerebellum. There were no specific effects of early parenting above and beyond later parenting in predicting hippocampal connectivity (though see Supplementary Material). This pattern of results suggests that hippocampal functional connections with the cerebellum are particularly sensitive to both negative and positive concurrent parenting behaviors.

Reciprocal connections have been reported between the hippocampus and the cerebellum (Heath, Dempesy, Fontana, & Myers, 1978; Newman & Reza, 1979; Sang et al., 2012), with evidence that the cerebellum modulates hippocampal activity under a variety of conditions (Onuki, Van Someren, De Zeeuw, & Van der Werf, 2015; Yu &

Krook-Magnuson, 2015). Recent evidence suggests that these functional connections increase during childhood (Blankenship et al., 2016). Thus, the current findings may indicate that concurrent maladaptive parenting behaviors (i.e., low positive and high negative parenting) may compromise the functional integrity of hippocampal-cerebellum communication.

Although the cerebellum has historically been considered to play an exclusive role in motor coordination, emerging evidence suggests diverse cognitive and affective functions that may be affected in depressive disorders, including verbal and temporal memory (Onuki et al., 2015; Rubia & Smith, 2004), attention (Schmahmann, Weilburg, & Sherman, 2007), specifically as it applies to oculomotor movements (Sweeney, Strojwas, Mann, & Thase, 1998), as well as, emotion regulation (Schutter & van Honk, 2005), emotion processing (Baumann & Mattingley, 2012; Turner et al., 2007), and fear conditioning (Sacchetti, Scelfo, Tempia, & Strata, 2004). Increased hippocampal-cerebellar connectivity has been linked to successful memory formation (Ranganath, Heller, Cohen, Brozinsky, & Rissman, 2005). Structural and functional changes in the cerebellum have been linked to depressive disorders (Canli et al., 2004; Guo et al., 2015; Konarski, McIntyre, Grupp, & Kennedy, 2005) and extreme parenting behaviors such as abuse (Hart & Rubia, 2012). In fact, cerebellar activity can be used to discriminate between adults with and without depression (Zeng et al., 2012), and there is evidence that differences in cerebellum connectivity with the hippocampus, in particular, may be a distinguishing neural characteristic of individual with depressive disorders (Liu et al., 2012). These individual differences in network connectivity may be linked to glucocorticoid activity as both the hippocampus and cerebellum have high densities of

glucocorticoid receptors (Pavlík & Buresová, 1984) and have a demonstrated sensitivity to exogenous elevations in corticosterone levels in the rat (Howard, 1968). As there are known increases in this connectivity during childhood, and the degree of connectivity is associated with improved memory performance in adults, the present finding that low positive and high negative parenting predict decreased hippocampal-cerebellar connectivity may signal atypical development, decreased functioning in the cognitive and affective domains mentioned above, and may indicate an early marker of increased risk for later depressive disorders.

Early (T1) AUCg, a measure of the total amount of cortisol released in response to a stressor, predicted increased anterior and posterior hippocampus connectivity with the precuneus and distinct regions of the cingulate cortex. Recent evidence suggests that hippocampal connectivity with the precuneus and the cingulate cortex increases during childhood (Blankenship et al., 2016). Therefore, evidence that greater total cortisol release is associated with increased connectivity between these regions may indicate that early cortisol in response to a stressor may accelerate, a pre-existing developmental process.

Both the precuneus and the cingulate cortex are important nodes in the default mode network (Fransson & Marrelec, 2008), and increased connectivity between these regions and the DMN have been implicated in the etiology of depression (Greicius et al., 2007; Sambataro, Wolf, Pennuto, Vasic, & Wolf, 2014). In particular, the DMN has been implicated in self-referential processing (Davey, Pujol, & Harrison, 2016; Sheline et al., 2009) and ruminative behaviors (Berman et al., 2011; Hamilton et al., 2011; Hamilton, Farmer, Fogelman, & Gotlib, 2015). Among DMN nodes, the precuneus and posterior

cingulate appear to play a particular role in self-referential processing (Northoff et al., 2006).

Additionally, the DMN has been linked to autobiographical (Philippi, Tranel, Duff, & Rudrauf, 2015; Spreng & Grady, 2010) and episodic memory performance (Riggins et al., 2016; Wang et al., 2010). In particular, greater hippocampal connectivity to the precuneus and cingulate gyrus in adults (Wang et al., 2010) and the precuneus in 6-year-olds (Riggins et al., 2016) has been linked to improved episodic memory performance. Moreover, both the anterior hippocampus and the cingulate gyrus have been widely implicated in the processing of and memory for emotional stimuli (Maddock, Garrett, & Buonocore, 2003; Maddock & Maddock, 1999; Poppenk et al., 2013). The anterior hippocampus has been linked to generalized memories versus memory for specific details – a function attributed to the posterior hippocampus (Evensmoen et al., 2013; Poppenk et al., 2013) though other theories of anterior-posterior functional distinction exist (see: Fanselow & Dong, 2010; Poppenk et al., 2013; Strange, Witter, Lein, & Moser, 2014). Taken together, increased anterior hippocampus connectivity with these regions of the DMN may indicate a tendency for over-generalized self-referential memories – a cognitive deficit common in adults with depressive disorders (Gibbs & Rude, 2004; Söderlund et al., 2014; Sumner, Griffith, & Mineka, 2010; Williams et al., 2007). Therefore, early cortisol reactivity may drive increased hippocampal connectivity to DMN nodes, leading to improvements in episodic memory and self-referential processing which may reflect a sensitivity to recalling personally-relevant (i.e., autobiographical memories) or emotional events and a propensity to

ruminate on those events, two defining features of depressive disorders (Disner et al., 2011; Nolen-Hoeksema & Susan, 2000).

There was a main effect of maternal lifetime history of depressive disorders on anterior hippocampus connectivity with a region of the left posterior parahippocampal gyrus extending into the left hippocampal tail, with offspring with a maternal lifetime history of depression demonstrating increased anterior hippocampus connectivity with these regions. There is abundant evidence of functional segregation between anterior and posterior subregions of the hippocampus (e.g., Fanselow & Dong, 2010; Poppenk et al., 2013; Strange, Witter, Lein, & Moser, 2014). Findings of increased functional connectivity between anterior and posterior segments may indicate normative processes driving longitudinal functional segregation are altered in offspring with a maternal lifetime history of depressive disorders. Although there are no previous reports of direct anterior hippocampus – posterior parahippocampal gyrus connectivity to our knowledge, both regions are widely implicated in emotional memory formation (Smith, Henson, Dolan, & Rugg, 2004; Van den Stock, Vandenbulcke, Sinke, & de Gelder, 2014) and have demonstrated increased activity to the processing of novel scenes (Köhler, Crane, & Milner, 2002). A meta-analysis of twenty functional MRI studies found that the anterior hippocampus and the posterior parahippocampal gyrus, along with other regions, are consistently activated during successful encoding of emotional images (Murty, Ritchey, Adcock, & LaBar, 2010). Therefore, increased connectivity between these regions may indicate an increased propensity for emotional memories in offspring of depressed mothers. Despite no evidence to our knowledge indicating that anterior hippocampus-posterior parahippocampal gyrus connectivity may be altered in depressive disorders,

both structures have been implicated in the pathophysiology of anxiety disorders (Kent & Rauch, 2003; Liotti et al., 2000). Therefore, the present findings may be driven by comorbidities between maternal depressive and anxiety disorders. Combining these disparate functions, perhaps increased anterior hippocampus connectivity with the posterior hippocampus in offspring of depressed mothers may facilitate increased ease of encoding novel scenes (Köhler et al., 2002), particularly when they are emotionally valenced.

There was also evidence that measures of maternal lifetime depression status and cumulative exposure to maternal depression moderated the associations between parenting and cortisol reactivity with hippocampal connectivity. The discussion below will focus on interactions that remained significant when multivariate outliers were removed.

Associations between T1 positive parenting and posterior hippocampal connectivity were moderated by measures of maternal depression. In offspring with a maternal lifetime history of depression, greater T1 positive parenting predicted increased posterior hippocampus connectivity with a number of regions (lingual gyrus, middle occipital gyrus, inferior temporal gyrus, cerebellum, inferior parietal lobule, precuneus, and cuneus), many of which are involved in the default mode network (Buckner, Andrews-Hanna, & Schacter, 2008; Fransson, 2005; Utevsky, Smith, & Huettel, 2014). As a general trend, in offspring without a maternal lifetime history, greater T1 Positive Parenting predicted reduced connectivity, though this effect was not significant in all regions. Similarly, in offspring with high exposure to maternal depression, greater T1 positive parenting predicted increased posterior hippocampus connectivity with the

cuneus, a region where the association between T1 positive parenting and posterior hippocampal connectivity was also moderated by a maternal lifetime history of depression (above). This effect was not significant in offspring with low cumulative exposure to maternal depression.

Nearly all of the regions demonstrating this effect demonstrate gray-matter reductions (Grieve, Korgaonkar, Koslow, Gordon, & Williams, 2013) and differences in functional activation during rumination (Cooney, Joormann, Eugène, Dennis, & Gotlib, 2010) in depressed adults. Moreover, many of these regions have also been identified as key nodes through which a pattern classification algorithm can distinguish between depressed and non-depressed adults while watching sad faces (Fu et al., 2008). In addition to the implications to rumination and self-referential processing described above, hippocampal connectivity to the DMN has been linked to episodic memory performance. Findings in adults have suggested that high hippocampal-DMN connectivity at rest predicts reduced hippocampal-cortical recruitment during memory encoding, and ultimately poorer memory performance (Salami, Pudas, & Nyberg, 2014). Therefore, it is possible that in offspring of depressed mothers, greater positive parenting facilitates increased resting-state connectivity which prevents appropriate task-based use of hippocampal networks. Considered differently, in offspring with high risk for depression, perhaps greater positive parenting is causing the hippocampus to become more tightly coupled to the DMN, effectively improving memory for self-referential events. Therefore, in offspring of depressed mothers, high early positive parenting predicting greater connectivity at rest may facilitate increased ruminative behaviors and self-referential autobiographical memories but may impair more general episodic memory

performance. The opposite may be true in offspring without a maternal lifetime history of depression: greater T1 Positive Parenting may facilitate improved episodic memory, but reduced self-referential processing. The present results indicate that hippocampal networks of offspring with or without a familial risk for depression may be differentially affected by early positive parenting. Moreover, greater self-referential processing or outwardly focused episodic memory abilities may be adaptive depending on genetic or environmental risk factors associated with maternal depression. The validity of this speculation and the cognitive consequences of increased or decreased hippocampal connectivity with the DMN should be explored.

Together, this pattern of effects suggests that posterior hippocampal connectivity is particularly sensitive to the interaction between the presence of early positive parenting behaviors and maternal depression status.

Maternal depression status moderated the association between early (T1) cortisol reactivity and anterior hippocampus connectivity, and the associations between later (T2) cortisol reactivity and posterior hippocampus connectivity. Despite early cortisol being linked to anterior connectivity with the prefrontal cortex, different aspects of the cortisol response (i.e., total magnitude of cortisol release: AUCg versus total change in cortisol over time: AUCi) are associated with different prefrontal regions, in different directions, and moderated by different measures of maternal depression. Specifically, in offspring with high exposure to maternal depression, greater T1 AUCi, a measure of total cortisol change, predicted *decreased* anterior hippocampal connectivity with the right superior orbital cortex. In contrast, in offspring with a maternal lifetime history of depression, greater T1 AUCg, a measure of total cortisol secreted, predicted *increased* anterior

hippocampal connectivity with the left dorsolateral prefrontal cortex (dlPFC). This suggests timing- and region-dependent patterns in the interaction between maternal depression and cortisol reactivity in predicting anterior hippocampus connectivity.

The different pattern of effects between these two regions may be attributed to different aspects of the cortisol response or different mechanisms. The prefrontal cortex, like the cerebellum and hippocampus, has a high density of glucocorticoid receptors (Perlman, Webster, Herman, Kleinman, & Weickert, 2007), making it particularly sensitive to the effects of increased cortisol. Interestingly, there is evidence that different regions of prefrontal cortex may be differentially responsive to cortisol: in some regions, increased cortisol is associated with cell death and in other cases there is just a structural reorganization (Wellman, 2001). These differential effects of cortisol depending on prefrontal region may be contributing to the divergent effects we find between measures of cortisol reactivity and hippocampal connectivity with prefrontal cortex. Additionally, the aspect of the cortisol response being tapped by each measure (i.e., AUCg, AUCi) may have different cellular and molecular effects on prefrontal cortical regions. Finally, the observed effects may be a consequence of different measures of maternal depression: greater cumulative exposure to maternal depression may tap more experiential or chronic risk factors associated with maternal depression whereas moderation by lifetime history of maternal depression may reflect more genetically-mediated mechanisms.

The hippocampus has known reciprocal connections with the orbitofrontal cortex (Catenoix et al., 2005; Cavada, Compañy, Tejedor, Cruz-Rizzolo, & Reinoso-Suárez, 2000). The strength of this connectivity has been linked to successful memory formation in healthy adults and may be particularly important for memory of rewarding social

stimuli (Tsukiura et al., 2011; Tsukiura & Cabeza, 2008). Moreover, orbitofrontal volume reductions have been reported in adults with depressive disorders (J Douglas Bremner et al., 2002; Drevets, 2007), in individuals from low SES backgrounds (Holz et al., 2015), and in individuals who have experienced early life stress, broadly defined (Hanson et al., 2010), suggesting this volumetric change may be driven by stress. Moreover, differences in hippocampal – orbitofrontal connectivity can reliably distinguish depressed from non-depressed adults (Cao et al., 2014). The present finding that greater cortisol reactivity predicts decreased hippocampal-orbitofrontal connectivity in offspring with a maternal risk for depression may reflect decreased memory for rewarding stimuli. A reduced capability for processing rewarding stimuli may have important implications for the development of anhedonia, a central symptom of depressive disorders (Pizzagalli, 2014). In offspring without a lifetime history, greater T1 total change in cortisol appears to facilitate development of healthy (i.e., increased) connectivity between the anterior hippocampus and orbitofrontal cortex. This may indicate an interaction between genetics and stress reactivity in shaping development of neural networks implicated in depressive disorders.

Greater total cortisol secreted in response to a laboratory stressor predicted increased anterior hippocampal connectivity with the left dorsolateral prefrontal cortex (dlPFC). The dlPFC is a prefrontal region implicated in executive control processes and has been linked to many functional domains including episodic memory (Demaster & Ghetti, 2013; Ghetti & Bunge, 2012; Ofen et al., 2007), possibly for personally-meaningful information (Keenan, Wheeler, Gallup, & Pascual-Leone, 2000), working memory (Curtis & D'Esposito, 2003; Owen, 1997; Smith & Jonides, 1999), voluntary

emotion regulation (Golkar et al., 2012), emotion recognition (Scheuerecker et al., 2010), and reward processing (Zhang et al., 2013). Increased hippocampal-dlPFC connectivity has been linked to developmental increases in episodic memory (Menon, Boyett-Anderson, & Reiss, 2005) and problem-solving skills (Cho et al., 2012) during childhood. Thus, in offspring with a maternal history of depression, the effects of early cortisol reactivity may support better cognitive functioning whereby the effects of cortisol reactivity on hippocampal-dlPFC connectivity in offspring with no maternal risk may be linked to deleterious effects on cognition.

Additionally, dlPFC structural and functional changes have been consistently associated with the effects of stress in depressed (Phillips, Ladouceur, & Drevets, 2008) and non-depressed (Philip et al., 2014) adults and individuals with a familial risk for depression (Amico et al., 2011). Individuals with a family history of depression and emotional abuse have the most profound effects on dlPFC (Carballedo et al., 2012), suggesting a particular sensitivity to the combinatorial effects of genetic risk and environmental stressors. dlPFC resting-state activity significantly differs between depressed and non-depressed adults (Hwang et al., 2015; Peters, Burkhouse, Feldhaus, Langenecker, & Jacobs, 2016; Sheline, Price, Yan, & Mintun, 2010) and individuals with depression demonstrate increased dlPFC activity in response to social threat words (Canli et al., 2004). In healthy adults, the hippocampus is linked to automatic regulation of emotion, whereas the dlPFC is involved with the voluntary top-down regulation of emotion. Depressed adults, however, appear to recruit the dlPFC more during tasks of automatic emotion regulation (Rive et al., 2013). Therefore, in offspring with a maternal history of depression, greater cortisol reactivity may be affecting the functional

connections between the hippocampus and dlPFC, perhaps reflecting increased dlPFC involvement in automatic regulation of emotions or a reduced ability to exert top-down influences on emotional responses. An alternative possibility is that increased hippocampal-dlPFC connectivity in offspring of depressed mothers may reflect compensatory mechanisms whereby greater connectivity is necessary to achieve the same level of cognitive functioning. For instance Harvey and colleagues (2005) found that depressed individuals demonstrated increased dlPFC activation despite maintaining similar levels of performance on a working memory task. The authors interpreted this to mean that the depressed individuals needed to dedicate more neural resources to accomplish the same level of cognitive performance. Similar processes may be at play in offspring of depressed mothers.

Later (T2) total change in cortisol in response to stress (AUCi) interacted with a maternal lifetime history of depression to predict increased posterior hippocampus connectivity with dorsolateral prefrontal cortex and temporal lobe structures including the fusiform gyrus. In all regions, greater change in the cortisol response to stress predicted increased connectivity in offspring with a maternal lifetime history of depression and decreased connectivity in offspring without maternal depression.

The middle temporal gyrus, inferior frontal gyrus (dlPFC), and the hippocampus are all linked to autobiographical memory (Fink et al., 1996; Greenberg et al., 2005; Piefke, Weiss, Markowitsch, & Fink, 2005; Piefke, Weiss, Zilles, Markowitsch, & Fink, 2003) the episodic memory network (Jeong, Kee Chung, Sic Kim, & Marinazzo, 2015) and are often found to have altered connectivity in depression (Guo et al., 2014; Ma et al., 2012). Moreover, greater connectivity between these regions and the hippocampus has

been linked to poorer episodic memory performance in a sample of typically-developing 6-year-olds (Riggins et al., 2016).

In depressive disorders, inferior frontal gyrus and middle temporal gyrus show increased connectivity with each other (Zhang et al., 2011), altered connectivity within the DMN (Hwang et al., 2016), and similar response to rewards and threats (Canli et al., 2004). Specifically, in depressed adults, both regions demonstrate reduced activity in response to happy faces but increased activity to physical threat (Mather et al., 2004). Similar directions of effects are apparent in the fusiform gyrus of depressed individuals: heightened activity in response to negative faces with reduced activation to happy faces (Stuhrmann et al., 2011). During recognition of previously encoded faces following a social stressor, adults demonstrated increased activity in the left inferior frontal gyrus and the hippocampus in response to fearful faces and decreased activity to neutral faces (Li, Weerda, Milde, Wolf, & Thiel, 2014), indicating a link between activation of these regions during fearful face processing and stress. In healthy individuals, the fusiform gyrus, along with the hippocampus and lingual gyrus, appears to be part of a network of regions involved in the encoding of novel images and faces whereby greater activity facilitates better encoding (Stern et al., 1996). Additionally, one study found that all four regions (the hippocampus, fusiform gyrus, inferior frontal gyrus, and middle temporal gyrus) were implicated in facial emotion perception in depressed women (Briceño et al., 2013).

Considered together, these findings may provide a neurobiological explanation for behavioral evidence that at-risk and depressed individuals have a selective memory bias for negative faces and events and tend to forget positive events (i.e., a positive blockade;

Disner et al., 2011) (Gupta & Kar, 2012; Guyer, Choate, Grimm, Pine, & Keenan, 2011). If these regions are tightly coupled with the hippocampus, but are not being appropriately activated during positive events and are being overly activated during negative events, the hippocampus may not be receiving the necessary signals for successful encoding of positive events, but heightened activity for negative events. Thus, in offspring with a maternal lifetime history of depression, greater cortisol reactivity predicting increased hippocampal connectivity with regions involved with memory may mirror network architectures similar to adults with depressive disorders and, moreover, these differences may reflect compromised episodic memory, particularly for positive faces, during childhood. In offspring of depressed mothers, greater cortisol reactivity may activate an epigenetic cascade that prepares children to function in stressful environments where faces are salient environmental features that require increased attentional processing (Joormann et al., 2007) and network connectivity; however, this increased connectivity may come at the expense of other cognitive functions such as episodic memory (Bai et al., 2009; Dietsche et al., 2014; Rao et al., 2016) or memory for positive or neutral faces.

In summary, the present study found evidence that the development of hippocampal network architectures may be shaped by the parenting environment and the neuroendocrine response to stress. Moreover, the present findings provide evidence that these factors may interact with additional genetic or environmental factors associated with maternal depression status. Critically, all regions demonstrating individual differences in hippocampal connectivity in the present study have been linked to the etiology of depressive disorders in adults. Specifically, we've demonstrated that early and concurrent experiences shape hippocampal networks involved in reward processing,

emotion recognition, episodic and autobiographical memory, and self-referential processing; all domains which are compromised in depression. Therefore, this study provides preliminary evidence that, perhaps in conjunction with other environmental or genetic risks, early parenting and neuroendocrine experiences can shape hippocampal network architectures, possibly putting individuals at increased risk for later depressive disorders.

Chapter 9: General Discussion

The present investigation examined the longitudinal associations between children's early (3-6 years) and concurrent (5-10 years) cortisol reactivity and observed parenting on children's hippocampal structure and functional connectivity at 5-10 years of age. Results revealed both timing- and region-dependent associations. Greater early (T1) positive parenting predicted larger hippocampal head volumes, whereas later (T2) positive parenting predicted smaller hippocampal body volumes. Early (T1) total cortisol release predicted larger body volumes and early total change in cortisol was associated with smaller body volumes. Later (T2) total change in cortisol predicted smaller tail volumes. Later T2 positive and negative parenting predicted increased and decreased anterior and posterior hippocampus connectivity, respectively, with the cerebellum, and early (T1) cortisol reactivity, as indexed by the total volume of cortisol (AUCg), predicted increased anterior and posterior connectivity with the cuneus and distinct regions of the cingulate gyrus. Significant mediation was observed, with greater T1 Negative Parenting predicting greater T2 change in cortisol (AUCi), which, in turn, predicted reduced hippocampal tail volume. We also found evidence that maternal lifetime history of depression and cumulative exposure to maternal depression moderated many associations between parenting and cortisol reactivity with indices of hippocampal structure and function indicating that the effects of these childhood experiences may differentially affect high- and low-risk children.

This is the first study in a young human population to find support for the hypothesis, derived from evidence in rodents, that the early caregiving environment shapes hippocampal structure and function by programming the HPA Axis response to

stress. The present study has many strengths that expand upon and make valuable contributions to the existing literature. First, use of a longitudinal sample afforded the capability to probe timing-dependent effects of early and concurrent parenting and cortisol reactivity on hippocampal structure and function. Second, unlike previous studies examining the effects of parenting on hippocampal development in children, the present study used observational measures of both positive and negative parenting behaviors. Evidence suggests that these measures may not exist on a continuum and, rather, represent two orthogonal indices that may correspond to different developmental outcomes (McLaughlin et al., 2014; Sheridan & McLaughlin, 2014). Testing both positive and negative indices of parenting enabled the evaluation of potential development differences in their effects on hippocampal structure and function. Moreover, observational measures provide more ecologically valid measurements of parenting behaviors and reduce the effects of the self-report bias common to questionnaires (van de Mortel, 2008). Third, the present investigation examined two measures of cortisol reactivity, total change in cortisol and total cortisol release. This methodological choice allowed for exploration of unique and potentially divergent effects of distinct aspects of the HPA response to stress on hippocampal development. Fourth, measuring maternal depression status by clinical interview at each time point allowed for accurate estimates of lifetime depression as well as total number of months the child was exposed to maternal depression. Fifth, this is the first study to assess associations between parenting and hippocampal subregion volumes. Investigation of subregions provides the advantage of determining region-specific differences in hippocampal volume that may be obscured by use of a whole hippocampal segmentation. Finally, and

most critically, the present study is the first to examine the effects of parenting and cortisol reactivity on hippocampal functional connectivity in childhood. Although previous studies have found that positive parenting predicts hippocampal volume during late childhood (Luby et al., 2012; Rao et al., 2011), network and volume changes may be driven by distinct mechanisms that are differentially affected by external inputs throughout the childhood period. Exploring the longitudinal associations between parenting and cortisol reactivity with hippocampal functional connectivity provides greater understanding how early experiences may shape the hippocampal network and provides greater insight into the cognitive systems that may be differentially affected. The present study provides great advances to our knowledge of how and when the early environment may alter developing neural networks and provides insight into the neural changes that may underlie the etiology of later impairments.

Despite providing necessary insights into how the early parenting environment and a child's neurobiological response to stress may shape neural architectures, the conclusions which can be drawn from the present results are restricted by a few critical methodological limitations. First, the present investigation may not have had sufficient power. Despite 103 children and families participating in the T2 behavioral assessments, MR contraindications and participant (parent and/or child) interest in participating in the MRI assessment significantly reduced the number of mother-child dyads included in the present analyses. Low power in the present analyses may have impaired our ability to detect effects (i.e., increasing the type II error rate), especially as it applies to statistical tests of mediation and moderation. It should be noted, however, that despite low power, there was evidence for significant mediation in the current sample. Furthermore, the

limited power afforded by the sample size precluded analysis of more complex models that incorporated the moderating effects of maternal depression, such as moderated mediation. Additionally, a small sample resulted in limited variability in the predictor variables of interest. In particular, in the present imaging subsample, high levels of negative parenting behaviors were rare, resulting in skewed distributions, limited ability to detect potentially meaningful effects, and an increased likelihood that effects may be driven or obscured by statistical outliers. Therefore, the significance of negative parenting in shaping hippocampal structure and functional connectivity remains an open question for future investigation.

Second, although longitudinal measures of parenting and cortisol reactivity were collected, the present investigation only acquired neuroimaging data at T2. A single timepoint of neuroimaging data does not allow for the determination of the temporal relations between variables. It is unknown whether or not baseline differences were present earlier in life, at what point in development individual differences emerged, and how these associations and the underlying neural substrates may change throughout development. Additionally, because imaging data was only collected at T2, it is impossible to make claims about how permanent observed effects are or how they may continue to change throughout development. Moreover, although there are ethical constraints to manipulating early parenting or stress reactivity, greater temporal resolution of brain indices would provide greater support for a causal association between variables. Future studies should strive to include multiple data points of longitudinal neuroimaging data in order to draw conclusions regarding developmental change or long-term outcomes of childhood experiences on brain development.

Despite these limitations, the present study provides a critical foundation on which future research can expand upon. Specifically, future investigations should use larger longitudinal samples with more variability and more frequent imaging and behavioral measures. Larger samples with more frequent data acquisition will provide greater sensitivity to detect possible sensitive periods and the onset of individual differences in outcome measures as well as increased statistical power to test more sophisticated and nuanced models (e.g., mediated moderation). There is evidence that the true relations between variables in the present model (i.e., parenting, cortisol reactivity, hippocampal structure and function) may be better captured by more complex models that incorporate possible moderating influences of maternal lifetime depression status (Dougherty et al., 2013), exposure to maternal depression (Lupien et al., 2011), gender (Miller et al., 2002; Oomen et al., 2009; Teicher et al., 2003; Weinstock, 2007), genetics (Frodl et al., 2010; Gotlib, Joormann, Minor, & Hallmayer, 2008; Hayden et al., 2010; Thomason, Yoo, Glover, & Gotlib, 2009; Wiggins et al., 2012), or interactions between parenting and stress reactivity (Buodo, Moscardino, Scrimin, Altoè, & Palomba, 2013; Kopala-Sibley et al., 2015; Sheikh et al., 2014). Additionally, there is evidence that the influence of parenting behaviors on long-term developmental outcomes may be moderated by race and socioeconomic status, with children from certain sociodemographic backgrounds responding more positively to some parenting behaviors than others. Therefore, the effects of parenting or cortisol reactivity on hippocampal development may not be universal and may be more nuanced to the actual or perceived quality and demands of an environment. Thus, the influence of sociocultural context on observed associations should be explored by future research. Finally, future

investigations of the effects of parenting on brain development would benefit from intervention designs (Belsky & de Haan, 2011). Specifically, by training parents to interact with their children in less hostile or more supportive ways at different points in development, direct causal links can be made between the timing and quality of parenting experiences and brain structure and function.

The field would also greatly benefit from designing and incorporating more advanced imaging technologies, such as high-resolution medial temporal lobe structural scans, to capture neural changes at higher resolutions (i.e., at the subfield level) to enable greater ease in comparing cross-species literatures. Moreover, additional work in human and other mammalian species is necessary to characterize the mechanistic processes that are driving the observed effects in the present study. Although we report individual differences in hippocampal connectivity, the current methods make it impossible to draw firm conclusions on the direction of information flow, whether the "target" region and not the hippocampus is the primary source of altered connectivity, or whether there are larger brain-wide network changes beyond the hippocampus. These questions of causality and brain-wide network changes should be addressed by advanced analytic techniques such as Granger causality and dynamic causal modeling (Bressler & Seth, 2011; Friston, Kahan, Biswal, & Razi, 2013; Friston, Moran, & Seth, 2013; Kim, Kim, Ahmad, & Park, 2013; Roebroeck, Formisano, & Goebel, 2005) and graph theory metrics (Bullmore & Sporns, 2009; Bullmore & Bassett, 2011; Power, Fair, Schlaggar, & Petersen, 2010).

Finally, and most critically, additional research is necessary to explore the immediate and long-term cognitive and behavioral implications of observed individual differences in hippocampal volume and resting-state functional connectivity. This will be

necessary to determine how neural changes may be associated with behavioral or cognitive deficits and risk for later psychopathology.

This is the first study to find evidence that the early parenting environment shapes brain development through programming of the HPA axis response to stress. The present investigation found that childhood experiences of parenting and stress reactivity are associated with individual differences in children's hippocampal structure and functional connectivity. Observed timing- and region- dependent changes of early parenting and stress reactivity on hippocampal structure and function may reflect increased risk for or resilience to later cognitive, emotional, and behavioral difficulties. Given the hypothesis that early parenting and cortisol reactivity play a role in the intergenerational transmission of depression, the present findings may provide important insights into the neurobiological underpinnings of depression risk. Identification of the early factors that shape neurobiological development can inform the development of more effective clinical interventions. Specifically, interventions designed to address the presence and quality of these factors during childhood may have great potential for improving developmental outcomes.

References

Aiken, L. S., West, S. G., & Reno, R. (1991). *Multiple regression: Testing and interpreting interactions*. Newbury Park, CA: Sage. Retrieved from https://books.google.com/books?hl=en&lr=&id=LcWLUyXcmnkC&oi=fnd&pg=PR9&dq=Multiple+Regression:+Testing+and+Interpreting+Interactions&ots=fnihUf_RZj&sig=pGq2KhUFszJ-LKX_kF04dCOKNMc

Alfarez, D. N., De Simoni, A., Velzing, E. H., Bracey, E., Joëls, M., Edwards, F. A., & Krugers, H. J. (2009). Corticosterone reduces dendritic complexity in developing hippocampal CA1 neurons. *Hippocampus*, *19*(9), 828–36. http://doi.org/10.1002/hipo.20566

Amico, F., Meisenzahl, E., Koutsouleris, N., Reiser, M., Möller, H.-J., & Frodl, T. (2011). Structural MRI correlates for vulnerability and resilience to major depressive disorder. *Journal of Psychiatry & Neuroscience : JPN*, *36*(1), 15–22. http://doi.org/10.1503/jpn.090186

Andersen, S. L., & Teicher, M. H. (2004). Delayed effects of early stress on hippocampal development. *Neuropsychopharmacology : Official Publication of the American College of Neuropsychopharmacology*, *29*(11), 1988–1993. http://doi.org/10.1038/sj.npp.1300528

Andersen, S. L., Tomada, A., Vincow, E. S., Valente, E., Polcari, A., & Teicher, M. H. (2008). Preliminary evidence for sensitive periods in the effect of childhood sexual abuse on regional brain development. *The Journal of Neuropsychiatry and Clinical Neurosciences*, *20*(3), 292–301. http://doi.org/10.1176/appi.neuropsych.20.3.292

Arnone, D., McKie, S., Elliott, R., Juhasz, G., Thomas, E. J., Downey, D., … Anderson,

I. M. (2013). State-dependent changes in hippocampal grey matter in depression. *Molecular Psychiatry*, *18*(12), 1265–72. http://doi.org/10.1038/mp.2012.150

Azak, S., & Raeder, S. (2013). Trajectories of parenting behavior and maternal depression. *Infant Behavior & Development*, *36*(3), 391–402. http://doi.org/10.1016/j.infbeh.2013.03.004

Baaré, W. F. C., Vinberg, M., Knudsen, G. M., Paulson, O. B., Langkilde, A. R., Jernigan, T. L., & Kessing, L. V. (2010). Hippocampal volume changes in healthy subjects at risk of unipolar depression. *Journal of Psychiatric Research*, *44*(10), 655–62. http://doi.org/10.1016/j.jpsychires.2009.12.009

Bai, F., Zhang, Z., Watson, D. R., Yu, H., Shi, Y., Yuan, Y., … Qian, Y. (2009). Abnormal functional connectivity of hippocampus during episodic memory retrieval processing network in amnestic mild cognitive impairment. *Biological Psychiatry*, *65*(11), 951–8. http://doi.org/10.1016/j.biopsych.2008.10.017

Barha, C. K., Pawluski, J. L., & Galea, L. a M. (2007). Maternal care affects male and female offspring working memory and stress reactivity. *Physiology & Behavior*, *92*(5), 939–50. http://doi.org/10.1016/j.physbeh.2007.06.022

Baron, R. M., & Kenny, D. A. (1986). The moderator-mediator variable distinction in social psychological research: conceptual, strategic, and statistical considerations. *Journal of Personality and Social Psychology*, *51*(6), 1173–82. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/3806354

Barry, T. J., Murray, L., Fearon, P., Moutsiana, C., Cooper, P., Goodyer, I. M., … Halligan, S. L. (2014). Maternal postnatal depression predicts altered offspring biological stress reactivity in adulthood. *Psychoneuroendocrinology*, *52*, 251–260.

http://doi.org/10.1016/j.psyneuen.2014.12.003

Bath, K. G., Manzano-Nieves, G., & Goodwill, H. (2016). Early life stress accelerates behavioral and neural maturation of the hippocampus in male mice. *Hormones and Behavior*, *82*, 64–71. http://doi.org/10.1016/j.yhbeh.2016.04.010

Baumann, O., & Mattingley, J. B. (2012). Functional topography of primary emotion processing in the human cerebellum. *NeuroImage*, *61*(4), 805–11. http://doi.org/10.1016/j.neuroimage.2012.03.044

Beeber, L. S., Schwartz, T. A., Martinez, M. I., Holditch-Davis, D., Bledsoe, S. E., Canuso, R., & Lewis, V. S. (2014). Depressive symptoms and compromised parenting in low-income mothers of infants and toddlers: distal and proximal risks. *Research in Nursing & Health*, *37*(4), 276–91. http://doi.org/10.1002/nur.21604

Belsky, J., & de Haan, M. (2011). Annual Research Review: Parenting and children's brain development: the end of the beginning. *Journal of Child Psychology and Psychiatry, and Allied Disciplines*, *52*(4), 409–28. http://doi.org/10.1111/j.1469-7610.2010.02281.x

Belsky, J., & Pluess, M. (2009). Beyond diathesis stress: differential susceptibility to environmental influences. *Psychological Bulletin*, *135*(6), 885–908. http://doi.org/10.1037/a0017376

Berman, M. G., Peltier, S., Nee, D. E., Kross, E., Deldin, P. J., & Jonides, J. (2011). Depression, rumination and the default network. *Social Cognitive and Affective Neuroscience*, *6*(5), 548–55. http://doi.org/10.1093/scan/nsq080

Biswal, B., Yetkin, F. Z., Haughton, V. M., & Hyde, J. S. (1995). Functional connectivity in th emotor cortex of resting human brain using echo-planar MRI. *Magnetic*

Resonance in Medicine.

Blankenship, S. L., Redcay, E., Dougherty, L. R., & Riggins, T. (2016). Development of hippocampal functional connectivity during childhood. *Human Brain Mapping*. http://doi.org/10.1002/hbm.23353

Boccia, M. L., Razzoli, M., Vadlamudi, S. P., Trumbull, W., Caleffie, C., & Pedersen, C. A. (2007). Repeated long separations from pups produce depression-like behavior in rat mothers. *Psychoneuroendocrinology*, *32*(1), 65–71. http://doi.org/10.1016/j.psyneuen.2006.10.004

Borkowski, J. G., Ramey, S. L., & Brisol-Power, M. (Eds.). (2002). *Parenting and the child's world: Influences on academic, intellectual, and social-emotional development*. Mahwah, NJ: Lawrence Erlbaum Associates.

Bremner, J. D., Narayan, M., Anderson, E. R., Staib, L. H., Miller, H. L., & Charney, D. S. (2000). Hippocampal volume reduction in major depression. *The American Journal of Psychiatry*, *157*(1), 115–8. http://doi.org/10.1176/ajp.157.1.115

Bremner, J. D., Vythilingam, M., Vermetten, E., Nazeer, A., Adil, J., Khan, S., … Charney, D. S. (2002). Reduced volume of orbitofrontal cortex in major depression. *Biological Psychiatry*, *51*(4), 273–9. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/11958777

Brennan, P. a, Pargas, R., Walker, E. F., Green, P., & Newport, D. J. (2008). Maternal depression and infant cortisol: influences of timing, comorbidity and treatment, *49*(10), 1099–1107. http://doi.org/10.1111/j.1469-7610.2008.01914.x.Maternal

Bressler, S. L., & Seth, A. K. (2011). Wiener–Granger Causality: A well established methodology. *NeuroImage*. http://doi.org/10.1016/j.neuroimage.2010.02.059

Briceño, E. M., Weisenbach, S. L., Rapport, L. J., Hazlett, K. E., Bieliauskas, L. A., Haase, B. D., … Langenecker, S. A. (2013). Shifted inferior frontal laterality in women with major depressive disorder is related to emotion-processing deficits. *Psychological Medicine*, *43*(7), 1433–45. http://doi.org/10.1017/S0033291712002176

Brown, E. S., Hughes, C. W., McColl, R., Peshock, R., King, K. S., & Rush, A. J. (2014). Association of depressive symptoms with hippocampal volume in 1936 adults. *Neuropsychopharmacology : Official Publication of the American College of Neuropsychopharmacology*, *39*(3), 770–9. http://doi.org/10.1038/npp.2013.271

Brummelte, S., Pawluski, J. L., & Galea, L. A. M. (2006). High post-partum levels of corticosterone given to dams influence postnatal hippocampal cell proliferation and behavior of offspring: A model of post-partum stress and possible depression. *Hormones and Behavior*, *50*(3), 370–82. http://doi.org/10.1016/j.yhbeh.2006.04.008

Buckner, R. L., Andrews-Hanna, J. R., & Schacter, D. L. (2008). The brain's default network: anatomy, function, and relevance to disease. *Annals of the New York Academy of Sciences*, *1124*, 1–38. http://doi.org/10.1196/annals.1440.011

Bugental, D. B., Martorell, G. A., & Barraza, V. (2003). The hormonal costs of subtle forms of infant maltreatment. *Hormones and Behavior*, *43*(1), 237–244. http://doi.org/10.1016/S0018-506X(02)00008-9

Bullmore, E., & Sporns, O. (2009). Complex brain networks: graph theoretical analysis of structural and functional systems. *Nature Reviews. Neuroscience*, *10*(3), 186–98. http://doi.org/10.1038/nrn2575

Bullmore, E. T., & Bassett, D. S. (2011). Brain graphs: graphical models of the human

brain connectome. *Annual Review of Clinical Psychology*, *7*, 113–40. http://doi.org/10.1146/annurev-clinpsy-040510-143934

Buodo, G., Moscardino, U., Scrimin, S., Altoè, G., & Palomba, D. (2013). Parenting Stress and Externalizing Behavior Symptoms in Children: The Impact of Emotional Reactivity. *Child Psychiatry & Human Development*, *44*(6), 786–797. http://doi.org/10.1007/s10578-013-0371-0

Buske-Kirschbaum, A., Jobst, S., Wustmans, A., Kirschbaum, C., Rauh, W., & Hellhammer, D. (1997). Attenuated free cortisol response to psychosocial stress in children with atopic dermatitis. *Psychosomatic Medicine*, *59*(4), 419–26. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/9251162

Caldji, C., Hellstrom, I. C., Zhang, T.-Y., Diorio, J., & Meaney, M. J. (2011). Environmental regulation of the neural epigenome. *FEBS Letters*, *585*(13), 2049–58. http://doi.org/10.1016/j.febslet.2011.03.032

Campbell, S. B., Matestic, P., von Stauffenberg, C., Mohan, R., & Kirchner, T. (2007). Trajectories of maternal depressive symptoms, maternal sensitivity, and children's functioning at school entry. *Developmental Psychology*, *43*(5), 1202–1215. http://doi.org/10.1037/0012-1649.43.5.1202

Campbell, S., Marriott, M., Nahmias, C., & Macqueen, G. M. (2004). Lower Hippocampal Volume in Patients Suffering From Depression: A Meta-Analysis. *American Journal of Psychiatry*, *161*(4), 598–607. http://doi.org/10.1176/appi.ajp.161.4.598

Canli, T., Sivers, H., Thomason, M. E., Whitfield-Gabrieli, S., Gabrieli, J. D. E., & Gotlib, I. H. (2004). Brain activation to emotional words in depressed vs healthy

subjects. *Neuroreport*, *15*(17), 2585–8. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/15570157

Cao, L., Guo, S., Xue, Z., Hu, Y., Liu, H., Mwansisya, T. E., … Liu, Z. (2014). Aberrant functional connectivity for diagnosis of major depressive disorder: A discriminant analysis. *Psychiatry and Clinical Neurosciences*, *68*(2), 110–119. http://doi.org/10.1111/pcn.12106

Carballedo, A., Lisiecka, D., Fagan, A., Saleh, K., Ferguson, Y., Connolly, G., … Frodl, T. (2012). Early life adversity is associated with brain changes in subjects at family risk for depression. *The World Journal of Biological Psychiatry : The Official Journal of the World Federation of Societies of Biological Psychiatry*, *13*(8), 569–78. http://doi.org/10.3109/15622975.2012.661079

Catenoix, H., Magnin, M., Guénot, M., Isnard, J., Mauguière, F., & Ryvlin, P. (2005). Hippocampal-orbitofrontal connectivity in human: an electrical stimulation study. *Clinical Neurophysiology : Official Journal of the International Federation of Clinical Neurophysiology*, *116*(8), 1779–84. http://doi.org/10.1016/j.clinph.2005.03.016

Cavada, C., Compañy, T., Tejedor, J., Cruz-Rizzolo, R. J., & Reinoso-Suárez, F. (2000). The anatomical connections of the macaque monkey orbitofrontal cortex. A review. *Cerebral Cortex (New York, N.Y. : 1991)*, *10*(3), 220–42. http://doi.org/10.1093/CERCOR/10.3.220

Champagne, D. L., Bagot, R. C., van Hasselt, F., Ramakers, G., Meaney, M. J., de Kloet, E. R., … Krugers, H. (2008). Maternal care and hippocampal plasticity: evidence for experience-dependent structural plasticity, altered synaptic functioning, and

differential responsiveness to glucocorticoids and stress. *The Journal of Neuroscience : The Official Journal of the Society for Neuroscience*, *28*(23), 6037–45. http://doi.org/10.1523/JNEUROSCI.0526-08.2008

Champagne, F. A., Francis, D. D., Mar, A., & Meaney, M. J. (2003). Variations in maternal care in the rat as a mediating influence for the effects of environment on development. *Physiology & Behavior*, *79*(3), 359–371. http://doi.org/10.1016/S0031-9384(03)00149-5

Chen, K. H. M., Chuah, L. Y. M., Sim, S. K. Y., & Chee, M. W. L. (2010). Hippocampal region-specific contributions to memory performance in normal elderly. *Brain and Cognition*, *72*(3), 400–7. http://doi.org/10.1016/j.bandc.2009.11.007

Chen, M. C. (2010). Decreased hippocampus volume in healthy girls at risk for depression, *67*(3), 270–276. http://doi.org/10.1001/archgenpsychiatry.2009.202.Decreased

Chen, M. C., Hamilton, J. P., & Gotlib, I. H. (2010). Decreased hippocampal volume in healthy girls at risk of depression. *Archives of General Psychiatry*, *67*(3), 270–6. http://doi.org/10.1001/archgenpsychiatry.2009.202

Cherbuin, N., Windsor, T. D., Anstey, K. J., Maller, J. J., Meslin, C., & Sachdev, P. S. (2008). Hippocampal volume is positively associated with behavioural inhibition (BIS) in a large community-based sample of mid-life adults: the PATH through life study. *Social Cognitive and Affective Neuroscience*, *3*(3), 262–9. http://doi.org/10.1093/scan/nsn018

Cho, S., Metcalfe, A. W. S., Young, C. B., Ryali, S., Geary, D. C., & Menon, V. (2012). Hippocampal–Prefrontal Engagement and Dynamic Causal Interactions in the

Maturation of Children's Fact Retrieval. *Journal of Cognitive Neuroscience*, *24*(9), 1849–1866. http://doi.org/10.1162/jocn_a_00246

Cline, E. M. (2015). *Families of Virtue: Confusian and Western Views on Child Development*. New York: Columbia University Press.

Connolly, C. G., Wu, J., Ho, T. C., Hoeft, F., Wolkowitz, O., Eisendrath, S., … Yang, T. T. (2013). Resting-State Functional Connectivity of Subgenual Anterior Cingulate Cortex in Depressed Adolescents. *Biological Psychiatry*, *74*(12), 898–907. http://doi.org/10.1016/j.biopsych.2013.05.036

Conrad, C. D. (2009). Chronic Stress-Induced Hippocampal Vulnerability: The Glucocorticoid Vulnerability Hypothesis, *19*(6), 395–411.

Cooney, R. E., Joormann, J., Eugène, F., Dennis, E. L., & Gotlib, I. H. (2010). Neural correlates of rumination in depression. *Cognitive, Affective & Behavioral Neuroscience*, *10*(4), 470–8. http://doi.org/10.3758/CABN.10.4.470

Cox, R. W. (1996). AFNI: software for analysis and visualization of functional magnetic resonance neuroimages. *Computers and Biomedical Research, an International Journal*, *29*(3), 162–73. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/8812068

Cullen, K. R., Westlund, M. K., Klimes-Dougan, B., Mueller, B. A., Houri, A., Eberly, L. E., & Lim, K. O. (2014). Abnormal amygdala resting-state functional connectivity in adolescent depression. *JAMA Psychiatry*, *71*(10), 1138–47. http://doi.org/10.1001/jamapsychiatry.2014.1087

Cummings, E. M., & Davies, P. T. (1994). Maternal depression and child development. *Journal of Child Psychology and Psychiatry*, *35*(1), 73–112.

http://doi.org/10.1111/j.1469-7610.1994.tb01133.x

Curtis, C. E., & D'Esposito, M. (2003). Persistent activity in the prefrontal cortex during working memory. *Trends in Cognitive Sciences*, *7*(9), 415–423. http://doi.org/10.1016/S1364-6613(03)00197-9

Davey, C. G., Pujol, J., & Harrison, B. J. (2016). Mapping the self in the brain's default mode network. *NeuroImage*, *132*, 390–397. http://doi.org/10.1016/j.neuroimage.2016.02.022

de Geus, E. J. C., van't Ent, D., Wolfensberger, S. P. a, Heutink, P., Hoogendijk, W. J. G., Boomsma, D. I., & Veltman, D. J. (2007). Intrapair differences in hippocampal volume in monozygotic twins discordant for the risk for anxiety and depression. *Biological Psychiatry*, *61*(9), 1062–71. http://doi.org/10.1016/j.biopsych.2006.07.026

Dedovic, K., Engert, V., Duchesne, A., Lue, S. D., Andrews, J., Efanov, S. I., … Pruessner, J. C. (2010). Cortisol awakening response and hippocampal volume: vulnerability for major depressive disorder? *Biological Psychiatry*, *68*(9), 847–53. http://doi.org/10.1016/j.biopsych.2010.07.025

Demaster, D. M., & Ghetti, S. (2012). Developmental differences in hippocampal and cortical contributions to episodic retrieval. *Cortex; a Journal Devoted to the Study of the Nervous System and Behavior*, *49*(6), 1–12. http://doi.org/10.1016/j.cortex.2012.08.004

Demaster, D., Pathman, T., Lee, J. K., & Ghetti, S. (2014). Structural Development of the Hippocampus and Episodic Memory: Developmental Differences Along the Anterior/Posterior Axis. *Cerebral Cortex*, *24*(11), 3036–3045.

http://doi.org/10.1093/cercor/bht160

Dietsche, B., Backes, H., Stratmann, M., Konrad, C., Kircher, T., & Krug, A. (2014). Altered neural function during episodic memory encoding and retrieval in major depression. *Human Brain Mapping*, *35*(9), 4293–4302. http://doi.org/10.1002/hbm.22475

Disner, S. G., Beevers, C. G., Haigh, E. a P., & Beck, A. T. (2011). Neural mechanisms of the cognitive model of depression. *Nature Reviews. Neuroscience*, *12*(8), 467–77. http://doi.org/10.1038/nrn3027

Dougherty, L. R., Klein, D. N., Congdon, E., Canli, T., & Hayden, E. P. (2010). Interaction between 5-HTTLPR and BDNF Val66Met polymorphisms on HPA axis reactivity in preschoolers. *Biological Psychology*, *83*(2), 93–100. http://doi.org/10.1016/j.biopsycho.2009.10.009

Dougherty, L. R., Klein, D. N., Rose, S., & Laptook, R. S. (2011). Hypothalamic-pituitary-adrenal axis reactivity in the preschool-age offspring of depressed parents: moderation by early parenting. *Psychological Science*, *22*(5), 650–8. http://doi.org/10.1177/0956797611404084

Dougherty, L. R., Smith, V. C., Olino, T. M., Dyson, M. W., Bufferd, S. J., Rose, S. a, & Klein, D. N. (2013). Maternal psychopathology and early child temperament predict young children's salivary cortisol 3 years later. *Journal of Abnormal Child Psychology*, *41*(4), 531–42. http://doi.org/10.1007/s10802-012-9703-y

Dougherty, L. R., Tolep, M. R., Smith, V. C., & Rose, S. (2013). Early Exposure to Parental Depression and Parenting: Associations with Young Offspring's Stress Physiology and Oppositional Behavior. *Journal of Abnormal Child Psychology*,

41(8), 1299–310. http://doi.org/10.1007/s10802-013-9763-7

Downey, G., & Coyne, J. C. (1990). Children of depressed parents: an integrative review. *Psychological Bulletin*, *108*(1), 50–76. http://doi.org/10.1037/0033-2909.108.1.50

Drevets, W. C. (2007). Orbitofrontal cortex function and structure in depression. *Annals of the New York Academy of Sciences*, *1121*, 499–527. http://doi.org/10.1196/annals.1401.029

Drevets, W. C., Price, J. L., & Furey, M. L. (2008). Brain structural and functional abnormalities in mood disorders: implications for neurocircuitry models of depression. *Brain Structure & Function*, *213*(1–2), 93–118. http://doi.org/10.1007/s00429-008-0189-x

Egeland, B., Weinfield, N., Hiester, M., Lawrence, C., Pierce, S., & Chippendale, K. (1995). Teaching tasks administration and scoring manual.

Ellenbogen, M. a., & Hodgins, S. (2009). Structure provided by parents in middle childhood predicts cortisol reactivity in adolescence among the offspring of parents with bipolar disorder and controls. *Psychoneuroendocrinology*, *34*(5), 773–785. http://doi.org/10.1016/j.psyneuen.2008.12.011

Ellis, B. J., & Boyce, W. T. (2008). Biological sensitivity to context. *Current Directions in Psychological Science*, *17*(3), 183–187. http://doi.org/10.1111/j.1467-8721.2008.00571.x

Engert, V., Efanov, S. I., Dedovic, K., Duchesne, A., Dagher, A., & Pruessner, J. C. (2010). Perceived early-life maternal care and the cortisol response to repeated psychosocial stress. *Journal of Psychiatry & Neuroscience : JPN*, *35*(6), 370–7. http://doi.org/10.1503/jpn.100022

Ertel, K. A., Rich-Edwards, J. W., & Koenen, K. C. (2011). Maternal depression in the United States: nationally representative rates and risks. *Journal of Women's Health (2002)*, *20*(11), 1609–17. http://doi.org/10.1089/jwh.2010.2657

Evensmoen, H. R., Lehn, H., Xu, J., Witter, M. P., Nadel, L., & Håberg, A. K. (2013). The anterior hippocampus supports a coarse, global environmental representation and the posterior hippocampus supports fine-grained, local environmental representations. *Journal of Cognitive Neuroscience*, *25*(11), 1908–1925. http://doi.org/10.1162/jocn_a_00436

Fairchild, G., van Goozen, S. H. M., Stollery, S. J., Brown, J., Gardiner, J., Herbert, J., & Goodyer, I. M. (2008). Cortisol diurnal rhythm and stress reactivity in male adolescents with early-onset or adolescence-onset conduct disorder. *Biological Psychiatry*, *64*(7), 599–606. http://doi.org/10.1016/j.biopsych.2008.05.022

Fanselow, M. S., & Dong, H.-W. (2010). Are the dorsal and ventral hippocampus functionally distinct structures? *Neuron*, *65*(1), 7–19. http://doi.org/10.1016/j.neuron.2009.11.031

Field, T. (1998). Maternal depression effects on infants and early interventions. *Preventive Medicine*, *27*(2), 200–203. http://doi.org/10.1097/00005721-199811000-00018

Field, T. (2010). Postpartum depression effects on early interactions, parenting, and safety practices: A review. *Infant Behavior and Development*, *33*(1), 1–9. http://doi.org/10.1016/j.infbeh.2009.10.005

Fink, G. R., Markowitsch, H. J., Reinkemeier, M., Bruckbauer, T., Kessler, J., & Heiss, W. D. (1996). Cerebral representation of one's own past: neural networks involved

in autobiographical memory. *The Journal of Neuroscience : The Official Journal of the Society for Neuroscience*, *16*(13), 4275–82. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/8753888

First, M. B., Spitzer, R. L., Gibbon, M., & Williams, J. B. W. (1996). *Structured Clinical Interview for DSM-IV Axis I Disorders: Non-patient edition* (Version 2.). New York, NY: New York State Psychiatric Institute, Biometrics Research.

Flint, J., & Kendler, K. S. (2014). The genetics of major depression. *Neuron*, *81*(3), 484–503. http://doi.org/10.1016/j.neuron.2014.01.027

Foland-ross, L. C., Hardin, M. G., & Gotlib, I. H. (2013). Neurobiological Markers of Familial Risk for Depression, (May 2012), 181–206. http://doi.org/10.1007/7854

Fonov, V., Evans, A. C., Botteron, K., Almli, C. R., McKinstry, R. C., & Collins, D. L. (2011). Unbiased average age-appropriate atlases for pediatric studies. *NeuroImage*, *54*(1), 313–27. http://doi.org/10.1016/j.neuroimage.2010.07.033

Fox, S. E., Levitt, P., & Nelson, C. a. (2010). How the timing and quality of early experiences influence the development of brain architecture. *Child Development*, *81*(1), 28–40. http://doi.org/10.1111/j.1467-8624.2009.01380.x

Fransson, P. (2005). Spontaneous low-frequency BOLD signal fluctuations: An fMRI investigation of the resting-state default mode of brain function hypothesis. *Human Brain Mapping*, *26*(1), 15–29. http://doi.org/10.1002/hbm.20113

Fransson, P., & Marrelec, G. (2008). The precuneus/posterior cingulate cortex plays a pivotal role in the default mode network: Evidence from a partial correlation network analysis. *NeuroImage*, *42*(3), 1178–1184. http://doi.org/10.1016/j.neuroimage.2008.05.059

Fries, E., Hesse, J., Hellhammer, J., & Hellhammer, D. H. (2005). A new view on hypocortisolism. *Psychoneuroendocrinology*, *30*(10), 1010–6. http://doi.org/10.1016/j.psyneuen.2005.04.006

Friston, K. J., Kahan, J., Biswal, B., & Razi, A. (2013). A DCM for resting state fMRI. *NeuroImage*. http://doi.org/10.1016/j.neuroimage.2013.12.009

Friston, K., Moran, R., & Seth, A. K. (2013). Analysing connectivity with Granger causality and dynamic causal modelling. *Current Opinion in Neurobiology*, *23*(2), 172–178. http://doi.org/10.1016/j.conb.2012.11.010

Frodl, T., & O'Keane, V. (2013). How does the brain deal with cumulative stress? A review with focus on developmental stress, HPA axis function and hippocampal structure in humans. *Neurobiology of Disease*, *52*, 24–37. http://doi.org/10.1016/j.nbd.2012.03.012

Frodl, T., Reinhold, E., Koutsouleris, N., Donohoe, G., Bondy, B., Reiser, M., … Meisenzahl, E. M. (2010). Childhood stress, serotonin transporter gene and brain structures in major depression. *Neuropsychopharmacology : Official Publication of the American College of Neuropsychopharmacology*, *35*(6), 1383–90. http://doi.org/10.1038/npp.2010.8

Frodl, T., Schaub, A., Banac, S., Charypar, M., Jäger, M., Kümmler, P., … Meisenzahl, E. M. (2006). Reduced hippocampal volume correlates with executive dysfunctioning in major depression. *Journal of Psychiatry & Neuroscience : JPN*, *31*(5), 316–23. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/16951734

Fu, C. H. Y., Mourao-Miranda, J., Costafreda, S. G., Khanna, A., Marquand, A. F., Williams, S. C. R., & Brammer, M. J. (2008). Pattern Classification of Sad Facial

Processing: Toward the Development of Neurobiological Markers in Depression. *Biological Psychiatry*, *63*(7), 656–662. http://doi.org/10.1016/j.biopsych.2007.08.020

Gee, D. G., & Casey, B. J. (2015). The impact of developmental timing for stress and recovery. *Neurobiology of Stress*, *1*, 184–194. http://doi.org/10.1016/j.ynstr.2015.02.001

Gee, D. G., Gabard-Durnam, L. J., Flannery, J., Goff, B., Humphreys, K. L., Telzer, E. H., … Tottenham, N. (2013). Early developmental emergence of human amygdala-prefrontal connectivity after maternal deprivation. *Proceedings of the National Academy of Sciences of the United States of America*, *110*(39), 15638–43. http://doi.org/10.1073/pnas.1307893110

Ghetti, S., & Bunge, S. a. (2012). Neural changes underlying the development of episodic memory during middle childhood. *Developmental Cognitive Neuroscience*, *2*(4), 381–95. http://doi.org/10.1016/j.dcn.2012.05.002

Gibbs, B. R., & Rude, S. S. (2004). Overgeneral Autobiographical Memory as Depression Vulnerability. *Cognitive Therapy and Research*, *28*(4), 511–526. http://doi.org/10.1023/B:COTR.0000045561.72997.7c

Giedd, J. N., Vaituzis, A. C., Hamburger, S. D., Lange, N., Rajapakse, J. C., Kaysen, D., … Rapoport, J. L. (1996). Quantitative MRI of the temporal lobe, amygdala, and hippocampus in normal human development: Ages 4–18 years. *The Journal of Comparative Neurology*, *366*(2), 223–230. http://doi.org/10.1002/(SICI)1096-9861(19960304)366:2<223::AID-CNE3>3.0.CO;2-7

Gilbertson, M. W., Shenton, M. E., Ciszewski, A., Kasai, K., Lasko, N. B., Orr, S. P., …

Pitman, R. K. (2002). Smaller hippocampal volume predicts pathologic vulnerability to psychological trauma. *Nature Neuroscience*, *5*(11), 1242–1247. http://doi.org/10.1038/nn958

Gilliam, M., Forbes, E. E., Gianaros, P. J., Erickson, K. I., Brennan, L. M., & Shaw, D. S. (2014). Maternal depression in childhood and aggression in young adulthood: evidence for mediation by offspring amygdala - hippocampal volume ratio. *Journal of Child Psychology and Psychiatry, and Allied Disciplines*. http://doi.org/10.1111/jcpp.12364

Gogtay, N., Iii, T. F. N., Herman, D. H., Ordonez, A., Greenstein, D., Hayashi, K. M., … Thompson, P. M. (2006). Dynamic Mapping of Normal Human Hippocampal Development, *672*, 664–672. http://doi.org/10.1002/hipo

Golkar, A., Lonsdorf, T. B., Olsson, A., Lindstrom, K. M., Berrebi, J., Fransson, P., … Lawrence, A. (2012). Distinct Contributions of the Dorsolateral Prefrontal and Orbitofrontal Cortex during Emotion Regulation. *PLoS ONE*, *7*(11), e48107. http://doi.org/10.1371/journal.pone.0048107

Goodman, S. H. (2007). Depression in mothers. *Annual Review of Clinical Psychology*, *3*, 107–35. http://doi.org/10.1146/annurev.clinpsy.3.022806.091401

Goodman, S. H., & Gotlib, I. H. (1999). Risk for psychopathology in the children of depressed mothers: a developmental model for understanding mechanisms of transmission. *Psychological Review*, *106*(3), 458–90. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/10467895

Goodman, S. H., & Gotlib, I. H. (Eds.). (2002). *Children of Depressed Parents: Mechanisms of Risk and Implications for Treatment*. Washington, D.C.: American

Psychological Association.

Goodman, S. H., Rouse, M. H., Connell, A. M., Broth, M. R., Hall, C. M., & Heyward, D. (2011). Maternal depression and child psychopathology: a meta-analytic review. *Clinical Child and Family Psychology Review*, *14*(1), 1–27. http://doi.org/10.1007/s10567-010-0080-1

Gotlib, I. H., Joormann, J., Minor, K. L., & Hallmayer, J. (2008). HPA axis reactivity: a mechanism underlying the associations among 5-HTTLPR, stress, and depression. *Biological Psychiatry*, *63*(9), 847–51. http://doi.org/10.1016/j.biopsych.2007.10.008

Gould, E., & Tanapat, P. (1999). Stress and hippocampal neurogenesis. *Biological Psychiatry*, *46*(11), 1472–9. http://doi.org/10.1016/S0006-3223(99)00247-4

Greenberg, D. L., Rice, H. J., Cooper, J. J., Cabeza, R., Rubin, D. C., & Labar, K. S. (2005). Co-activation of the amygdala , hippocampus and inferior frontal gyrus during autobiographical memory retrieval, *43*, 659–674. http://doi.org/10.1016/j.neuropsychologia.2004.09.002

Greicius, M. D., Flores, B. H., Menon, V., Glover, G. H., Solvason, H. B., Kenna, H., … Schatzberg, A. F. (2007). Resting-state functional connectivity in major depression: Abnormally increased contributions from subgenual cingulate cortex and thalamus, *62*(5), 429–437.

Greicius, M. D., Krasnow, B., Reiss, A. L., & Menon, V. (2003). Functional connectivity in the resting brain: a network analysis of the default mode hypothesis. *Proceedings of the National Academy of Sciences of the United States of America*, *100*(1), 253–8. http://doi.org/10.1073/pnas.0135058100

Grieve, S. M., Korgaonkar, M. S., Koslow, S. H., Gordon, E., & Williams, L. M. (2013).

Widespread reductions in gray matter volume in depression. *NeuroImage: Clinical*, *3*, 332–339. http://doi.org/10.1016/j.nicl.2013.08.016

Gunnar, M. R., Wewerka, S., Frenn, K., Long, J. D., & Griggs, C. (2009). Developmental changes in hypothalamus–pituitary–adrenal activity over the transition to adolescence: Normative changes and associations with puberty. *Development and Psychopathology*, *21*(1), 69. http://doi.org/10.1017/S0954579409000054

Guo, H., Cheng, C., Cao, X., Xiang, J., Chen, J., & Zhang, K. (2014). Resting-state functional connectivity abnormalities in first-onset unmedicated depression. *Neural Regeneration Research*, *9*(2), 153–63. http://doi.org/10.4103/1673-5374.125344

Guo, W., Liu, F., Liu, J., Yu, M., Zhang, Z., Liu, G., … Zhao, J. (2015). Increased cerebellar-default-mode-network connectivity in drug-naive major depressive disorder at rest. *Medicine*, *94*(9), e560. http://doi.org/10.1097/MD.0000000000000560

Gupta, R., & Kar, B. R. (2012). Attention and memory biases as stable abnormalities among current depressed and currently remitted individuals with unipolar depression. *Frontiers in Psychiatry2*, *8*(99).

Guyer, A. E., Choate, V. R., Grimm, K. J., Pine, D. S., & Keenan, K. (2011). Emerging depression is associated with face memory deficits in adolescent girls. *Journal of the American Academy of Child and Adolescent Psychiatry*, *50*(2), 180–90. http://doi.org/10.1016/j.jaac.2010.11.008

Halligan, S. L., Herbert, J., Goodyer, I. M., & Murray, L. (2004). Exposure to postnatal depression predicts elevated cortisol in adolescent offspring. *Biological Psychiatry*, *55*(4), 376–81. http://doi.org/10.1016/j.biopsych.2003.09.013

Hamilton, J. P., Farmer, M., Fogelman, P., & Gotlib, I. H. (2015). Depressive Rumination, the Default-Mode Network, and the Dark Matter of Clinical Neuroscience. *Biological Psychiatry*, *78*(4), 224–230. http://doi.org/10.1016/j.biopsych.2015.02.020

Hamilton, J. P., Furman, D. J., Chang, C., Thomason, M. E., Dennis, E., & Gotlib, I. H. (2011). Default-mode and task-positive network activity in major depressive disorder: implications for adaptive and maladaptive rumination. *Biological Psychiatry*, *70*(4), 327–333. http://doi.org/10.1016/j.biopsych.2011.02.003

Hanson, J. L., Chung, M. K., Avants, B. B., Shirtcliff, E. A., Gee, J. C., Davidson, R. J., … Pollak, S. D. (2010). Early stress is associated with alterations in the orbitofrontal cortex: a tensor-based morphometry investigation of brain structure and behavioral risk. *The Journal of Neuroscience : The Official Journal of the Society for Neuroscience*, *30*(22), 7466–72. http://doi.org/10.1523/JNEUROSCI.0859-10.2010

Hart, H., & Rubia, K. (2012). Neuroimaging of child abuse: a critical review. *Frontiers in Human Neuroscience*, *6*(March), 1–24. http://doi.org/10.3389/fnhum.2012.00052

Harvey, P.-O., Fossati, P., Pochon, J.-B., Levy, R., Lebastard, G., Lehéricy, S., … Dubois, B. (2005). Cognitive control and brain resources in major depression: an fMRI study using the n-back task. *NeuroImage*, *26*(3), 860–9. http://doi.org/10.1016/j.neuroimage.2005.02.048

Hayden, E. P., Klein, D. N., Dougherty, L. R., Olino, T. M., Dyson, M. W., Durbin, C. E., … Singh, S. M. (2010). The role of brain-derived neurotrophic factor genotype, parental depression, and relationship discord in predicting early-emerging negative emotionality. *Psychological Science*, *21*(11), 1678–85.

http://doi.org/10.1177/0956797610385357

Hayes, A. F. A. F. (2013). *Introduction to Mediation, Moderation, and Conditional Process Analysis: A Regression-Based Approach*. New York: Guilford Press. Retrieved from https://books.google.com/books?hl=en&lr=&id=iWFSpQFh-y4C&pgis=1

Heath, R. G., Dempesy, C. W., Fontana, C. J., & Myers, W. A. (1978). Cerebellar stimulation: effects on septal region, hippocampus, and amygdala of cats and rats. *Biological Psychiatry*, *13*(5), 501–29. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/728506

Hellstrom, I. C., Dhir, S. K., Diorio, J. C., & Meaney, M. J. (2012). Maternal licking regulates hippocampal glucocorticoid receptor transcription through a thyroid hormone-serotonin-NGFI-A signalling cascade. *Philosophical Transactions of the Royal Society B: Biological Sciences*, *367*(1601), 2495–2510. http://doi.org/10.1098/rstb.2012.0223

Henry, M. L., & Joormann, J. (2010). Neural processing of reward and loss in girls at risk for major depression. *Archives of General Psychiatry*, *67*(4), 380–387. http://doi.org/10.1001/archgenpsychiatry.2010.13.Neural

Hipwell, a E., Goossens, F. a, Melhuish, E. C., & Kumar, R. (2000). Severe maternal psychopathology and infant-mother attachment. *Development and Psychopathology*, *12*(2), 157–175. http://doi.org/10.1017/S0954579400002030

Holz, N. E., Boecker, R., Hohm, E., Zohsel, K., Buchmann, A. F., Blomeyer, D., … Laucht, M. (2015). The long-term impact of early life poverty on orbitofrontal cortex volume in adulthood: results from a prospective study over 25 years.

Neuropsychopharmacology : Official Publication of the American College of Neuropsychopharmacology, *40*(4), 996–1004. http://doi.org/10.1038/npp.2014.277

Howard, E. (1968). Reductions in size and total DNA of cerebrum and cerebellum in adult mice after corticosterone treatment in infancy. *Experimental Neurology*, *22*(2), 191–208. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/5724943

Hu, S., Pruessner, J. C., Coupé, P., & Collins, D. L. (2013). Volumetric analysis of medial temporal lobe structures in brain development from childhood to adolescence. *NeuroImage*, *74*, 276–287. http://doi.org/10.1016/j.neuroimage.2013.02.032

Hughes, C., Roman, G., Hart, M. J., & Ensor, R. (2013). Does maternal depression predict young children's executive function? - a 4-year longitudinal study. *Journal of Child Psychology and Psychiatry, and Allied Disciplines*, *54*(2), 169–77. http://doi.org/10.1111/jcpp.12014

Hulvershorn, L. A., Cullen, K., & Anand, A. (2011). Toward dysfunctional connectivity: A review of neuroimaging findings in pediatric major depressive disorder. *Brain Imaging and Behavior*, *5*(4), 307–28. http://doi.org/10.1007/s11682-011-9134-3

Hwang, J. W., Egorova, N., Yang, X. Q., Zhang, W. Y., Chen, J., Yang, X. Y., … Kong, J. (2015). Subthreshold depression is associated with impaired resting-state functional connectivity of the cognitive control network. *Translational Psychiatry*, *5*, e683. http://doi.org/10.1038/tp.2015.174

Hwang, J. W., Xin, S. C., Ou, Y. M., Zhang, W. Y., Liang, Y. L., Chen, J., … Kong, J. (2016). Enhanced default mode network connectivity with ventral striatum in subthreshold depression individuals. *Journal of Psychiatric Research*, *76*, 111–120.

http://doi.org/10.1016/j.jpsychires.2016.02.005

Jacobson, L., & Sapolsky, R. (1991). The role of the hippocampus in feedback regulation of the hypothalamic-pituitary-adrenocortical axis. *Endocrine Reviews*, *12*(2), 118–34. http://doi.org/10.1210/edrv-12-2-118

Jensen, S. K. G., Dumontheil, I., & Barker, E. D. (2014). Developmental inter-relations between early maternal depression, contextual risks, and interpersonal stress, and their effect on later child cognitive functioning. *Depression and Anxiety*, *31*(7), 599–607. http://doi.org/10.1002/da.22147

Jeong, W., Kee Chung, C., Sic Kim, J., & Marinazzo, D. (2015). Episodic memory in aspects of large-scale brain networks. http://doi.org/10.3389/fnhum.2015.00454

Joëls, M., Karten, Y., Hesen, W., & de Kloet, E. R. (1997). Corticosteroid effects on electrical properties of brain cells: temporal aspects and role of antiglucocorticoids. *Psychoneuroendocrinology*, *22 Suppl 1*, S81-6. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/9264152

Johnson, P. O., & Fay, L. C. (1950). The Johnson-Neyman technique, its theory and application. *Psychometrika*, *15*(4), 349–367. http://doi.org/10.1007/BF02288864

Joormann, J., Cooney, R. E., Henry, M. L., & Gotlib, I. H. (2012). Neural correlates of automatic mood regulation in girls at high risk for depression. *Journal of Abnormal Psychology*, *121*(1), 61–72. http://doi.org/10.1037/a0025294

Joormann, J., Talbot, L., & Gotlib, I. H. (2007). Biased processing of emotional information in girls at risk for depression. *Journal of Abnormal Psychology*, *116*(1), 135–43. http://doi.org/10.1037/0021-843X.116.1.135

Kaplan, S. J., Pelcovitz, D., & Labruna, V. (1999). Child and adolescent abuse and

neglect research: a review of the past 10 years. Part I: Physical and emotional abuse and neglect. *Journal of the American Academy of Child and Adolescent Psychiatry*, *38*(10), 1214–1222. http://doi.org/10.1097/00004583-199910000-00009

Keenan, Wheeler, Gallup, & Pascual-Leone. (2000). Self-recognition and the right prefrontal cortex. *Trends in Cognitive Sciences*, *4*(9), 338–344. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/10962615

Kent, J. M., & Rauch, S. L. (2003). Neurocircuitry of anxiety disorders. *Current Psychiatry Reports*, *5*(4), 266–273. http://doi.org/10.1007/s11920-003-0055-8

Kiem, S. A., Andrade, K. C., Spoormaker, V. I., Holsboer, F., Czisch, M., & Sämann, P. G. (2013). Resting state functional MRI connectivity predicts hypothalamus-pituitary-axis status in healthy males. *Psychoneuroendocrinology*, *38*(8), 1338–48. http://doi.org/10.1016/j.psyneuen.2012.11.021

Kiernan, K. E., & Huerta, M. C. (2008). Economic deprivation, maternal depression, parenting and children's cognitive and emotional development in early childhood. *British Journal of Sociology*, *59*(4), 783–806. http://doi.org/10.1111/j.1468-4446.2008.00219.x

Kim, E., Kim, D.-S., Ahmad, F., & Park, H. (2013). Pattern-based Granger causality mapping in FMRI. *Brain Connectivity*, *3*(6), 569–77. http://doi.org/10.1089/brain.2013.0148

Kirby, E. D., Muroy, S. E., Sun, W. G., Covarrubias, D., Leong, M. J., Barchas, L. A., & Kaufer, D. (2013). Acute stress enhances adult rat hippocampal neurogenesis and activation of newborn neurons via secreted astrocytic FGF2. *eLife*, *2*, e00362. http://doi.org/10.7554/eLife.00362

Knoops, A. J. G., Gerritsen, L., van der Graaf, Y., Mali, W. P. T. M., & Geerlings, M. I. (2010). Basal hypothalamic pituitary adrenal axis activity and hippocampal volumes: the SMART-Medea study. *Biological Psychiatry*, *67*(12), 1191–8. http://doi.org/10.1016/j.biopsych.2010.01.025

Knudsen, E. I. (2004). Sensitive periods in the development of the brain and behavior. *Journal of Cognitive Neuroscience*, *16*(8), 1412–25. http://doi.org/10.1162/0898929042304796

Köhler, S., Crane, J., & Milner, B. (2002). Differential contributions of the parahippocampal place area and the anterior hippocampus to human memory for scenes. *Hippocampus*, *12*(6), 718–723. http://doi.org/10.1002/hipo.10077

Konarski, J. Z., McIntyre, R. S., Grupp, L. A., & Kennedy, S. H. (2005). Is the cerebellum relevant in the circuitry of neuropsychiatric disorders? *Journal of Psychiatry & Neuroscience : JPN*, *30*(3), 178–86. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/15944742

Kopala-Sibley, D. C., Dougherty, L. R., Dyson, M. W., Laptook, R. S., Olino, T. M., Bufferd, S. J., & Klein, D. N. (2015). Early childhood cortisol reactivity moderates the effects of parent-child relationship quality on the development of children's temperament in early childhood. *Developmental Science*, n/a-n/a. http://doi.org/10.1111/desc.12378

Kremen, W. S., O'Brien, R. C., Panizzon, M. S., Prom-Wormley, E., Eaves, L. J., Eisen, S. A., … Franz, C. E. (2010). Salivary cortisol and prefrontal cortical thickness in middle-aged men: A twin study. *Neuroimage*, *53*(3).

Kryski, K. R., Smith, H. J., Sheikh, H. I., Singh, S. M., & Hayden, E. P. (2011).

Assessing stress reactivity indexed via salivary cortisol in preschool-aged children. *Psychoneuroendocrinology*, *36*(8), 1127–36. http://doi.org/10.1016/j.psyneuen.2011.02.003

Kudielka, B. M., & Wüst, S. (2015). Human models in acute and chronic stress: Assessing determinants of individual hypothalamus–pituitary–adrenal axis activity and reactivity. *Stress*. Retrieved from http://www.tandfonline.com/doi/full/10.3109/10253890902874913#.VdfyhPlViko

Kuhlman, K. R., Olson, S. L., & Lopez-Duran, N. L. (2014). Predicting developmental changes in internalizing symptoms: examining the interplay between parenting and neuroendocrine stress reactivity. *Developmental Psychobiology*, *56*(5), 908–23. http://doi.org/10.1002/dev.21166

Kujawa, A., Proudfit, G. H., & Klein, D. N. (2014). Neural reactivity to rewards and losses in offspring of mothers and fathers with histories of depressive and anxiety disorders. *Journal of Abnormal Child Psychology*, *123*(2), 287–297.

Lavi-Avnon, Y., Yadid, G., Overstreet, D. H., & Weller, A. (2005). Abnormal patterns of maternal behavior in a genetic animal model of depression. *Physiology & Behavior*, *84*(4), 607–15. http://doi.org/10.1016/j.physbeh.2005.02.006

Lavretsky, H., Zheng, L., Weiner, M. W., Mungas, D., Reed, B., Kramer, J. H., … Mack, W. J. (2008). The MRI brain correlates of depressed mood, anhedonia, apathy, and anergia in older adults with and without cognitive impairment or dementia. *International Journal of Geriatric Psychiatry*, *23*(10), 1040–50. http://doi.org/10.1002/gps.2030

Lee, J. K., Ekstrom, A. D., & Ghetti, S. (2014). Volume of hippocampal subfields and

episodic memory in childhood and adolescence. *NeuroImage*, *94*, 162–71. http://doi.org/10.1016/j.neuroimage.2014.03.019

Leppert, K. A., Kushner, M., Smith, V. C., Lemay, E. P., & Dougherty, L. R. (2016). Children's cortisol responses to a social evaluative laboratory stressor from early to middle childhood. *Developmental Psychobiology*. http://doi.org/10.1002/dev.21435

Letourneau, N. L., Tramonte, L., & Willms, J. D. (2013). Maternal depression, family functioning and children's longitudinal development. *Journal of Pediatric Nursing*, *28*(3), 223–34. http://doi.org/10.1016/j.pedn.2012.07.014

Letourneau, N., Salmani, M., & Duffett-Leger, L. (2010). Maternal depressive symptoms and parenting of children from birth to 12 years. *Western Journal of Nursing Research*, *32*(5), 662–685. http://doi.org/10.1177/0193945909359409

Lewis, M., & Ramsay, D. (2002). Cortisol Response to Embarrassment and Shame. *Child Development*, *73*(4), 1034–1045. http://doi.org/10.1111/1467-8624.00455

Li, S., Weerda, R., Milde, C., Wolf, O. T., & Thiel, C. M. (2014). Effects of acute psychosocial stress on neural activity to emotional and neutral faces in a face recognition memory paradigm. *Brain Imaging and Behavior*, *8*(4), 598–610. http://doi.org/10.1007/s11682-013-9287-3

Liotti, M., Mayberg, H. S., Brannan, S. K., McGinnis, S., Jerabek, P., & Fox, P. T. (2000). Differential limbic-cortical correlates of sadness and anxiety in healthy subjects: Implications for affective disorders. *Biol Psychiatry*, *48*, 30–42. http://doi.org/10.1016/S0006-3223(00)00874-X

Liu, D., Diorio, J., Day, J. C., Francis, D. D., & Meaney, M. J. (2000). Maternal care, hippocampal synaptogenesis and cognitive development in rats. *Nature*

Neuroscience, *3*(8), 799–806. http://doi.org/10.1038/77702

Liu, D., Diorio, J., Tannenbaum, B., Caldji, C., Francis, D., Freedman, A., … Meaney, M. J. (1997). Maternal Care, Hippocampal Glucocorticoid Receptors, and Hypothalamic-Pituitary-Adrenal Responses to Stress. *Science*, *277*(5332), 1659–1662. http://doi.org/10.1126/science.277.5332.1659

Liu, L., Zeng, L.-L., Li, Y., Ma, Q., Li, B., Shen, H., … Dierker, D. (2012). Altered Cerebellar Functional Connectivity with Intrinsic Connectivity Networks in Adults with Major Depressive Disorder. *PLoS ONE*, *7*(6), e39516. http://doi.org/10.1371/journal.pone.0039516

Liu, R., Yang, X.-D., Liao, X.-M., Xie, X.-M., Su, Y.-A., Li, J.-T., … Si, T.-M. (2016). Early postnatal stress suppresses the developmental trajectory of hippocampal pyramidal neurons: the role of CRHR1. *Brain Structure & Function*. http://doi.org/10.1007/s00429-016-1182-4

Lopez-Duran, N. L., McGinnis, E., Kuhlman, K., Geiss, E., Vargas, I., & Mayer, S. (2015). HPA-axis stress reactivity in youth depression: evidence of impaired regulatory processes in depressed boys. *Stress*, 1–9. http://doi.org/10.3109/10253890.2015.1053455

Lovejoy, M. C., Graczyk, P. a, O'Hare, E., & Neuman, G. (2000). Maternal depression and parenting behavior: a meta-analytic review. *Clinical Psychology Review*, *20*(5), 561–92. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/10860167

Luby, J. L., Barch, D. M., Belden, A., Gaffrey, M. S., Tillman, R., Babb, C., … Botteron, K. N. (2012). Maternal support in early childhood predicts larger hippocampal volumes at school age. *Proceedings of the National Academy of Sciences of the*

United States of America, *109*(8), 2854–9. http://doi.org/10.1073/pnas.1118003109

Luby, J. L., Heffelfinger, A., Mrakotsky, C., Brown, K., Hessler, M., & Spitznagel, E. (2003). Alterations in stress cortisol reactivity in depressed preschoolers relative to psychiatric and no-disorder comparison groups. *Archives of General Psychiatry*, *60*(12), 1248–55. http://doi.org/10.1001/archpsyc.60.12.1248

Lupien, S. J., King, S., Meaney, M. J., & McEwen, B. S. (2000). Child's stress hormone levels correlate with mother's socioeconomic status and depressive state. *Biological Psychiatry*, *48*(10), 976–980. http://doi.org/10.1016/S0006-3223(00)00965-3

Lupien, S. J., McEwen, B. S., Gunnar, M. R., & Heim, C. (2009). Effects of stress throughout the lifespan on the brain, behaviour and cognition. *Nature Reviews. Neuroscience*, *10*(6), 434–45. http://doi.org/10.1038/nrn2639

Lupien, S. J., Parent, S., Evans, A. C., Tremblay, R. E., Zelazo, P. D., Corbo, V., … Corbo, V. (2011). Larger amygdala but no change in hippocampal volume in 10-year-old children exposed to maternal depressive symptomatology since birth. *Proceedings of the National Academy of Sciences of the United States of America*, *108*(34), 14324–9. http://doi.org/10.1073/pnas.1105371108

Lyons, D. M., Yang, C., Sawyer-Glover, A. M., Moseley, M. E., & Schatzberg, A. F. (2001). Early life stress and inherited variation in monkey hippocampal volumes. *Archives of General Psychiatry*, *58*(12), 1145–51. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/11735843

Ma, C., Ding, J., Li, J., Guo, W., Long, Z., Liu, F., … Chen, H. (2012). Resting-State Functional Connectivity Bias of Middle Temporal Gyrus and Caudate with Altered Gray Matter Volume in Major Depression. *PLoS ONE*, *7*(9), e45263.

http://doi.org/10.1371/journal.pone.0045263

MacMaster, F. P., & Kusumakar, V. (2004). Hippocampal volume in early onset depression. *BMC Medicine*, *2*, 2. http://doi.org/10.1186/1741-7015-2-2

MacQueen, G., & Frodl, T. (2011). The hippocampus in major depression: evidence for the convergence of the bench and bedside in psychiatric research? *Molecular Psychiatry*, *16*(3), 252–264. http://doi.org/10.1038/mp.2010.80

Maddock, R. J., Garrett, A. S., & Buonocore, M. H. (2003). Posterior cingulate cortex activation by emotional words: fMRI evidence from a valence decision task. *Human Brain Mapping*, *18*(1), 30–41. http://doi.org/10.1002/hbm.10075

Maddock, R. J., & Maddock, R. L. (1999). The retrosplenial cortex and emotion: new insights from functional neuroimaging of the human brain. *Trends Neurosci*, *22*, 310–316.

Maheu, F. S., Dozier, M., Guyer, A. E., Mandell, D., Peloso, E., Poeth, K., … Ernst, M. (2010). A preliminary study of medial temporal lobe function in youths with a history of caregiver deprivation and emotional neglect. *Cognitive, Affective & Behavioral Neuroscience*, *10*(1), 34–49. http://doi.org/10.3758/CABN.10.1.34

Malberg, J. E., Eisch, A. J., Nestler, E. J., & Duman, R. S. (2000). Chronic Antidepressant Treatment Increases Neurogenesis in Adult Rat Hippocampus. *J. Neurosci.*, *20*(24), 9104–9110. Retrieved from http://www.jneurosci.org/content/20/24/9104.full

Malphurs, J. E., Field, T. M. ., Larraine, C., Pickens, J., Pelaez-Nogueras, M., Yando, R., & Bendell, D. (1996). Altering withdrawn and intrusive interaction behaviors of depressed mothers. *Infant Mental Health Journal*, *17*(2), 152–160.

http://doi.org/10.1002/(SICI)1097-0355(199622)17:2<152::AID-IMHJ5>3.0.CO;2-S

Marceau, K., Ram, N., Neiderhiser, J. M., Laurent, H. K., Shaw, D. S., Fisher, P., … Leve, L. D. (2013). Disentangling the effects of genetic, prenatal and parenting influences on children's cortisol variability. *Stress (Amsterdam, Netherlands)*, *16*(6), 607–15. http://doi.org/10.3109/10253890.2013.825766

Marchetti, I., Koster, E. H. W., Sonuga-Barke, E. J., & De Raedt, R. (2012). The default mode network and recurrent depression: a neurobiological model of cognitive risk factors. *Neuropsychology Review*, *22*(3), 229–51. http://doi.org/10.1007/s11065-012-9199-9

Marsman, R., Nederhof, E., Rosmalen, J. G. M., Oldehinkel, A. J., Ormel, J., & Buitelaar, J. K. (2012). Family environment is associated with HPA-axis activity in adolescents. The TRAILS study. *Biological Psychology*, *89*(2), 460–6. http://doi.org/10.1016/j.biopsycho.2011.12.013

Mather, M., Canli, T., English, T., Whitfield, S., Wais, P., Ochsner, K., … Carstensen, L. L. (2004). Amygdala responses to emotionally valenced stimuli in older and younger adults. *Psychological Science*, *15*(4), 259–63. http://doi.org/10.1111/j.0956-7976.2004.00662.x

Matsuoka, Y., Nagamine, M., Mori, E., Imoto, S., Kim, Y., & Uchitomi, Y. (2007). Left hippocampal volume inversely correlates with enhanced emotional memory in healthy middle-aged women. *The Journal of Neuropsychiatry and Clinical Neurosciences*, *19*(3), 335–8. http://doi.org/10.1176/jnp.2007.19.3.335

Maurer, D., Mondloch, C. J., & Lewis, T. L. (2007). Sleeper effects. *Developmental*

Science, *10*(1), 40–7. http://doi.org/10.1111/j.1467-7687.2007.00562.x

McCabe, C., & Mishor, Z. (2011). Antidepressant medications reduce subcortical-cortical resting-state functional connectivity in healthy volunteers. *NeuroImage*, *57*(4), 1317–23. http://doi.org/10.1016/j.neuroimage.2011.05.051

McCabe, J. E. (2014). Maternal personality and psychopathology as determinants of parenting behavior: a quantitative integration of two parenting literatures. *Psychological Bulletin*, *140*(3), 722–50. http://doi.org/10.1037/a0034835

McEwen, B. S. (2012). Brain on stress: how the social environment gets under the skin. *Proceedings of the National Academy of Sciences of the United States of America*, *109 Suppl*, 17180–5. http://doi.org/10.1073/pnas.1121254109

McKinnon, M. C., Yucel, K., Nazarov, A., & MacQueen, G. M. (2009). A meta-analysis examining clinical predictors of hippocampal volume in patients with major depressive disorder. *Journal of Psychiatry & Neuroscience : JPN*, *34*(1), 41–54. Retrieved from http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2612082&tool=pmcentrez&rendertype=abstract

McLaughlin, K. A., Sheridan, M. A., & Lambert, H. K. (2014). Childhood adversity and neural development: deprivation and threat as distinct dimensions of early experience. *Neuroscience and Biobehavioral Reviews*, *47*, 578–91. http://doi.org/10.1016/j.neubiorev.2014.10.012

McLaughlin, K. A., Sheridan, M. A., Tibu, F., Fox, N. A., Zeanah, C. H., & Nelson, C. A. (2015). Causal effects of the early caregiving environment on development of stress response systems in children. *Proceedings of the National Academy of*

Sciences of the United States of America, *112*(18), 5637–5642. http://doi.org/10.1073/pnas.1423363112

McLearn, K. T., Minkovitz, C. S., Strobino, D. M., Marks, E., & Hou, W. (2006). Maternal depressive symptoms at 2 to 4 months post partum and early parenting practices. *Archives of Pediatrics & Adolescent Medicine*, *160*(3), 279–284. http://doi.org/10.1001/archpedi.160.3.279

Meaney, M. J., & Szyf, M. (2005). Environmental programming of stress responses through DNA methylation: life at the interface between a dynamic environment and a fixed genome, *3*, 103–123.

Menon, V., Boyett-Anderson, J. M., & Reiss, a L. (2005). Maturation of medial temporal lobe response and connectivity during memory encoding. *Brain Research. Cognitive Brain Research*, *25*(1), 379–85. http://doi.org/10.1016/j.cogbrainres.2005.07.007

Miller, A., Fox, N. A., Cohn, J. F., Forbes, E. E., Joel Sherrill, M. T., & Kovacs, M. (2002). Regional Patterns of Brain Activity in Adults With a History of Childhood-Onset Depression: Gender Differences and Clinical Variability. *Am J Psychiatry*, *1596*.

Murray, L., Cooper, P., & Hipwell, a. (2003). Mental health of parents caring for infants. *Archives of Women's Mental Health*, *6*(SUPPL. 2), 71–77. http://doi.org/10.1007/s00737-003-0007-7

Murray, L., Fiori-Cowley, A., Hooper, R., & Cooper, P. (1996). The impact of postnatal depression and associated adversity on early mother-infant interactions and later infant outcome. *Child Development*, *67*(5), 2512–2526. http://doi.org/10.1111/j.1467-8624.1996.tb01871.x

Murray, L., Halligan, S. L., Goodyer, I., & Herbert, J. (2010). Disturbances in early parenting of depressed mothers and cortisol secretion in offspring: A preliminary study. *Journal of Affective Disorders*, *122*(3), 218–223. http://doi.org/10.1016/j.jad.2009.06.034

Murty, V. P., Ritchey, M., Adcock, R. A., & LaBar, K. S. (2010). fMRI studies of successful emotional memory encoding: A quantitative meta-analysis. *Neuropsychologia*, *48*(12), 3459–3469. http://doi.org/10.1016/j.neuropsychologia.2010.07.030

Narita, K., Fujihara, K., Takei, Y., Suda, M., Aoyama, Y., Uehara, T., … Mikuni, M. (2012). Associations among parenting experiences during childhood and adolescence, hypothalamus-pituitary-adrenal axis hypoactivity, and hippocampal gray matter volume reduction in young adults. *Human Brain Mapping*, *33*(9), 2211–23. http://doi.org/10.1002/hbm.21354

Newman, P. P., & Reza, H. (1979). Functional relationships between the hippocampus and the cerebellum: an electrophysiological study of the cat. *The Journal of Physiology*, *287*, 405–26. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/430426

Newport, D. J., Stowe, Z. N., & Nemeroff, C. B. (2002). Parental depression: Animal models of an adverse life event. *American Journal of Psychiatry*, *159*(8), 1265–1283. http://doi.org/10.1176/appi.ajp.159.8.1265

Nolen-Hoeksema, S., & Susan. (2000). The role of rumination in depressive disorders and mixed anxiety/depressive symptoms. *Journal of Abnormal Psychology*, *109*(3), 504–511. http://doi.org/10.1037/0021-843X.109.3.504

Northoff, G., Heinzel, A., de Greck, M., Bermpohl, F., Dobrowolny, H., & Panksepp, J. (2006). Self-referential processing in our brain—A meta-analysis of imaging studies on the self. *NeuroImage*, *31*(1), 440–457. http://doi.org/10.1016/j.neuroimage.2005.12.002

O'Brien, J. T., Lloyd, A., McKeith, I., Gholkar, A., & Ferrier, N. (2004). A longitudinal study of hippocampal volume, cortisol levels, and cognition in older depressed subjects. *The American Journal of Psychiatry*, *161*(11), 2081–90. http://doi.org/10.1176/appi.ajp.161.11.2081

Ofen, N., Kao, Y.-C., Sokol-Hessner, P., Kim, H., Whitfield-Gabrieli, S., & Gabrieli, J. D. E. (2007). Development of the declarative memory system in the human brain. *Nature Neuroscience*, *10*(9), 1198–205. http://doi.org/10.1038/nn1950

Oitzl, M. S., Champagne, D. L., van der Veen, R., & de Kloet, E. R. (2010). Brain development under stress: hypotheses of glucocorticoid actions revisited. *Neuroscience and Biobehavioral Reviews*, *34*(6), 853–66. http://doi.org/10.1016/j.neubiorev.2009.07.006

Olino, T. M., McMakin, D. L., Morgan, J. K., Silk, J. S., Birmaher, B., Axelson, D. a., … Forbes, E. E. (2013). Reduced reward anticipation in youth at high-risk for unipolar depression: A preliminary study. *Developmental Cognitive Neuroscience*. http://doi.org/10.1016/j.dcn.2013.11.005

Onuki, Y., Van Someren, E. J. W., De Zeeuw, C. I., & Van der Werf, Y. D. (2015). Hippocampal-cerebellar interaction during spatio-temporal prediction. *Cerebral Cortex (New York, N.Y. : 1991)*, *25*(2), 313–21. http://doi.org/10.1093/cercor/bht221

Oomen, C. A., Girardi, C. E. N., Cahyadi, R., Verbeek, E. C., Krugers, H., Joëls, M., &

Lucassen, P. J. (2009). Opposite Effects of Early Maternal Deprivation on Neurogenesis in Male versus Female Rats. *PLoS ONE*, *4*(1), e3675. http://doi.org/10.1371/journal.pone.0003675

Owen, A. M. (1997). The Functional Organization of Working Memory Processes Within Human Lateral Frontal Cortex: The Contribution of Functional Neuroimaging. *European Journal of Neuroscience*, *9*(7), 1329–1339. http://doi.org/10.1111/j.1460-9568.1997.tb01487.x

Pagliaccio, D., Luby, J. L., Bogdan, R., Agrawal, A., Gaffrey, M. S., Belden, A. C., … Barch, D. M. (2014). Stress-system genes and life stress predict cortisol levels and amygdala and hippocampal volumes in children. *Neuropsychopharmacology : Official Publication of the American College of Neuropsychopharmacology*, *39*(5), 1245–53. http://doi.org/10.1038/npp.2013.327

Pagliaccio, D., Luby, J. L., Bogdan, R., Agrawal, A., Gaffrey, M. S., Belden, A. C., … Barch, D. M. (2015). HPA axis genetic variation, pubertal status, and sex interact to predict amygdala and hippocampus responses to negative emotional faces in school-age children. *NeuroImage*, *109*, 1–11. http://doi.org/10.1016/j.neuroimage.2015.01.017

Pariante, C. M., & Lightman, S. L. (2008). The HPA axis in major depression: classical theories and new developments. *Trends in Neurosciences*, *31*(9), 464–8. http://doi.org/10.1016/j.tins.2008.06.006

Pavlides, C., Watanabe, Y., & McEwen, B. S. (1993). Effects of glucocorticoids on hippocampal long-term potentiation. *Hippocampus*, *3*(2), 183–92. http://doi.org/10.1002/hipo.450030210

Pavlík, A., & Buresová, M. (1984). The neonatal cerebellum: the highest level of glucocorticoid receptors in the brain. *Brain Research, 314*(1), 13–20. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/6697248

Pechtel, P., & Pizzagalli, D. A. (2011). Effects of early life stress on cognitive and affective function: an integrated review of human literature. *Psychopharmacology, 214*(1), 55–70. http://doi.org/10.1007/s00213-010-2009-2

Peng, D., Shi, F., Shen, T., Peng, Z., Zhang, C., Liu, X., … Shen, D. (2014). Altered brain network modules induce helplessness in major depressive disorder. *Journal of Affective Disorders*, *168*, 21–29. http://doi.org/10.1016/j.jad.2014.05.061

Perlman, W. R., Webster, M. J., Herman, M. M., Kleinman, J. E., & Weickert, C. S. (2007). Age-related differences in glucocorticoid receptor mRNA levels in the human brain. *Neurobiology of Aging*, *28*(3), 447–58. http://doi.org/10.1016/j.neurobiolaging.2006.01.010

Peters, A. T., Burkhouse, K., Feldhaus, C. C., Langenecker, S. A., & Jacobs, R. H. (2016). Aberrant resting-state functional connectivity in limbic and cognitive control networks relates to depressive rumination and mindfulness: A pilot study among adolescents with a history of depression. *Journal of Affective Disorders*, *200*, 178–81. http://doi.org/10.1016/j.jad.2016.03.059

Philip, N. S., Valentine, T. R., Sweet, L. H., Tyrka, A. R., Price, L. H., & Carpenter, L. L. (2014). Early life stress impacts dorsolateral prefrontal cortex functional connectivity in healthy adults: informing future studies of antidepressant treatments. *Journal of Psychiatric Research*, *52*, 63–9. http://doi.org/10.1016/j.jpsychires.2014.01.014

Philippi, C. L., Tranel, D., Duff, M., & Rudrauf, D. (2015). Damage to the default mode network disrupts autobiographical memory retrieval. *Social Cognitive and Affective Neuroscience*, *10*(3), 318–26. http://doi.org/10.1093/scan/nsu070

Phillips, M., Ladouceur, C., & Drevets, W. (2008). A neural model of voluntary and automatic emotion regulation: Implications for understanding the pathophysiology and neurodevelopment of bipolar disorder. *Molecular Psychiatry*, *13*(9), 829–857. http://doi.org/10.1038/mp.2008.65

Piefke, M., Weiss, P. H., Markowitsch, H. J., & Fink, G. R. (2005). Gender differences in the functional neuroanatomy of emotional episodic autobiographical memory. *Human Brain Mapping*, *24*(4), 313–324. http://doi.org/10.1002/hbm.20092

Piefke, M., Weiss, P. H., Zilles, K., Markowitsch, H. J., & Fink, G. R. (2003). Differential remoteness and emotional tone modulate the neural correlates of autobiographical memory. *Brain*, *126*, 650–668. http://doi.org/10.1093/brain/awg064

Pizzagalli, D. A. (2014). Depression, stress, and anhedonia: toward a synthesis and integrated model. *Annual Review of Clinical Psychology*, *10*, 393–423. http://doi.org/10.1146/annurev-clinpsy-050212-185606

Poppenk, J., Evensmoen, H. R., Moscovitch, M., & Nadel, L. (2013). Long-axis specialization of the human hippocampus. *Trends in Cognitive Sciences*, *17*(5), 230–240. http://doi.org/10.1016/j.tics.2013.03.005

Poppenk, J., & Moscovitch, M. (2011). A hippocampal marker of recollection memory ability among healthy young adults: contributions of posterior and anterior segments. *Neuron*, *72*(6), 931–7. http://doi.org/10.1016/j.neuron.2011.10.014

Power, J. D., Barnes, K. A., Snyder, A. Z., Schlaggar, B. L., Petersen, S. E., Synder, A. Z., … Peterson, S. E. (2013). Spurious but systematic correlations in functional connectivity MRI networks arise from subject motion. *NeuroImage*, *59*(3), 2142–2154. http://doi.org/10.1016/j.neuroimage.2011.10.018.Spurious

Power, J. D., Fair, D. a, Schlaggar, B. L., & Petersen, S. E. (2010). The development of human functional brain networks. *Neuron*, *67*(5), 735–48. http://doi.org/10.1016/j.neuron.2010.08.017

Power, J. D., Mitra, A., Laumann, T. O., Snyder, A. Z., Schlaggar, B. L., & Petersen, S. E. (2014). Methods to detect, characterize, and remove motion artifact in resting state fMRI. *NeuroImage*, *84*, 320–341. http://doi.org/10.1016/j.neuroimage.2013.08.048

Power, J. D., Schlaggar, B. L., & Petersen, S. E. (2015). Recent progress and outstanding issues in motion correction in resting state fMRI. *NeuroImage*, *105*, 536–551. http://doi.org/10.1016/j.neuroimage.2014.10.044

Price, J. L., & Drevets, W. C. (2010). Neurocircuitry of mood disorders. *Neuropsychopharmacology : Official Publication of the American College of Neuropsychopharmacology*, *35*(1), 192–216. http://doi.org/10.1038/npp.2009.104

Pruessner, J. C., Kirschbaum, C., Meinlschmid, G., & Hellhammer, D. H. (2003). Two formulas for computation of the area under the curve represent measures of total hormone concentration versus time-dependent change. *Psychoneuroendocrinology*, *28*(7), 916–31. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/12892658

Pruessner, M., Pruessner, J. C., Hellhammer, D. H., Bruce Pike, G., & Lupien, S. J. (2007). The associations among hippocampal volume, cortisol reactivity, and

memory performance in healthy young men. *Psychiatry Research*, *155*(1), 1–10. http://doi.org/10.1016/j.pscychresns.2006.12.007

Pryce, C. R., Rüedi-Bettschen, D., Dettling, A. C., Weston, A., Russig, H., Ferger, B., & Feldon, J. (2005). Long-term effects of early-life environmental manipulations in rodents and primates: Potential animal models in depression research. *Neuroscience and Biobehavioral Reviews*, *29*(4–5), 649–74. http://doi.org/10.1016/j.neubiorev.2005.03.011

Ranganath, C., Heller, A., Cohen, M. X., Brozinsky, C. J., & Rissman, J. (2005). Functional connectivity with the hippocampus during successful memory formation. *Hippocampus*, *15*(8), 997–1005. http://doi.org/10.1002/hipo.20141

Rao, H., Betancourt, L., Giannetta, J. M., Brodsky, N. L., Avants, B. B., Gee, J. C., … Farah, M. J. (2011). Early parental care is important for hippocampal maturation: evidence from brain morphology in humans, *49*(1), 1144–1150. http://doi.org/10.1016/j.neuroimage.2009.07.003.Early

Rao, H., Betancourt, L., Giannetta, J. M., Brodsky, N. L., Korczykowski, M., Avants, B. B., … John, A. (2010). Early parental care is important for hippocampal maturation: evidence from brain morphology in humans. *NeuroImage*, *49*(1), 1144–50. http://doi.org/10.1016/j.neuroimage.2009.07.003.Early

Rao, J. A., Jenkins, L. M., Hymen, E., Feigon, M., Weisenbach, S. L., Zubieta, J.-K., & Langenecker, S. A. (2016). Differential Resting State Connectivity Patterns and Impaired Semantically Cued List Learning Test Performance in Early Course Remitted Major Depressive Disorder. *Journal of the International Neuropsychological Society : JINS*, *22*(2), 225–39.

http://doi.org/10.1017/S1355617716000011

Rao, U., Chen, L. A. L.-A., Bidesi, A. S., Shad, M. U., Thomas, M. A., Hammen, C. L. C. L., … al., et. (2010). Hippocampal changes associated with early-life adversity and vulnerability to depression. *Biological Psychiatry*, *67*(4), 357–64. http://doi.org/10.1016/j.biopsych.2009.10.017

Raz, N., Lindenberger, U., Rodrigue, K. M., Kennedy, K. M., Head, D., Williamson, A., … Acker, J. D. (2005). Regional brain changes in aging healthy adults: General trends, individual differences and modifiers. *Cerebral Cortex*, *15*(11), 1676–1689. http://doi.org/10.1093/cercor/bhi044

Riggins, T., Blankenship, S. L., Mulligan, E., Rice, K., & Redcay, E. (2015). Developmental Differences in Relations Between Episodic Memory and Hippocampal Subregion Volume During Early Childhood. *Child Development*, *86*(6), 1710–1718. http://doi.org/10.1111/cdev.12445

Riggins, T., Geng, F., Blankenship, S. L., & Redcay, E. (2016). Hippocampal functional connectivity and episodic memory in early childhood. *Developmental Cognitive Neuroscience*, *19*, 58–69. http://doi.org/10.1016/j.dcn.2016.02.002

Rive, M. M., van Rooijen, G., Veltman, D. J., Phillips, M. L., Schene, A. H., & Ruhé, H. G. (2013). Neural correlates of dysfunctional emotion regulation in major depressive disorder. A systematic review of neuroimaging studies. *Neuroscience and Biobehavioral Reviews*, *37*(10 Pt 2), 2529–53. http://doi.org/10.1016/j.neubiorev.2013.07.018

Roebroeck, A., Formisano, E., & Goebel, R. (2005). Mapping directed influence over the brain using Granger causality and fMRI. *NeuroImage*, *25*(1), 230–42.

http://doi.org/10.1016/j.neuroimage.2004.11.017

Rohde, P., Lewinsohn, P. M., & Seeley, J. R. (1997). Comparability of telephone and face-to-face interviews in assessing axis I and II disorders. *The American Journal of Psychiatry*, *154*(11), 1593–8. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/9356570

Rubia, K., & Smith, A. (2004). The neural correlates of cognitive time management: a review. *Acta Neurobiologiae Experimentalis*, *64*(3), 329–40. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/15283476

Rusch, B. D., Abercrombie, H. C., Oakes, T. R., Schaefer, S. M., & Davidson, R. J. (2001). Hippocampal morphometry in depressed patients and control subjects: relations to anxiety symptoms. *Biological Psychiatry*, *50*(12), 960–964. http://doi.org/10.1016/S0006-3223(01)01248-3

Sacchetti, B., Scelfo, B., Tempia, F., & Strata, P. (2004). Long-term synaptic changes induced in the cerebellar cortex by fear conditioning. *Neuron*, *42*(6), 973–82. http://doi.org/10.1016/j.neuron.2004.05.012

Salami, A., Pudas, S., & Nyberg, L. (2014). Elevated hippocampal resting-state connectivity underlies deficient neurocognitive function in aging. *Proceedings of the National Academy of Sciences*, *111*(49), 201410233. http://doi.org/10.1073/pnas.1410233111

Sambataro, F., Wolf, N. D., Pennuto, M., Vasic, N., & Wolf, R. C. (2014). Revisiting default mode network function in major depression: evidence for disrupted subsystem connectivity. *Psychological Medicine*, *44*(10), 2041–51. http://doi.org/10.1017/S0033291713002596

Sánchez, M. M., Ladd, C. O., & Plotsky, P. M. (2001). Early adverse experience as a developmental risk factor for later psychopathology: evidence from rodent and primate models. *Development and Psychopathology*, *13*(3), 419–49. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/11523842

Sang, L., Qin, W., Liu, Y., Han, W., Zhang, Y., Jiang, T., & Yu, C. (2012). Resting-state functional connectivity of the vermal and hemispheric subregions of the cerebellum with both the cerebral cortical networks and subcortical structures. http://doi.org/10.1016/j.neuroimage.2012.04.011

Sapolsky. (1987). Glucocorticoids and hippocampal damage. *Trends in Neurosciences*, *10*(9), 346–349.

Sapolsky, R., Krey, L., & McEwen, B. (1985). Prolonged glucocorticoid exposure reduces hippocampal neuron number: implications for aging. *J. Neurosci.*, *5*(5), 1222–1227. Retrieved from http://www.jneurosci.org/content/5/5/1222.short

Sapolsky, R. M. (1988). Glucocorticoid toxicity in the hippocampus : in vitro demonstration. *Brain Research*, *453*(1–2), 367–371.

Sapolsky, R. M. (2000). Glucocorticoids and hippocampal atrophy in neuropsychiatric disorders. *Archives of General Psychiatry*, *57*(10), 925–935.

Sapolsky, R. M., Krey, L. C., & McEwen, B. S. (1986). The neuroendocrinology of stress and aging: the glucocorticoid cascade hypothesis. *Endocrine Reviews*, *7*(3), 284–301. http://doi.org/10.1210/edrv-7-3-284

Sapolsky, R. M., Uno, H., Rebert, C. S., & Finch, C. E. (1990). Hippocampal damage associated with prolonged glucocorticoid exposure in primates. *The Journal of Neuroscience : The Official Journal of the Society for Neuroscience*, *10*(9), 2897–

2902.

Satterthwaite, T. D., Wolf, D. H., Loughead, J., Ruparel, K., Elliott, M. A., Hakonarson, H., … Gur, R. E. (2012). Impact of in-scanner head motion on multiple measures of functional connectivity: relevance for studies of neurodevelopment in youth. *NeuroImage*, *60*(1), 623–632. http://doi.org/10.1016/j.neuroimage.2011.12.063

Sawyer, K., Corsentino, E., Sachs-Ericsson, N., & Steffens, D. C. (2012). Depression, hippocampal volume changes, and cognitive decline in a clinical sample of older depressed outpatients and non-depressed controls. *Aging & Mental Health*, *16*(6), 753–62. http://doi.org/10.1080/13607863.2012.678478

Scheuerecker, J., Meisenzahl, E. M., Koutsouleris, N., Roesner, M., Schöpf, V., Linn, J., … Frodl, T. (2010). Orbitofrontal volume reductions during emotion recognition in patients with major depression. *Journal of Psychiatry & Neuroscience : JPN*, *35*(5), 311–20. http://doi.org/10.1503/jpn.090076

Schlichting, M. L., Guarino, K. F., Schapiro, A. C., Turk-Browne, N. B., & Preston, A. R. (2016). Hippocampal Structure Predicts Statistical Learning and Associative Inference Abilities during Development. *Journal of Cognitive Neuroscience*, 1–15. http://doi.org/10.1162/jocn_a_01028

Schmahmann, J. D., Weilburg, J. B., & Sherman, J. C. (2007). The neuropsychiatry of the cerebellum – insights from the clinic. *The Cerebellum*, *6*, 254–267. http://doi.org/10.1080/14734220701490995

Schutter, D. J. L. G., & van Honk, J. (2005). The cerebellum on the rise in human emotion. *Cerebellum (London, England)*, *4*(4), 290–4. http://doi.org/10.1080/14734220500348584

Sharp, C., Kim, S., Herman, L., Pane, H., Reuter, T., & Strathearn, L. (2014). Major depression in mothers predicts reduced ventral striatum activation in adolescent female offspring with and without depression. *Journal of Abnormal Child Psychology*, *123*(2), 398–309. http://doi.org/10.1037/a0036191

Sheikh, H. I., Joanisse, M. F., Mackrell, S. M., Kryski, K. R., Smith, H. J., Singh, S. M., & Hayden, E. P. (2014). Links between white matter microstructure and cortisol reactivity to stress in early childhood: Evidence for moderation by parenting. *NeuroImage: Clinical*, *6*, 77–85. http://doi.org/10.1016/j.nicl.2014.08.013

Sheline, Y. I., Barch, D. M., Price, J. L., Rundle, M. M., Vaishnavi, S. N., Snyder, A. Z., … Raichle, M. E. (2009). The default mode network and self-referential processes in depression. *Proceedings of the National Academy of Sciences of the United States of America*, *106*(6), 1942–7. http://doi.org/10.1073/pnas.0812686106

Sheline, Y. I., Price, J. L., Yan, Z., & Mintun, M. a. (2010). Resting-state functional MRI in depression unmasks increased connectivity between networks via the dorsal nexus. *Proceedings of the National Academy of Sciences of the United States of America*, *107*(24), 11020–5. http://doi.org/10.1073/pnas.1000446107

Sheridan, M. A., & McLaughlin, K. A. (2014). Dimensions of early experience and neural development: deprivation and threat. *Trends in Cognitive Sciences*, *18*(11), 580–5. http://doi.org/10.1016/j.tics.2014.09.001

Smith, A. P. . P. R., Henson, R. N. . N. a, Dolan, R. . J., & Rugg, M. . D. (2004). fMRI correlates of the episodic retrieval of emotional contexts. *NeuroImage*, *22*(2), 868–78. http://doi.org/10.1016/j.neuroimage.2004.01.049

Smith, E. E., & Jonides, J. (1999). Storage and Executive Processes in the Frontal Lobes.

Science, *283*(5408).

Sobel, M. E. (1982). Asymptotic confidence intervals for indirect effects in structural equation models. In S. Leindhartdt (Ed.), *Sociological Methodology* (pp. 290–312). Washington, D.C.: American Sociological Association.

Söderlund, H., Moscovitch, M., Kumar, N., Daskalakis, Z. J., Flint, A., Herrmann, N., & Levine, B. (2014). Autobiographical episodic memory in major depressive disorder. *Journal of Abnormal Psychology*, *123*(1), 51–60. http://doi.org/10.1037/a0035610

Spreng, R. N., & Grady, C. L. (2010). Patterns of brain activity supporting autobiographical memory, prospection, and theory of mind, and their relationship to the default mode network. *Journal of Cognitive Neuroscience*, *22*(6), 1112–23. http://doi.org/10.1162/jocn.2009.21282

Sripada, R. K., Swain, J. E., Evans, G. W., Welsh, R. C., & Liberzon, I. (2014). Childhood poverty and stress reactivity are associated with aberrant functional connectivity in default mode network. *Neuropsychopharmacology : Official Publication of the American College of Neuropsychopharmacology*, *39*(9), 2244–51. http://doi.org/10.1038/npp.2014.75

Stein, M. B., Koverola, C., Hanna, C., Torchia, M. G., & McClarty, B. (1997). Hippocampal volume in women victimized by childhood sexual abuse. *Psychological Medicine*, *27*(4), 951–9. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/9234472

Stern, C. E., Corkin, S., González, R. G., Guimaraes, A. R., Baker, J. R., Jennings, P. J., … Rosen, B. R. (1996). The hippocampal formation participates in novel picture encoding: evidence from functional magnetic resonance imaging. *Proceedings of the*

National Academy of Sciences of the United States of America, *93*(16), 8660–5. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/8710927

Strange, B. A., Witter, M. P., Lein, E. S., & Moser, E. I. (2014). Functional organization of the hippocampal longitudinal axis. *Nature Reviews Neuroscience*, *15*(10), 655–669. http://doi.org/10.1038/nrn3785

Stuhrmann, A., Suslow, T., Dannlowski, U., Leppänen, J., Mathews, A., MacLeod, C., … Joormann, J. (2011). Facial emotion processing in major depression: a systematic review of neuroimaging findings. *Biology of Mood & Anxiety Disorders*, *1*(1), 10. http://doi.org/10.1186/2045-5380-1-10

Sudheimer, K. D., O'Hara, R., Spiegel, D., Powers, B., Kraemer, H. C., Neri, E., … Dhabhar, F. S. (2014). Cortisol, cytokines, and hippocampal volume interactions in the elderly. *Frontiers in Aging Neuroscience*, *6*, 153. http://doi.org/10.3389/fnagi.2014.00153

Sumner, J. A., Griffith, J. W., & Mineka, S. (2010). Overgeneral autobiographical memory as a predictor of the course of depression: a meta-analysis. *Behaviour Research and Therapy*, *48*(7), 614–25. http://doi.org/10.1016/j.brat.2010.03.013

Suzuki, H., Botteron, K. N., Luby, J. L., Belden, A. C., Gaffrey, M. S., Babb, C. M., … Barch, D. M. (2013). Structural-functional correlations between hippocampal volume and cortico-limbic emotional responses in depressed children. *Cognitive, Affective & Behavioral Neuroscience*, *13*(1), 135–51. http://doi.org/10.3758/s13415-012-0121-y

Sweeney, J. A., Strojwas, M. H., Mann, J. J., & Thase, M. E. (1998). Prefrontal and cerebellar abnormalities in major depression: evidence from oculomotor studies.

Biological Psychiatry, *43*(8), 584–94. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/9564443

Talge, N. M., Donzella, B., Kryzer, E. M., Gierens, A., & Gunnar, M. R. (2005). It's not that bad: error introduced by oral stimulants in salivary cortisol research. *Developmental Psychobiology*, *47*(4), 369–76. http://doi.org/10.1002/dev.20097

Taylor, Z. E., Spinrad, T. L., VanSchyndel, S. K., Eisenberg, N., Huynh, J., Sulik, M. J., & Granger, D. a. (2013). Sociodemographic risk, parenting, and effortful control: Relations to salivary alpha-amylase and cortisol in early childhood. *Developmental Psychobiology*, *55*(8), 869–880. http://doi.org/10.1002/dev.21079

Teicher, M. H., Andersen, S. L., Polcari, A., Anderson, C. M., Navalta, C. P., & Kim, D. M. (2003). The neurobiological consequences of early stress and childhood maltreatment. *Neuroscience & Biobehavioral Reviews*, *27*(1–2), 33–44. http://doi.org/10.1016/S0149-7634(03)00007-1

Teicher, M. H., Anderson, C. M., & Polcari, A. (2012). Childhood maltreatment is associated with reduced volume in the hippocampal subfields CA3, dentate gyrus, and subiculum. *Proceedings of the National Academy of Sciences of the United States of America*, *109*(9), E563-72. http://doi.org/10.1073/pnas.1115396109

Thomason, M. E., Tocco, M. A., Quednau, K. A., Bedway, A. R., & Carré, J. M. (2013). Idle behaviors of the hippocampus reflect endogenous cortisol levels in youth. *Journal of the American Academy of Child and Adolescent Psychiatry*, *52*(6), 642–52.e1. http://doi.org/10.1016/j.jaac.2013.04.004

Thomason, M. E., Yoo, D. J., Glover, G. H., & Gotlib, I. H. (2009). BDNF genotype modulates resting functional connectivity in children. *Frontiers in Human*

Neuroscience, *3*(November), 55. http://doi.org/10.3389/neuro.09.055.2009

Tolep, M. R., & Dougherty, L. R. (2014). The Conundrum of the Laboratory: Challenges of Assessing Preschool-Age Children's Salivary Cortisol Reactivity. *Journal of Psychopathology and Behavioral Assessment*, *36*(3), 350–357. http://doi.org/10.1007/s10862-014-9410-9

Tottenham, N., & Sheridan, M. a. (2009). A review of adversity, the amygdala and the hippocampus: a consideration of developmental timing. *Frontiers in Human Neuroscience*, *3*(January), 68. http://doi.org/10.3389/neuro.09.068.2009

Trickett, P. K., & McBride-Chang, C. (1995). The Developmental Impact of Different Forms of Child Abuse and Neglect. *Developmental Review*, *15*(3), 311–337. http://doi.org/10.1006/drev.1995.1012

Tsukiura, T., & Cabeza, R. (2008). Orbitofrontal and hippocampal contributions to memory for face–name associations: The rewarding power of a smile. *Neuropsychologia*, *46*(9), 2310–2319. http://doi.org/10.1016/j.neuropsychologia.2008.03.013

Tsukiura, T., Sekiguchi, A., Yomogida, Y., Nakagawa, S., Shigemune, Y., Kambara, T., … Kawashima, R. (2011). Effects of Aging on Hippocampal and Anterior Temporal Activations during Successful Retrieval of Memory for Face–Name Associations. *Journal of Cognitive Neuroscience*, *23*(1), 200–213. http://doi.org/10.1162/jocn.2010.21476

Turner, B. M., Paradiso, S., Marvel, C. L., Pierson, R., Boles Ponto, L. L., Hichwa, R. D., & Robinson, R. G. (2007). The cerebellum and emotional experience. *Neuropsychologia*, *45*(6), 1331–41.

http://doi.org/10.1016/j.neuropsychologia.2006.09.023

Uematsu, A., Matsui, M., Tanaka, C., Takahashi, T., Noguchi, K., Suzuki, M., & Nishijo, H. (2012). Developmental trajectories of amygdala and hippocampus from infancy to early adulthood in healthy individuals. *PloS One*, *7*(10), e46970. http://doi.org/10.1371/journal.pone.0046970

Uno, H., Eisele, S., Sakai, A., Shelton, S., Baker, E., DeJesus, O., & Holden, J. (1994). Neurotoxicity of glucocorticoids in the primate brain. *Hormones and Behavior*, *28*(4), 336–48. http://doi.org/10.1006/hbeh.1994.1030

Utevsky, A. V, Smith, D. V, & Huettel, S. A. (2014). Precuneus is a functional core of the default-mode network. *The Journal of Neuroscience : The Official Journal of the Society for Neuroscience*, *34*(3), 932–40. http://doi.org/10.1523/JNEUROSCI.4227-13.2014

van de Mortel, T. F. (n.d.). Faking It: Social Desirability Response Bias in Self-report Research. *Australian Journal of Advanced Nursing, The*, *25*(4), 40. Retrieved from http://search.informit.com.au/documentSummary;dn=210155003844269;res=IELHEA

Van den Stock, J., Vandenbulcke, M., Sinke, C. B. A., & de Gelder, B. (2014). Affective scenes influence fear perception of individual body expressions. *Human Brain Mapping*, *35*(2), 492–502. http://doi.org/10.1002/hbm.22195

Van Dijk, K. R. A., Sabuncu, M. R., & Buckner, R. L. (2012). The Influence of Head Motion on Intrinsic Functional Connectivity MRI. *NeuroImage*, *59*(1), 431–438. http://doi.org/10.1016/j.neuroimage.2011.07.044

van Oers, H. J., de Kloet, E. R., & Levine, S. (1997). Persistent, but paradoxical, effects

on HPA regulation of infants maternally deprived at different ages. *Stress (Amsterdam, Netherlands)*, *1*(4), 249–262. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/9787249

Van Petten, C. (2004). Relationship between hippocampal volume and memory ability in healthy individuals across the lifespane: review and meta-analysis. *Neuropsychologia*, *42*(10), 1394–413. http://doi.org/10.1016/j.neuropsychologia.2004.04.006

Vanderwal, T., Kelly, C., Eilbott, J., Mayes, L. C., & Castellanos, F. X. (2015). Inscapes: A movie paradigm to improve compliance in functional magnetic resonance imaging. *NeuroImage*, *122*, 222–32. http://doi.org/10.1016/j.neuroimage.2015.07.069

Varghese, F. P., & Brown, E. S. (2001). The Hypothalamic-Pituitary-Adrenal Axis in Major Depressive Disorder: A Brief Primer for Primary Care Physicians. *Primary Care Companion to the Journal of Clinical Psychiatry*, *3*(4), 151–155. http://doi.org/10.2174/1566523013348869

Videbech, P., Ravnkilde, B., & Ph, D. (2004). Hippocampal volume and depression: a meta-analysis of MRI studies. *The American Journal of Psychiatry*, *161*(11), 1957–66. http://doi.org/10.1176/appi.ajp.161.11.1957

Virgin, C. E., Ha, T. P., Packan, D. R., Tombaugh, G. C., Yang, S. H., Horner, H. C., & Sapolsky, R. M. (1991). Glucocorticoids inhibit glucose transport and glutamate uptake in hippocampal astrocytes: implications for glucocorticoid neurotoxicity. *Journal of Neurochemistry*, *57*(4), 1422–8. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/1680166

Vreeburg, S. A., Hoogendijk, W. J. G., van Pelt, J., Derijk, R. H., Verhagen, J. C. M., van Dyck, R., … Penninx, B. W. J. H. (2009). Major depressive disorder and hypothalamic-pituitary-adrenal axis activity: results from a large cohort study. *Archives of General Psychiatry*, *66*(6), 617–26. http://doi.org/10.1001/archgenpsychiatry.2009.50

Wang, L., Hermens, D. F., Hickie, I. B., & Lagopoulos, J. (2012). A systematic review of resting-state functional-MRI studies in major depression. *Journal of Affective Disorders*, *142*(1–3), 6–12. http://doi.org/10.1016/j.jad.2012.04.013

Wang, L., Laviolette, P., O'Keefe, K., Putcha, D., Bakkour, A., Van Dijk, K. R. a, … Sperling, R. a. (2010). Intrinsic connectivity between the hippocampus and posteromedial cortex predicts memory performance in cognitively intact older individuals. *NeuroImage*, *51*(2), 910–7. http://doi.org/10.1016/j.neuroimage.2010.02.046

Wang, Y., & Dix, T. (2013). Patterns of depressive parenting: Why they occur and their role in early developmental risk. *Journal of Family Psychology*, *27*(6), 884–95. http://doi.org/<a data-auto="ep_link" href="http://dx.doi.org/10.1037/a0034829" target="_blank" id="linkhttp:dx.doi.org10.1037a0034829" title="http://dx.doi.org/10.1037/a0034829" data-title="http://dx.doi.org/10.1037/a0034829">http://dx.doi.org/10.1037/a0034829

Wang, Z., Yuan, Y., Bai, F., Shu, H., You, J., Li, L., & Zhang, Z. (2015). Altered functional connectivity networks of hippocampal subregions in remitted late-onset depression: a longitudinal resting-state study. *Neuroscience Bulletin*, *31*(1), 13–21. http://doi.org/10.1007/s12264-014-1489-1

Watson, C., Andermann, F., Gloor, P., Jones-Gotman, M., Peters, T., Evans, A., … Leroux, G. (1992). Anatomic basis of amygdaloid and hippocampal volume measurement by magnetic resonance imaging. *Neurology*, *42*(9), 1743–1743. http://doi.org/10.1212/WNL.42.9.1743

Weaver, I. C. G., Cervoni, N., Champagne, F. a, D'Alessio, A. C., Sharma, S., Seckl, J. R., … Meaney, M. J. (2004). Epigenetic programming by maternal behavior. *Nature Neuroscience*, *7*(8), 847–854. http://doi.org/10.1038/nn1276

Weaver, I. C. G., D'Alessio, A. C., Brown, S. E., Hellstrom, I. C., Dymov, S., Sharma, S., … Meaney, M. J. (2007). The transcription factor nerve growth factor-inducible protein a mediates epigenetic programming: altering epigenetic marks by immediate-early genes. *The Journal of Neuroscience : The Official Journal of the Society for Neuroscience*, *27*(7), 1756–1768. http://doi.org/10.1523/JNEUROSCI.4164-06.2007

Wei, L., Simen, A., Mane, S., & Kaffman, A. (2012). Early Life Stress Inhibits Expression of a Novel Innate Immune Pathway in the Developing Hippocampus. *Neuropsychopharmacology*, *37*(2), 567–580. http://doi.org/10.1038/npp.2011.239

Weinstock, M. (2007). Gender Differences in the Effects of Prenatal Stress on Brain Development and Behaviour. *Neurochemical Research*, *32*(10), 1730–1740. http://doi.org/10.1007/s11064-007-9339-4

Weiss, A. P., Dewitt, I., Goff, D., Ditman, T., & Heckers, S. (2005). Anterior and posterior hippocampal volumes in schizophrenia. *Schizophrenia Research*, *73*(1), 103–112. http://doi.org/10.1016/j.schres.2004.05.018

Weissman, M. M., Wickramaratne, P., Nomura, Y., Warner, V., Pilowsky, D., & Verdeli,

H. (2006). Offspring of depressed parents: 20 years later. *The American Journal of Psychiatry*, *163*(6), 1001–8. http://doi.org/10.1176/appi.ajp.163.6.1001

Wellman, C. L. (2001). Dendritic reorganization in pyramidal neurons in medial prefrontal cortex after chronic corticosterone administration. *Journal of Neurobiology*, *49*(3), 245–53. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/11745662

Whittle, S., Simmons, J. G., Dennison, M., Vijayakumar, N., Schwartz, O., Yap, M. B. H., … Allen, N. B. (2014). Positive parenting predicts the development of adolescent brain structure: A longitudinal study. *Developmental Cognitive Neuroscience*, *8*(June), 7–17. http://doi.org/10.1016/j.dcn.2013.10.006

Wiedenmayer, C. P., Bansal, R., Anderson, G. M., Zhu, H., Amat, J., Whiteman, R., & Peterson, B. S. (2006). Cortisol levels and hippocampus volumes in healthy preadolescent children. *Biological Psychiatry*, *60*(8), 856–61. http://doi.org/10.1016/j.biopsych.2006.02.011

Wierenga, L., Langen, M., Ambrosino, S., van Dijk, S., Oranje, B., & Durston, S. (2014). Typical development of basal ganglia, hippocampus, amygdala and cerebellum from age 7 to 24. *NeuroImage*, *96*, 67–72. http://doi.org/10.1016/j.neuroimage.2014.03.072

Wiesel, T. N., & Hubel, D. H. (1965). EXTENT OF RECOVERY FROM THE EFFECTS OF VISUAL DEPRIVATION IN KITTENS. *J Neurophysiol*, *28*(6), 1060–1072. Retrieved from http://jn.physiology.org/content/28/6/1060

Wiggins, J. L., Bedoyan, J. K., Peltier, S. J., Ashinoff, S., Carrasco, M., Weng, S.-J., … Monk, C. S. (2012). The impact of serotonin transporter (5-HTTLPR) genotype on

the development of resting-state functional connectivity in children and adolescents: a preliminary report. *NeuroImage*, *59*(3), 2760–70. http://doi.org/10.1016/j.neuroimage.2011.10.030

Willard, S. L., Hemby, S. E., Register, T. C., McIntosh, S., & Shively, C. a. (2014). Altered expression of glial and synaptic markers in the anterior hippocampus of behaviorally depressed female monkeys. *Neuroscience Letters*, 1–5. http://doi.org/10.1016/j.neulet.2014.01.012

Williams, J. M. G., Barnhofer, T., Crane, C., Herman, D., Raes, F., Watkins, E., & Dalgleish, T. (2007). Autobiographical memory specificity and emotional disorder. *Psychological Bulletin*, *133*(1), 122–48. http://doi.org/10.1037/0033-2909.133.1.122

Woolley, C. S., Gould, E., & McEwen, B. S. (1990). Exposure to excess glucocorticoids alters dendritic morphology of adult hippocampal pyramidal neurons. *Brain Research*, *531*(1–2), 225–231.

Yang, X., Goh, A., Chen, S.-H. A., & Qiu, A. (2013). Evolution of hippocampal shapes across the human lifespan. *Human Brain Mapping*, *34*(11), 3075–3085. http://doi.org/10.1002/hbm.22125

Yu, W., & Krook-Magnuson, E. (2015). Cognitive Collaborations: Bidirectional Functional Connectivity Between the Cerebellum and the Hippocampus. *Frontiers in Systems Neuroscience*, *9*, 177. http://doi.org/10.3389/fnsys.2015.00177

Zakzanis, K. K., Leach, L., & Kaplan, E. (1998). On the nature and pattern of neurocognitive function in major depressive disorder. *Neuropsychiatry, Neuropsychology, and Behavioral Neurology*, *11*(3), 111–9. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/9742509

Zalewski, M., Lengua, L. J., Kiff, C. J., & Fisher, P. a. (2012). Understanding the relation of low income to HPA-axis functioning in preschool children: Cumulative family risk and parenting as pathways to disruptions in cortisol. *Child Psychiatry and Human Development*, *43*(6), 924–942. http://doi.org/10.1007/s10578-012-0304-3

Zeng, L.-L. L., Shen, H., Liu, L., Wang, L., Li, B., Fang, P., … Hu, D. (2012). Identifying major depression using whole-brain functional connectivity: A multivariate pattern analysis. *Brain*, *135*(5), 1498–1507. http://doi.org/10.1093/brain/aws059

Zhang, J., Wang, J., Wu, Q., Kuang, W., Huang, X., He, Y., & Gong, Q. (2011). Disrupted Brain Connectivity Networks in Drug-Naive, First-Episode Major Depressive Disorder. *Biological Psychiatry*, *70*(4), 334–342. http://doi.org/10.1016/j.biopsych.2011.05.018

Zhang, W.-N., Chang, S.-H., Guo, L.-Y., Zhang, K.-L., & Wang, J. (2013). The neural correlates of reward-related processing in major depressive disorder: a meta-analysis of functional magnetic resonance imaging studies. *Journal of Affective Disorders*, *151*(2), 531–9. http://doi.org/10.1016/j.jad.2013.06.039

Supplementary Material

Analyses provided in the main text test timing-dependent associations between parenting and cortisol reactivity on hippocampal structure and volume. To this end, all analyses included in the main text include both T1 and T2 measurements of each independent variable. This effectively answers the question: does T1 parenting/cortisol reactivity significantly predict hippocampal volume above and beyond T2 parenting/cortisol reactivity? This method disregards any shared variance between T1 and T2 measures. The supplementary materials contained below evaluate the non-specific effects of each independent variable on hippocampal structure and functional connectivity.

Hippocampal Volume

Aim 1: Associations between Parenting and Children's Hippocampal Volume

T1 Negative Parenting did not predict any whole or segmented hippocampal volume at T2 (Supplementary Table 1). Greater T1 Positive Parenting predicted larger bilateral head and left total hippocampal volume at T2 (Supplementary Table 1). Greater T2 Negative Parenting predicted larger right hippocampal body (Supplementary Table 1). Inversely, greater T2 Positive Parenting predicted smaller bilateral body volumes (Supplementary Table 1).

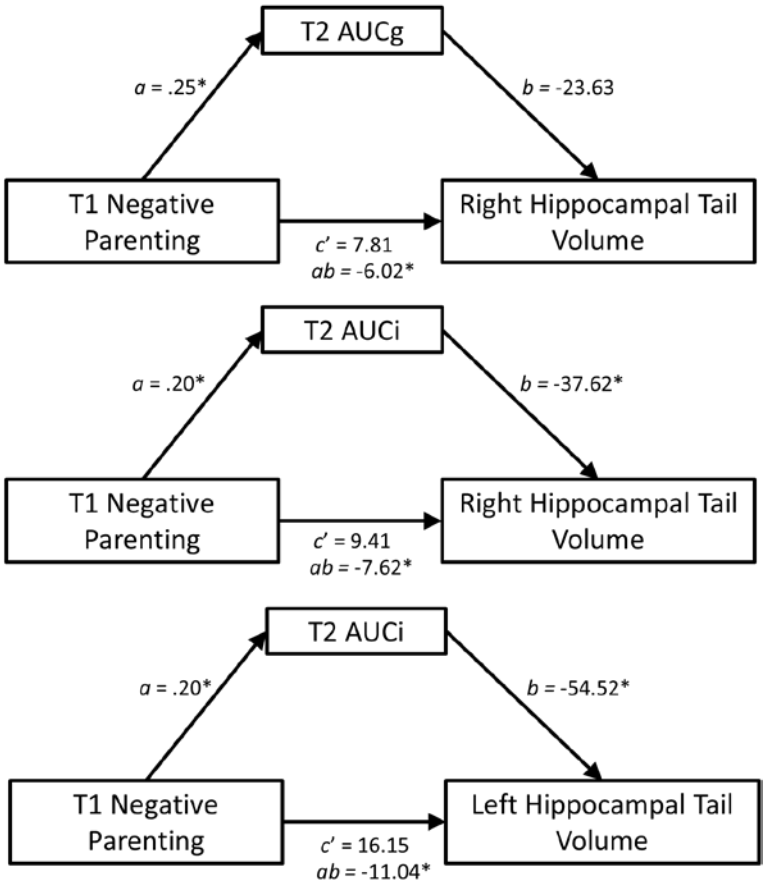
Aim 2: Associations between Children's Cortisol Reactivity and Hippocampal Volume

Greater T1 AUCg predicted larger right hippocampal body, tail, and bilateral total volume (Supplementary Table 2). In contrast, greater T1 AUCi predicted smaller bilateral

body (Supplementary Table 2). Both greater T2 AUCi and T2 AUCg predicted smaller left hippocampal tail volume (Supplementary Table 2).

Aim 3: Mediation of Association between Parenting and Hippocampal Volume by Cortisol Reactivity

As seen in Table 3, parenting did not significantly predict children's cortisol reactivity. Nevertheless, using Preacher and Hayes' bootstrap method (Hayes, 2013), we tested whether cortisol reactivity (T1 or T2; AUCg or AUCi) mediated associations between any parenting composite (T1 or T2; Positive or Negative) and bilateral whole or segmented hippocampal volume (Supplementary Table 3). Results revealed that both T2 AUCg and T2 AUCi mediated the association between T1 Negative Parenting and right hippocampal tail volume and T1 AUCi mediated the association between T1 Negative Parenting and left hippocampal tail volume (Supplementary Figure 1).



Supplementary Figure 1. Models of significant mediation of the association between T1 Negative Parenting and hippocampal subregion volume by T2 cortisol reactivity. *p<.05.

Greater T1 Negative Parenting significantly predicted greater T2 AUCg (a = .25, p = .038). T2 AUCg did not significantly predict right tail volume (b = -23.63, p = .102). Hayes bootstrapping method revealed that T2 AUCg significantly mediated the association between T1 Negative Parenting and right hippocampal tail volume (ab = -6.02, CI = -29.75, -0.03) (Supplementary Figure 1). The direct effect of T1 Negative Parenting on right hippocampal tail volume was not significant (c' = 7.81, p = .561).

Greater T1 Negative Parenting significantly predicted greater T2 AUCi (a = .20, p = .034) which, in turn, significantly predicted smaller right hippocampal tail volume (b =

-37.62, p = .041) (Supplementary Figure 1). This indirect effect was significant using the Hayes' (2013) bootstrapping method (ab = -7.62, CI = -30.78, -0.07). T1 Negative Parenting did not significantly predict right tail volume independently of its effects on T2 AUCi (c' = 9.41, p = .480).

Greater T1 Negative parenting significantly predicted greater T1 AUCi (a = .20, p = .034) which, in turn, predicted smaller left hippocampal tail volume (b = -54.52, p = .009) (Supplementary Figure 1). The bootstrapping method found this indirect effect to be statistically significant (ab = -11.04, CI = -40.47, -1.22). T1 Negative Parenting did not significantly predict left tail volume independently of its effects on T2 AUCi (c' = 16.15, p = .281).

Exploratory Aim: Role of Maternal Depression

Interactions Between Parenting and Maternal Depression. Neither maternal lifetime depression status nor proportion of lifetime exposed to maternal depression (Table 6) or their interactions (Supplementary Table 4-Supplementary Table 11) with either parenting composite predicted whole or segmented hippocampal volume at T2.

Maternal lifetime history of depressive disorders interacted with T2 Positive Parenting to predict left hippocampal head volume (Supplementary Table 8). Specifically, in offspring without a maternal lifetime history of depression, greater T2 Positive Parenting predicted larger left hippocampal head volumes (β =.70, b=178.02, SE=59.58, pr=-.38, p=.004). This association was not significant in offspring with a lifetime history of maternal depression (β =-.07, b=-16.78, SE=35.86, pr=-.06, p=.642). This effect was in the same direction, but only reached marginal significance in the right head (Supplementary Table 4). No other significant interactions were observed.

Interactions Between Cortisol Reactivity and Maternal Depression. There was a significant interaction between proportion lifetime exposure to maternal depression and T1 AUCg in predicting right hippocampal tail volume (Supplementary Table 14). Specifically, in offspring with low exposure to maternal depression, greater T1 AUCg predicted larger right hippocampal tail (β =.62, b=72.60, SE=21.86, *pr*=.41, *p*=.002). This effect was not significant in offspring with high exposure to maternal depression (β =.01, b=1.14, SE=23.39, *pr*=.01, *p*=.961). Results of the Johnson-Neyman procedure indicated that this effect was significant for values of exposure less than 0.18 (72.41% of the sample).

There were significant interactions between lifetime exposure to maternal depression and child T2 AUCi in predicting right hippocampal head (Supplementary Table 12), tail (Supplementary Table 14), and total (Supplementary Table 15) volumes. Specifically, in offspring with high exposure to maternal depression, greater T2 AUCi predicted smaller right hippocampal head (β =-.42, b=-138.97, SE=54.87, *pr*=-.32, *p*=.014; significant at standardized levels of exposure 0.60 (24.59% of the sample)), tail (β =-.50, b=-67.74, SE=23.14, *pr*=-.36, *p*=.005; significant at standardized levels of exposure greater than 0.28 (27.87% of the sample)), and total volumes (β =-.57, b=-206.49, SE=59.45, *pr*=-.42, *p*=.001; significant at standardized levels of exposure greater than 0.25 (27.87% of the sample)). In offspring with low lifetime exposure to maternal depression, T2 AUCi did not significantly predict right head (β =.32, b=107.14, SE=66.06, *pr*=.21, *p*=.110, tail (β =.19, b=25.49, SE=27.71, *pr*=.12, *p*=.361, or total volumes (β =.30, b=110.34, SE=71.19, *pr*=.20, *p*=.127.

Supplementary Table 1

Associations between T1 and T2 parenting and hippocampal volume

Dependent Variable	Predictor (IV)	Covariate	IV β	IV b(SE)	IV *pr*	IV *p*
Right Head						
Model 1	T1 Negative Parenting	Gender	-.14	-34.84(31.83)	-.14	.278
Model 2	T2 Negative Parenting	Gender	-.22	-68.81(39.76)	-.23	.089
Model 3	T1 Positive Parenting	Gender	.29	79.80(33.53)	.30	**.021**
Model 4	T2 Positive Parenting	Gender	.16	39.98(31.22)	.17	.206
Right Body						
Model 5	T1 Negative Parenting	Scan Age	.16	25.78(20.51)	.16	.214
Model 6	T2 Negative Parenting	Scan Age	.29	56.49(23.88)	.30	**.021**
Model 7	T1 Positive Parenting	Scan Age	-.06	-10.09(22.54)	-.06	.656
Model 8	T2 Positive Parenting	Scan Age	-.31	-47.39(18.61)	-.32	**.014**
Right Tail						
Model 9	T1 Negative Parenting	-	.05	5.64(13.75)	.05	.683
Model 10	T2 Negative Parenting	-	-.02	2.57 (17.22)	.02	.882
Model 11	T1 Positive Parenting	-	-.16	-18.21(14.85)	-.16	.225
Model 12	T2 Positive Parenting	-	-.20	-19.92 (13.24)	-.20	.138
Right Total						
Model 13	T1 Negative Parenting	-	-.07	-20.23(36.65)	-.07	.583
Model 14	T2 Negative Parenting	-	<.01	0.61(45.91)	<.01	.990
Model 15	T1 Positive Parenting	-	.22	67.66(39.13)	.22	.089
Model 16	T2 Positive Parenting	-	-.06	-15.22(35.94)	-.06	.674
Left Head						
Model 17	T1 Negative Parenting	Gender	-.15	-40.45(33.05)	-.16	.226
Model 18	T2 Negative Parenting	Gender	-.22	-72.29(41.16)	-.23	.084
Model 19	T1 Positive Parenting	Gender	.27	76.48(35.16)	.28	**.034**
Model 20	T2 Positive Parenting	Gender	.14	36.41(32.45)	.15	.267
Left Body						
Model 21	T1 Negative Parenting	-	.01	2.83(26.11)	.01	.914
Model 22	T2 Negative Parenting	-	.13	32.13(31.59)	.13	.313
Model 23	T1 Positive Parenting	-	.04	7.74(28.50)	.04	.787
Model 24	T2 Positive Parenting	-	-.26	-48.42(24.15)	-.26	**.050**
Left Tail						
Model 25	T1 Negative Parenting	-	.05	6.05(14.87)	.05	.686
Model 26	T2 Negative Parenting	-	.04	5.70(18.56)	.04	.760
Model 27	T1 Positive Parenting	-	<-.01	-0.42(16.26)	<-.01	.979
Model 28	T2 Positive Parenting	-	-.23	-24.92(14.19)	-.23	.084
Left Total						
Model 29	T1 Negative Parenting	-	-.03	-9.26(37.32)	-.03	.805
Model 30	T2 Negative Parenting	-	-.01	-3.54(46.73)	-.01	.940
Model 31	T1 Positive Parenting	-	.25	78.89(39.44)	.25	**.050**
Model 32	T2 Positive Parenting	-	-.15	-41.48(36.23)	-.15	.257

Supplementary Table 2

Main effects of cortisol reactivity on hippocampal volume.

Dependent Variable	Predictor (IV)	Covariate	IV β	IV b(SE)	IV *pr*	IV *p*
Right Head						
Model 1	T1 AUCg	Gender	.17	45.12(34.88)	.17	.201
Model 2	T1 AUCi	Gender	.09	61.48(87.41)	.09	.485
Model 3	T2 AUCg	Gender	.02	3.94(33.17)	.02	.906
Model 4	T2 AUCi	Gender	-.09	-29.54 (41.65)	-.09	.481
Right Body						
Model 5	T1 AUCg	Scan Age	.32	52.29(20.14)	.33	**.012**
Model 6	T1 AUCi	Scan Age	-.50	-207.05(45.31)	-.52	**<.001**
Model 7	T2 AUCg	Scan Age	-.15	-24.14(20.07)	-.16	.234
Model 8	T2 AUCi	Scan Age	-.02	-3.00(25.86)	-.02	.908
Right Tail						
Model 9	T1 AUCg	-	.33	38.75(14.77)	-	**.011**
Model 10	T1 AUCi	-	-.16	-46.99(38.59)	-	.228
Model 11	T2 AUCg	-	-.20	-21.09(13.57)	-	.125
Model 12	T2 AUCi	-	-.19	-26.27(17.28)	-	.134
Right Total						
Model 13	T1 AUCg	-	.38	116.91(37.46)	-	**.003**
Model 14	T1 AUCi	-	-.21	-158.83 (99.14)	-	.115
Model 15	T2 AUCg	-	-.12	-35.10(37.38)	-	.351
Model 16	T2 AUCi	-	-.17	-61.53(47.23)	-	.198
Left Head						
Model 17	T1 AUCg	Gender	.09	26.50(37.71)	.09	.485
Model 18	T1 AUCi	Gender	.10	73.91(93.43)	.11	.432
Model 19	T2 AUCg	Gender	-.13	35.06(34.63)	-.13	.316
Model 20	T2 AUCi	Gender	-.19	-65.33(43.22)	-.19	.136
Left Body						
Model 21	T1 AUCg	-	.25	50.70(26.56)	-	.061
Model 22	T1 AUCi	-	-.36	-184.51(64.00)	-	**.006**
Model 23	T2 AUCg	-	.07	13.22(25.98)	-	.613
Model 24	T2 AUCi	-	.13	33.59(32.83)	-	.310
Left Tail						
Model 25	T1 AUCg	-	.17	20.06(15.49)	-	.200
Model 26	T1 AUCi	-	-.16	-46.88(38.79)	-	.232
Model 27	T2 AUCg	-	-.26	-30.94(14.85)	-	**.041**
Model 28	T2 AUCi	-	-.35	-53.22(18.31)	-	**.005**
Left Total						
Model 29	T1 AUCg	-	.27	82.74(39.45)	-	**.040**
Model 30	T1 AUCi	-	-.19	146.22(100.52)	-	.151
Model 31	T2 AUCg	-	-.11	-33.55(38.43)	-	.386
Model 32	T2 AUCi	-	-.17	-64.65(48.47)	-	.187

Supplementary Table 3

Mediation of the association between parenting and hippocampal volume by cortisol reactivity

Dependent Measure	Predictor	Mediator	Covariate	Total Effect	Direct Effect	Indirect Effect	SE	Lower CI	Upper CI	*p*
Right Head	T1 Positive Parenting	T1 AUCg	Gender	65.26	58.74	6.51	9.95	-4.65	36.17	.514
		T1 AUCi	Gender	65.26	62.38	2.88	8.37	-5.94	32.08	.719
		T2 AUCg	Gender	81.03	84.35	-3.32	8.43	-25.68	10.85	.687
		T2 AUCi	Gender	81.03	80.15	0.88	5.57	-6.33	19.83	.883
	T1 Negative Parenting	T1 AUCg	Gender	-21.26	-21.12	-0.14	6.53	-12.38	13.83	.987
		T1 AUCi	Gender	-21.26	-23.14	1.88	3.90	-2.51	14.14	.782
		T2 AUCg	Gender	-37.53	-40.98	3.45	11.37	-16.82	31.29	.734
		T2 AUCi	Gender	-37.53	-32.10	-5.44	12.82	-44.92	10.38	.605
	T2 Positive Parenting	T2 AUCg	Gender	39.73	40.14	-0.41	5.51	-19.19	6.29	.936
		T2 AUCi	Gender	39.73	39.46	0.27	5.25	-8.21	14.14	.962
	T2 Negative Parenting	T2 AUCg	Gender	-71.42	-71.78	0.36	6.96	-5.35	24.87	.952
		T2 AUCi	Gender	-71.42	-68.05	-3.36	9.41	-39.40	5.67	.682
Right Body	T1 Positive Parenting	T1 AUCg	Scan Age	9.80	0.41	9.38	10.22	-3.64	39.73	.301
		T1 AUCi	Scan Age	9.80	20.49	-10.70	18.25	-53.76	19.09	.443
		T2 AUCg	Scan Age	-11.01	-16.53	5.53	5.36	-0.51	21.38	.391
		T2 AUCi	Scan Age	-11.01	-11.04	0.03	2.82	-5.97	5.80	.992
	T1 Negative Parenting	T1 AUCg	Scan Age	6.11	9.07	-2.95	-0.02	-19.12	4.20	.699
		T1 AUCi	Scan Age	6.11	14.95	-8.83	5.93	-22.72	0.74	.484
		T2 AUCg	Scan Age	29.07	39.04	-9.98	11.26	-51.37	0.18	.199
		T2 AUCi	Scan Age	29.07	32.34	-3.27	7.65	-27.34	5.84	.604

	T2 Positive Parenting	T2 AUCg	Scan Age	-46.63	-48.67	2.05	4.44	-3.26	15.78	.679
		T2 AUCi	Scan Age	-46.63	-46.63	<0.01	2.67	-6.59	3.19	>.999
	T2 Negative Parenting	T2 AUCg	Scan Age	60.92	64.27	-3.35	7.43	-27.93	4.26	.609
		T2 AUCi	Scan Age	60.92	62.38	-1.46	5.90	-21.11	4.33	.756
Right Tail	T1 Positive Parenting	T1 AUCg	-	-34.28	-40.32	6.04	6.68	-4.71	21.85	.376
		T1 AUCi	-	-34.28	-31.49	-2.80	5.79	-23.28	3.21	.514
		T2 AUCg	-	-16.77	-21.36	4.59	3.75	-0.04	15.58	.314
		T2 AUCi	-	-16.77	-17.59	0.83	3.56	-5.09	10.13	.841
	T1 Negative Parenting	T1 AUCg	-	14.94	15.23	-0.29	3.81	-8.22	7.22	.957
		T1 AUCi	-	14.94	16.58	-1.64	2.17	-7.67	1.25	.686
		T2 AUCg	-	1.79	7.81	-6.02	6.28	**-29.75**	**-0.03**	.220
		T2 AUCi	-	1.79	9.41	-7.62	6.94	**-30.78**	**-0.07**	.154
	T2 Positive Parenting	T2 AUCg	-	-20.73	-22.20	1.47	3.08	-2.09	11.95	.659
		T2 AUCi	-	-20.73	-20.96	0.23	3.19	-5.64	7.90	.951
	T2 Negative Parenting	T2 AUCg	-	-1.86	0.08	-1.94	4.05	-14.37	2.82	.638
		T2 AUCi	-	-1.86	2.03	-3.88	5.63	-23.07	1.76	.448
Right Total	T1 Positive Parenting	T1 AUCg	-	55.36	38.92	16.44	18.26	-11.50	62.31	.377
		T1 AUCi	-	55.36	66.37	-11.01	19.62	-75.04	12.16	.445
		T2 AUCg	-	69.05	62.75	6.30	11.27	-6.78	41.14	.526
		T2 AUCi	-	69.05	66.93	2.13	9.46	-12.22	29.04	.844

	T1 Negative Parenting	T1 AUCg	-	-19.88	-18.96	-0.92	11.90	-24.45	22.70	.956
		T1 AUCi	-	-19.88	-15.23	-4.65	5.79	-19.05	3.01	.681
		T2 AUCg	-	-23.92	-13.32	-10.59	16.52	-69.17	5.48	.396
		T2 AUCi	-	-23.92	-5.72	-18.20	17.52	-74.00	0.46	.200
	T2 Positive Parenting	T2 AUCg	-	-15.92	-19.03	3.11	8.32	-3.90	35.67	.697
		T2 AUCi	-	-15.92	-16.52	0.60	8.58	-14.08	22.79	.952
	T2 Negative Parenting	T2 AUCg	-	-3.29	1.02	-4.30	12.49	-45.19	5.29	.673
		T2 AUCi	-	-3.29	6.90	-10.18	15.00	-62.20	4.58	.460
Left Head	T1 Positive Parenting	T1 AUCg	Gender	71.89	67.46	4.44	9.31	-5.38	33.47	.634
		T1 AUCi	Gender	71.89	68.72	3.18	9.76	-6.85	34.21	.710
		T2 AUCg	Gender	76.72	74.42	2.30	7.27	-7.75	22.70	.787
		T2 AUCi	Gender	76.72	75.18	1.53	7.62	-9.35	25.14	.852
	T1 Negative Parenting	T1 AUCg	Gender	-35.60	-35.50	-0.10	5.53	-10.49	11.31	.989
		T1 AUCi	Gender	-35.60	-37.72	2.12	4.54	-3.61	15.38	.773
		T2 AUCg	Gender	-41.07	-37.29	-3.78	11.28	-37.62	10.56	.722
		T2 AUCi	Gender	-41.07	-30.19	-10.89	14.99	-58.88	7.58	.353
	T2 Positive Parenting	T2 AUCg	Gender	36.38	34.84	1.55	5.30	-3.42	22.10	.790
		T2 AUCi	Gender	36.38	35.91	0.47	7.35	-11.99	16.96	.952
	T2 Negative Parenting	T2 AUCg	Gender	-72.99	-71.62	-1.38	7.05	-24.40	5.57	.843
		T2 AUCi	Gender	-72.99	-66.34	-6.64	11.26	-51.03	4.26	.526
Left Body	T1 Positive Parenting	T1 AUCg	-	33.28	25.86	7.42	8.41	-5.78	27.88	.439

		T1 AUCi	-	33.28	44.62	-11.34	17.21	-57.91	12.28	.395
		T2 AUCg	-	6.48	9.52	-3.05	5.22	-16.75	5.18	.654
		T2 AUCi	-	6.48	7.40	-0.92	5.08	-16.64	5.52	.870
	T1 Negative Parenting	T1 AUCg	-	-21.33	-20.91	-0.42	5.65	-12.59	10.28	.959
		T1 AUCi	-	-21.33	-16.36	-4.97	4.60	-14.28	2.57	.649
		T2 AUCg	-	6.24	2.61	3.63	8.70	-9.02	27.95	.664
		T2 AUCi	-	6.24	-1.70	7.93	11.54	-7.72	44.73	.379
	T2 Positive Parenting	T2 AUCg	-	-47.74	-47.22	-0.53	3.64	-15.58	3.16	.890
		T2 AUCi	-	-47.74	-47.46	-0.28	4.97	-13.24	7.08	.957
	T2 Negative Parenting	T2 AUCg	-	36.35	35.49	0.87	5.69	-4.55	25.63	.866
		T2 AUCi	-	36.35	32.03	4.33	9.16	-4.14	43.91	.558
Left Tail	T1 Positive Parenting	T1 AUCg	-	-20.64	-24.21	3.57	6.41	-2.90	24.24	.468
		T1 AUCi	-	-20.64	-18.37	-2.28	5.85	-26.41	3.71	.577
		T2 AUCg	-	-0.04	-5.54	5.49	4.77	-0.44	20.45	.308
		T2 AUCi	-	-0.04	-1.20	1.15	4.61	-7.19	11.65	.835
	T1 Negative Parenting	T1 AUCg	-	18.38	18.55	-0.17	2.84	-6.81	4.91	.963
		T1 AUCi	-	18.38	19.68	-1.30	2.26	-7.84	1.60	.715
		T2 AUCg	-	5.11	13.51	-8.39	8.48	-41.34	0.01	.164
		T2 AUCi	-	5.11	16.15	-11.04	8.73	**-40.47**	**-1.22**	.105
	T2 Positive Parenting	T2 AUCg	-	-25.14	-27.11	1.97	4.16	-2.75	16.14	.644
		T2 AUCi	-	-25.14	-25.46	0.33	4.39	-7.68	10.57	.949

	T2 Negative Parenting	T2 AUCg	-	4.60	7.26	-2.67	5.96	-21.89	3.92	.617
		T2 AUCi	-	4.60	10.26	-5.66	7.47	-29.22	3.11	.415
Left Total	T1 Positive Parenting	T1 AUCg	-	78.85	65.48	13.37	18.38	-5.73	72.29	.402
		T1 AUCi	-	78.85	88.33	-9.48	17.90	-77.09	9.66	.470
		T2 AUCg	-	78.74	77.24	1.49	10.09	-12.24	30.67	.869
		T2 AUCi	-	78.74	77.56	1.17	7.00	-8.33	23.43	.876
	T1 Negative Parenting	T1 AUCg	-	-11.55	-10.77	-0.78	10.28	-24.29	17.18	.957
		T1 AUCi	-	-11.55	-7.75	-3.80	5.98	-21.51	2.99	.703
		T2 AUCg	-	-8.67	-3.41	-5.26	16.73	-63.05	12.99	.663
		T2 AUCi	-	-8.67	2.08	-10.75	16.63	-64.32	8.49	.407
	T2 Positive Parenting	T2 AUCg	-	-41.36	-42.97	1.61	6.87	-5.76	27.60	.799
		T2 AUCi	-	-41.36	-41.71	0.35	6.32	-9.77	17.11	.961
	T2 Negative Parenting	T2 AUCg	-	-2.79	-0.81	-1.98	10.10	-33.25	9.55	.807
		T2 AUCi	-	-2.79	3.10	-5.89	11.21	-50.01	5.16	.583

CI = Confidence Interval; SE = Standard Error

Supplementary Table 4

Interactions between parenting and maternal depression on right hippocampal head volume.

	β	**b (SE)**	***pr***	***p***
Model 1				
T1 Negative Parenting	.04	10.26(50.66)	.03	.840
Maternal Lifetime Depressive Disorder	-.01	-7.05(7310)	-.01	.924
Gender	-.27	-148.06(71.87)	-.27	.044
T1 Negative Parenting x Maternal DD	-.23	-75.68(66.00)	-.15	.256
Model 2				
T1 Negative Parenting	-.07	-16.97(35.76)	-.06	.637
Percent Exposure to Maternal DD	-.04	-9.53(36.89)	-.04	.797
Gender	-.24	-131.14(71.64)	-.24	.073
T1 Negative Parenting x Exposure to Maternal DD	-.15	-28.66(27.77)	-.14	.307
Model 3				
T1 Positive Parenting	.18	48.58(48.17)	.14	.318
Maternal Lifetime Depressive Disorder	-.01	-4.13(70.77)	-.01	.954
Gender	-.22	-121.61(68.93)	-.23	.083
T1 Positive Parenting x Maternal DD	.16	61.60(67.77)	.12	.367
Model 4				
T1 Positive Parenting	.03	77.12(34.92)	.29	.031
Percent Exposure to Maternal DD	-.05	-13.56(35.68)	-.05	.705
Gender	-.21	-115.66(69.65)	-.22	.103
T1 Positive Parenting x Exposure to Maternal DD	.02	4.13(36.16)	.02	.910
Model 5				
T2 Negative Parenting	-.34	-105.79(97.58)	-.15	.283
Maternal Lifetime Depressive Disorder	.03	14.56(77.03)	.03	.851
Gender	-.28	-154.33(72.75)	-.28	.038
T2 Negative Parenting x Maternal DD	.13	43.84(106.80)	.06	.683
Model 6				
T2 Negative Parenting	-.28	-86.82(55.11)	-.21	.121
Percent Exposure to Maternal DD	-.02	-5.31(38.84)	-.02	.892
Gender	-.27	-151.47(74.45)	-.27	.047
T2 Negative Parenting x Exposure to Maternal DD	.10	19.27(32.36)	.08	.554
Model 7				
T2 Positive Parenting	.57	139.35(59.73)	.30	.023
Maternal Lifetime Depressive Disorder	-.07	-40.38(73.76)	-.07	.586
Gender	-.25	-137.62(70.69)	-.26	.057
T2 Positive Parenting x Maternal DD	-.48	-135.10(69.82)	-26	.058
Model 8				
T2 Positive Parenting	.26	62.88(38.63)	.22	.109
Percent Exposure to Maternal DD	-.11	-29.85(36.61)	-.11	.419
Gender	-.22	-120.24(72.58)	-.22	.103
T2 Positive Parenting x Exposure to Maternal DD	-.19	-24.21(21.61)	-.15	.268

Note. DD = Depressive Disorder, including Major Depressive Disorder or Dysthymic Disorder

Supplementary Table 5

Interactions between parenting and maternal depression on right hippocampal body volume.

	β	**b (SE)**	***pr***	***p***
Model 1				
T1 Negative Parenting	.09	14.77(32.41)	.06	.650
Maternal Lifetime Depressive Disorder	.01	2.97(45.96)	.01	.949
Scan Age	.28	55.16(26.17)	.27	.040
T1 Negative Parenting x Maternal DD	.09	18.21(41.33)	.06	.661
Model 2				
T1 Negative Parenting	.10	16.10(22.96)	.10	.486
Percent Exposure to Maternal DD	.08	13.26(22.92)	.08	.565
Scan Age	.26	50.51(25.97)	.26	.057
T1 Negative Parenting x Exposure to Maternal DD	.08	8.45(17.20)	.08	.585
Model 3				
T1 Positive Parenting	.06	9.51(32.40)	.04	.770
Maternal Lifetime Depressive Disorder	.01	4.52(46.21)	.01	.922
Scan Age	.25	48.55(26.27)	.24	.070
T1 Positive Parenting x Maternal DD	-.16	-37.88(44.72)	-.11	.401
Model 4				
T1 Positive Parenting	-.03	-4.35(22.93)	-.03	.850
Percent Exposure to Maternal DD	.10	16.74(23.03)	.10	.471
Scan Age	.25	47.29(25.97)	.24	.074
T1 Positive Parenting x Exposure to Maternal DD	-.09	-14.66(23.23)	-.09	.531
Model 5				
T2 Negative Parenting	.46	87.74(58.91)	.20	.142
Maternal Lifetime Depressive Disorder	-.02	-7.80(46.66)	-.02	.868
Scan Age	.22	42.82(24.59)	.23	.087
T2 Negative Parenting x Maternal DD	-.18	-37.66(64.80)	-.08	.564
Model 6				
T2 Negative Parenting	.28	53.23(32.27)	.22	.105
Percent Exposure to Maternal DD	.04	5.75(23.14)	.03	.805
Scan Age	.22	41.85(24.57)	.23	.094
T2 Negative Parenting x Exposure to Maternal DD	<-.01	-0.40(19.46)	<-.01	.984
Model 7				
T2 Positive Parenting	-.45	-68.65(36.84)	-.25	.068
Maternal Lifetime Depressive Disorder	.07	25.83(44.91)	.08	.568
Scan Age	.27	52.15(24.39)	.28	.037
T2 Positive Parenting x Maternal DD	.16	28.20(42.83)	.09	.513
Model 8				
T2 Positive Parenting	-.28	-41.50(23.14)	-.24	.079
Percent Exposure to Maternal DD	.09	14.68(21.87)	.09	.505
Scan Age	.25	48.44(24.29)	.26	.051
T2 Positive Parenting x Exposure to Maternal DD	-.01	-0.95(12.87)	-.01	.942

Note. DD = Depressive Disorder, including Major Depressive Disorder or Dysthymic Disorder

Supplementary Table 6

Interactions between parenting and maternal depression on right hippocampal tail volume.

	β	**b (SE)**	***pr***	***p***
Model 1				
T1 Negative Parenting	.12	12.02(21.93)	.07	.586
Maternal Lifetime Depressive Disorder	-.09	-21.08(31.49)	-.09	.506
T1 Negative Parenting x Maternal DD	-.08	-10.33(28.38)	-.05	.717
Model 2				
T1 Negative Parenting	.05	5.46(15.67)	.05	.729
Percent Exposure to Maternal DD	-.03	-3.86(16.10)	-.03	.812
T1 Negative Parenting x Exposure to Maternal DD	.02	1.78(12.14)	.02	.884
Model 3				
T1 Positive Parenting	-.31	-35.03(21.18)	-.22	.104
Maternal Lifetime Depressive Disorder	-.09	-21.37(30.78)	-.09	.490
T1 Positive Parenting x Maternal DD	.20	32.67(29.77)	.15	.277
Model 4				
T1 Positive Parenting	-.17	-18.97(15.52)	-.16	.227
Percent Exposure to Maternal DD	-.04	-4.89(15.86)	-.04	.759
T1 Positive Parenting x Exposure to Maternal DD	<-.01	-0.46(16.06)	<-.01	.977
Model 5				
T2 Negative Parenting	.20	26.50(42.15)	.08	.532
Maternal Lifetime Depressive Disorder	-.12	-29.78(33.48)	-.12	.378
T2 Negative Parenting x Maternal DD	-.18	-26.20(46.40)	-.08	.575
Model 6				
T2 Negative Parenting	-.03	-4.02(23.52)	-.02	.865
Percent Exposure to Maternal DD	-.04	-4.89(16.92)	-.04	.774
T2 Negative Parenting x Exposure to Maternal DD	.11	8.47(14.13)	.08	.552
Model 7				
T2 Positive Parenting	-.31	-31.46(26.11)	-.16	.233
Maternal Lifetime Depressive Disorder	-.08	-18.58(31.96)	-.08	.563
T2 Positive Parenting x Maternal DD	.14	16.32(30.43)	.07	.594
Model 8				
T2 Positive Parenting	-.17	-17.63(16.70)	-.14	.296
Percent Exposure to Maternal DD	-.07	-7.83(15.82)	-.07	.623
T2 Positive Parenting x Exposure to Maternal DD	-.06	-3.19(9.33)	-.05	.734

Note. DD = Depressive Disorder, including Major Depressive Disorder or Dysthymic Disorder

Supplementary Table 7

Interactions between parenting and maternal depression on right total hippocampal volume.

	β	**b (SE)**	***pr***	***p***
Model 1				
T1 Negative Parenting	<-.01	-.40(58.66)	<-.01	.995
Maternal Lifetime Depressive Disorder	<-.01	-.52(84.25)	<-.01	.995
T1 Negative Parenting x Maternal DD	-.10	-33.17(75.92)	-.06	.664
Model 2				
T1 Negative Parenting	-.06	-16.60(40.76)	-.06	.685
Percent Exposure to Maternal DD	-.01	-1.58(41.88)	-.01	.970
T1 Negative Parenting x Exposure to Maternal DD	-.04	-7.57(31.58)	-.03	.811
Model 3				
T1 Positive Parenting	.13	38.18(56.42)	.09	.501
Maternal Lifetime Depressive Disorder	<.01	1.69(81.99)	<.01	.984
T1 Positive Parenting x Maternal DD	.14	58.23(79.31)	.10	.466
Model 4				
T1 Positive Parenting	.23	68.65(39.93)	.23	.091
Percent Exposure to Maternal DD	<.01	0.49(40.79)	<.01	.990
T1 Positive Parenting x Exposure to Maternal DD	-.02	-4.77(41.31)	-.02	.908
Model 5				
T2 Negative Parenting	.08	29.18(113.23)	.04	.798
Maternal Lifetime Depressive Disorder	-.01	-4.00(89.96)	-.01	.965
T2 Negative Parenting x Maternal DD	-.09	-34.86(124.67)	-.04	.781
Model 6				
T2 Negative Parenting	-.05	-15.97(61.30)	-.04	.795
Percent Exposure to Maternal DD	-.04	-12.28(44.09)	-.04	.782
T2 Negative Parenting x Exposure to Maternal DD	.09	19.43(36.83)	.07	.600
Model 7				
T2 Positive Parenting	.18	49.59(70.62)	.09	.485
Maternal Lifetime Depressive Disorder	-.02	-10.99(86.43)	-.02	.899
T2 Positive Parenting x Maternal DD	-.28	-88.14(82.29)	-.14	.289
Model 8				
T2 Positive Parenting	.07	17.52(43.78)	.05	.691
Percent Exposure to Maternal DD	-.08	-23.55(41.48)	-.08	.573
T2 Positive Parenting x Exposure to Maternal DD	-.21	-29.60(24.45)	-.16	.231

Note. DD = Depressive Disorder, including Major Depressive Disorder or Dysthymic Disorder

Supplementary Table 8

Interactions between parenting and maternal depression on left hippocampal head volume.

	β	**b (SE)**	***pr***	***p***
Model 1				
T1 Negative Parenting	-.17	-43.91(53.67)	-.11	.408
Maternal Lifetime Depressive Disorder	.14	81.70(76.00)	.14	.287
Gender	-.27	-154.58(74.72)	-.27	.043
T1 Negative Parenting x Maternal DD	.01	4.77(68.62)	.01	.945
Model 2				
T1 Negative Parenting	-.14	-37.60(37.61)	-.14	.322
Percent Exposure to Maternal DD	.05	13.81(38.80)	.05	.723
Gender	-.29	-167.53(75.34)	-.29	.030
T1 Negative Parenting x Exposure to Maternal DD	-.06	-11.08(29.21)	-.05	.706
Model 3				
T1 Positive Parenting	.31	89.28(50.23)	.23	.081
Maternal Lifetime Depressive Disorder	.14	84.80(73.81)	.15	.256
Gender	-.25	-144.75(71.89)	-.26	.049
T1 Positive Parenting x Maternal DD	-.06	-22.60(70.67)	-.04	.750
Model 4				
T1 Positive Parenting	.28	80.94(36.61)	.29	.031
Percent Exposure to Maternal DD	.02	4.35(37.40)	.02	.908
Gender	-.27	-157.00(73.02)	-.28	.036
T1 Positive Parenting x Exposure to Maternal DD	-.09	-24.76(37.91)	-.09	.516
Model 5				
T2 Negative Parenting	-.52	-168.64(98.87)	-.23	.094
Maternal Lifetime Depressive Disorder	.19	113.51(78.04)	.19	.152
Gender	-.30	-175.10(73.70)	-.31	.021
T2 Negative Parenting x Maternal DD	.30	106.59(108.20)	.13	.329
Model 6				
T2 Negative Parenting	-.37	-119.38(56.59)	-.28	.040
Percent Exposure to Maternal DD	.08	23.13(39.88)	.08	.564
Gender	-.33	-192.98(76.45)	-.33	.015
T2 Negative Parenting x Exposure to Maternal DD	.17	33.35(33.22)	.14	.320
Model 7				
T2 Positive Parenting	.70	178.02(59.58)	.38	.004
Maternal Lifetime Depressive Disorder	.06	34.96(73.57)	.07	.637
Gender	-.27	-157.86(70.51)	-.29	.029
T2 Positive Parenting x Maternal DD	-.66	-194.80(69.64)	-.36	**.007**
Model 8				
T2 Positive Parenting	.28	70.18(40.10)	.23	.086
Percent Exposure to Maternal DD	-.03	-9.67(38.00)	-.04	.800
Gender	-.26	-153.11(75.34)	-.27	.047
T2 Positive Parenting x Exposure to Maternal DD	-.23	-32.05(22.43)	-.19	.159

Note. DD = Depressive Disorder, including Major Depressive Disorder or Dysthymic Disorder

Supplementary Table 9

Interactions between parenting and maternal depression on left hippocampal body volume.

	β	**b (SE)**	***pr***	***p***
Model 1				
T1 Negative Parenting	-.04	-8.00(41.50)	-.03	.848
Maternal Lifetime Depressive Disorder	-.13	-56.57(59.61)	-.13	.347
T1 Negative Parenting x Maternal DD	.07	19.05(53.71)	.05	.724
Model 2				
T1 Negative Parenting	-.04	-7.58(29.09)	-.04	.795
Percent Exposure to Maternal DD	-.13	-27.21(29.89)	-.12	.367
T1 Negative Parenting x Exposure to Maternal DD	.20	29.25(22.54)	.17	.200
Model 3				
T1 Positive Parenting	.13	28.17(40.79)	.09	.493
Maternal Lifetime Depressive Disorder	-.13	-56.10(59.27)	-.13	.348
T1 Positive Parenting x Maternal DD	-.14	-41.73(57.33)	-.10	.470
Model 4				
T1 Positive Parenting	.05	9.82(29.00)	.05	.736
Percent Exposure to Maternal DD	-.13	-28.31(29.62)	-.13	.344
T1 Positive Parenting x Exposure to Maternal DD	-.21	-45.99(30.00)	-.20	.131
Model 5				
T2 Negative Parenting	.44	106.54(76.76)	.18	.171
Maternal Lifetime Depressive Disorder	-.15	-65.59(60.98)	-.14	.287
T2 Negative Parenting x Maternal DD	-.32	-84.54(84.51)	-.13	.322
Model 6				
T2 Negative Parenting	.13	30.02(42.66)	.10	.485
Percent Exposure to Maternal DD	-.15	-30.43(30.68)	-.13	.326
T2 Negative Parenting x Exposure to Maternal DD	.10	15.30(25.63)	.08	.553
Model 7				
T2 Positive Parenting	-.44	-82.99(47.48)	-.23	.086
Maternal Lifetime Depressive Disorder	-.06	-25.58(58.12)	-.06	.662
T2 Positive Parenting x Maternal DD	.22	47.97(55.33)	.12	.390
Model 8				
T2 Positive Parenting	-.19	-35.80(30.02)	-.16	.238
Percent Exposure to Maternal DD	-.14	-29.53(28.44)	-.14	.304
T2 Positive Parenting x Exposure to Maternal DD	-.15	-15.32(16.77)	-.12	.365

Note. DD = Depressive Disorder, including Major Depressive Disorder or Dysthymic Disorder

Supplementary Table 10

Interactions between parenting and maternal depression on left hippocampal tail volume.

	β	**b (SE)**	***pr***	***p***
Model 1				
T1 Negative Parenting	.19	21.86(23.67)	.12	.360
Maternal Lifetime Depressive Disorder	-.04	-9.11(33.99)	-.04	.790
T1 Negative Parenting x Maternal DD	-.18	-26.30(30.63)	-.11	.394
Model 2				
T1 Negative Parenting	.04	3.97(16.79)	.03	.814
Percent Exposure to Maternal DD	.04	4.54(17.25)	.04	.793
T1 Negative Parenting x Exposure to Maternal DD	.02	1.44(13.01)	.02	.912
Model 3				
T1 Positive Parenting	-.19	-23.42(23.15)	-.13	.316
Maternal Lifetime Depressive Disorder	-.04	-9.18(33.63)	-.04	.786
T1 Positive Parenting x Maternal DD	.26	45.16(32.53)	.18	.171
Model 4				
T1 Positive Parenting	<.01	.01(16.82)	<.01	.999
Percent Exposure to Maternal DD	.07	8.43(17.18)	.07	.626
T1 Positive Parenting x Exposure to Maternal DD	.06	7.11(17.40)	.06	.684
Model 5				
T2 Negative Parenting	.22	30.76(45.59)	.09	.503
Maternal Lifetime Depressive Disorder	-.08	-21.73(36.22)	-.08	.551
T2 Negative Parenting x Maternal DD	-.18	-28.50(50.20)	-.08	.572
Model 6				
T2 Negative Parenting	-.11	-15.51(24.82)	-.09	.535
Percent Exposure to Maternal DD	.01	1.01(17.85)	.01	.955
T2 Negative Parenting x Exposure to Maternal DD	.23	19.51(14.91)	.18	.196
Model 7				
T2 Positive Parenting	-.51	-56.07(27.70)	-.26	.048
Maternal Lifetime Depressive Disorder	-.02	-4.28(33.91)	-.02	.900
T2 Positive Parenting x Maternal DD	.33	42.65(32.28)	.18	.192
Model 8				
T2 Positive Parenting	-.21	-22.68(17.80)	-.17	.208
Percent Exposure to Maternal DD	<.01	-0.03(16.87)	<.01	.998
T2 Positive Parenting x Exposure to Maternal DD	-.02	-0.99(9.94)	-.01	.921

Note. DD = Depressive Disorder, including Major Depressive Disorder or Dysthymic Disorder

Supplementary Table 11

Interactions between parenting and maternal depression on left total hippocampal volume.

	β	**b (SE)**	***pr***	***p***
Model 1				
T1 Negative Parenting	-.01	-4.00(59.70)	-.01	.947
Maternal Lifetime Depressive Disorder	.07	43.45(85.74)	.07	.614
T1 Negative Parenting x Maternal DD	-.03	-9.51(77.26)	-.02	.903
Model 2				
T1 Negative Parenting	-.05	-14.07(41.56)	-.05	.736
Percent Exposure to Maternal DD	-.05	-16.17(42.71)	-.05	.706
T1 Negative Parenting x Exposure to Maternal DD	.07	13.63(32.20)	.06	.674
Model 3				
T1 Positive Parenting	.29	89.34(56.95)	.21	.122
Maternal Lifetime Depressive Disorder	.07	45.77(82.76)	.07	.582
T1 Positive Parenting x Maternal DD	-.05	-19.49(80.05)	-.03	.808
Model 4				
T1 Positive Parenting	.28	84.81(39.62)	.28	.037
Percent Exposure to Maternal DD	-.06	-17.58(40.48)	-.06	.666
T1 Positive Parenting x Exposure to Maternal DD	-.19	-58.54(40.99)	-.19	.159
Model 5				
T2 Negative Parenting	.12	40.82(114.84)	.05	.724
Maternal Lifetime Depressive Disorder	.05	35.22(91.24)	.05	.701
T2 Negative Parenting x Maternal DD	-.15	-58.82(126.45)	-.06	.644
Model 6				
T2 Negative Parenting	-.13	-44.34(61.75)	-.10	.476
Percent Exposure to Maternal DD	-.08	-22.43(44.41)	-.07	.616
T2 Negative Parenting x Exposure to Maternal DD	.23	47.68(37.08)	.17	.204
Model 7				
T2 Positive Parenting	.08	22.24(71.00)	.04	.755
Maternal Lifetime Depressive Disorder	.05	33.20(86.90)	.05	.704
T2 Positive Parenting x Maternal DD	-.27	-88.01(82.74)	-.14	.292
Model 8				
T2 Positive Parenting	-.01	-1.60(43.77)	-.01	.971
Percent Exposure to Maternal DD	-.13	-39.77(41.47)	-.13	.342
T2 Positive Parenting x Exposure to Maternal DD	-.27	-39.28(24.44)	-.21	.114

Note. DD = Depressive Disorder, including Major Depressive Disorder or Dysthymic Disorder

Supplementary Table 12

Interactions between cortisol reactivity and maternal depression on right hippocampal head volume.

	β	**b (SE)**	***pr***	***p***
Model 1				
T1 AUCg	.10	26.41(77.58)	.05	.735
Maternal Lifetime Depressive Disorder	.04	24.00(72.32)	.05	.741
Gender	-.27	-144.12(72.19)	-.26	.051
T1 AUCg x Maternal DD	.08	23.49(86.74)	.04	.788
Model 2				
T1 AUCg	.16	43.31(35.59)	.17	.229
Percent Exposure to Maternal DD	-.02	-5.57(37.27)	-.02	.882
Gender	-.26	-140.72(71.97)	-.26	.056
T1 AUCg x Exposure to Maternal DD	-.10	-32.56(41.82)	-.11	.440
Model 3				
T1 AUCi	.17	114.48(137.30)	.11	.408
Maternal Lifetime Depressive Disorder	.05	28.64(73.00)	.05	.696
Gender	-.25	-136.73(74.50)	-.24	.072
T1 AUCi x Maternal DD	-.10	-91.70(184.71)	-.07	.622
Model 4				
T1 AUCi	.10	69.41(89.80)	.11	.443
Percent Exposure to Maternal DD	-.01	-2.12(37.87)	-.01	.956
Gender	-.22	-121.40(72.49)	-.22	.100
T1 AUCi x Exposure to Maternal DD	.09	79.90(119.26)	.09	.506
Model 5				
T2 AUCg	.18	46.09(57.74)	.11	.428
Maternal Lifetime Depressive Disorder	.02	12.13(72.81)	.02	.868
Gender	-.25	-138.28(71.74)	-.25	.059
T2 AUCg x Maternal DD	-.20	-62.85(70.45)	-.12	.376
Model 6				
T2 AUCg	.04	10.33(34.28)	.04	.764
Percent Exposure to Maternal DD	-.14	-36.56(35.34)	-.14	.305
Gender	-.23	-127.03(71.33)	-.23	.080
T2 AUCg x Exposure to Maternal DD	-.14	-40.08(39.52)	-.13	.315
Model 7				
T2 AUCi	.14	45.67(62.24)	.10	.466
Maternal Lifetime Depressive Disorder	.03	14.90(72.46)	.03	.838
Gender	-.25	-138.86(69.76)	-.26	.051
T2 AUCi x Maternal DD	-.30	-138.61(84.25)	-.21	.105
Model 8				
T2 AUCi	-.05	-15.92(40.84)	-.05	.698
Percent Exposure to Maternal DD	-.15	-40.11(32.72)	-.16	.225
Gender	-.21	-117.51(66.70)	-.23	.084
T2 AUCi x Exposure to Maternal DD	-.34	-123.05(44.94)	-.34	**.008**

Note. DD = Depressive Disorder, including Major Depressive Disorder or Dysthymic Disorder

Supplementary Table 13

Interactions between cortisol reactivity and maternal depression on right hippocampal body volume.

	β	**b (SE)**	***pr***	***p***
Model 1				
T1 AUCg	.60	99.64(175.76)	.30	.027
Maternal Lifetime Depressive Disorder	-.06	-21.23(40.56)	-.07	.603
Scan Age	.35	66.22(23.18)	.36	.006
T1 AUCg x Maternal DD	-.32	-60.22(49.27)	-.16	.227
Model 2				
T1 AUCg	.33	53.39(20.21)	.34	.011
Percent Exposure to Maternal DD	-.04	-6.06(21.22)	-.04	.776
Scan Age	.35	64.86(23.54)	.35	.008
T1 AUCg x Exposure to Maternal DD	.06	10.76(23.98)	.06	.655
Model 3				
T1 AUCi	-.39	-161.58(69.50)	-.30	.024
Maternal Lifetime Depressive Disorder	-.08	-26.29(36.89)	-.10	.479
Scan Age	.38	71.61(20.94)	.42	.001
T1 AUCi x Maternal DD	-.15	-80.46(91.47)	-.12	.383
Model 4				
T1 AUCi	-.51	-206.48(45.86)	-.53	<.001
Percent Exposure to Maternal DD	-.08	-13.26(19.30)	-.09	.495
Scan Age	.38	70.26(21.05)	.42	.002
T1 AUCi x Exposure to Maternal DD	-.01	-4.03(60.44)	-.01	.947
Model 5				
T2 AUCg	.04	7.00(34.77)	.03	.841
Maternal Lifetime Depressive Disorder	-.04	-14.44(43.51)	-.04	.741
Scan Age	.27	51.40(24.01)	.27	.037
T2 AUCg x Maternal DD	-.24	-48.30(42.78)	-.15	.264
Model 6				
T2 AUCg	-.17	-26.48(20.43)	-.17	.200
Percent Exposure to Maternal DD	.14	23.29(21.21)	.15	.277
Scan Age	.25	47.24(23.88)	.26	.053
T2 AUCg x Exposure to Maternal DD	<.01	0.56(23.80)	<.01	.981
Model 7				
T2 AUCi	-.06	-12.94(39.54)	-.04	.745
Maternal Lifetime Depressive Disorder	-.05	-16.47(45.23)	-.05	.717
Scan Age	.27	52.36(25.14)	.27	.042
T2 AUCi x Maternal DD	.06	16.00(57.56)	.04	.770
Model 8				
T2 AUCi	-.04	-8.81(26.20)	-.05	.738
Percent Exposure to Maternal DD	.15	24.96(20.96)	.16	.239
Scan Age	.27	51.88(24.19)	.28	.036
T2 AUCi x Exposure to Maternal DD	.15	32.81(29.05)	.15	.264

Supplementary Table 14

Interactions between cortisol reactivity and maternal depression on right hippocampal tail volume.

	β	**b (SE)**	***Pr***	***p***
Model 1				
T1 AUCg	.64	75.35(32.30)	.30	.023
Maternal Lifetime Depressive Disorder	-.12	-29.46(29.88)	-.13	.329
T1 AUCg x Maternal DD	-.35	-46.53(36.25)	-.17	.205
Model 2				
T1 AUCg	.31	36.87(14.59)	.33	.014
Percent Exposure to Maternal DD	-.06	-7.45(15.44)	-.07	.631
T1 AUCg x Exposure to Maternal DD	-.26	-35.73(17.31)	-.27	**.044**
Model 3				
T1 AUCi	-.32	-95.21(59.16)	-.21	.113
Maternal Lifetime Depressive Disorder	-.15	-36.92(34.45)	-.16	.246
T1 AUCi x Maternal DD	.21	82.29(77.92)	.14	.296
Model 4				
T1 AUCi	-.15	-42.84(38.78)	-.15	.274
Percent Exposure to Maternal DD	-.06	-7.42(16.42)	-.06	.653
T1 AUCi x Exposure to Maternal DD	.22	86.49(51.53)	.22	.099
Model 5				
T2 AUCg	-.12	-12.36(23.45)	-.07	.600
Maternal Lifetime Depressive Disorder	-.15	-33.55(29.36)	-.15	.258
T2 AUCg x Maternal DD	-.12	-15.46(28.85)	-.07	.594
Model 6				
T2 AUCg	-.20	-21.19(14.19)	-.19	.141
Percent Exposure to Maternal DD	-.07	-8.08(14.72)	-.07	.585
T2 AUCg x Exposure to Maternal DD	-.03	-2.99(16.47)	-.02	.857
Model 7				
T2 AUCi	-.13	-17.66(25.81)	-.09	.496
Maternal Lifetime Depressive Disorder	-.16	-35.58(29.74)	-.16	.236
T2 AUCi x Maternal DD	-.12	-22.48(35.08)	-.08	.524
Model 8				
T2 AUCi	-.15	-21.13(17.20)	-.16	.224
Percent Exposure to Maternal DD	-.12	-13.00(13.76)	-.12	.349
T2 AUCi x Exposure to Maternal DD	-.31	-46.62(18.86)	-.31	**.016**

Note. DD = Depressive Disorder, including Major Depressive Disorder or Dysthymic Disorder

Supplementary Table 15

Interactions between cortisol reactivity and maternal depression on right total hippocampal volume.

	β	**b (SE)**	***pr***	***p***
Model 1				
T1 AUCg	.62	189.83(83.21)	.29	.026
Maternal Lifetime Depressive Disorder	-.01	-5.46(76.99)	-.01	.944
T1 AUCg x Maternal DD	-.27	-92.00(93.40)	-.13	.329
Model 2				
T1 AUCg	.39	116.26(36.86)	.39	.003
Percent Exposure to Maternal DD	-.05	-15.53(39.00)	-.05	.692
T1 AUCg x Exposure to Maternal DD	-.13	-45.52(43.75)	-.14	.303
Model 3				
T1 AUCi	-.23	-174.15(155.01)	-.15	.266
Maternal Lifetime Depressive Disorder	-.03	-17.84(82.41)	-.03	.829
T1 AUCi x Maternal DD	.03	25.90(204.17)	.02	.900
Model 4				
T1 AUCi	-.20	-145.22(98.40)	-.20	.146
Percent Exposure to Maternal DD	-.06	-17.71(41.65)	-.06	.672
T1 AUCi x Exposure to Maternal DD	.16	160.21(130.75)	.16	.226
Model 5				
T2 AUCg	.16	45.15(64.13)	.09	.484
Maternal Lifetime Depressive Disorder	-.02	-14.57(80.31)	-.02	.857
T2 AUCg x Maternal DD	-.34	-123.08(78.92)	-.20	.124
Model 6				
T2 AUCg	-.11	-30.52(37.57)	-.11	.420
Percent Exposure to Maternal DD	-.10	-29.00(39.00)	-.10	.460
T2 AUCg x Exposure to Maternal DD	-.17	-56.13(43.62)	-.17	.203
Model 7				
T2 AUCi	.09	32.81(69.55)	.06	.639
Maternal Lifetime Depressive Disorder	-.02	-12.93(80.15)	-.02	.872
T2 AUCi x Maternal DD	-.35	-180.21(94.54)	-.24	.062
Model 8				
T2 AUCi	-.13	-48.08(44.20)	-.14	.281
Percent Exposure to Maternal DD	-.12	-34.45(35.35)	-.13	.334
T2 AUCi x Exposure to Maternal DD	-.40	-158.41(48.45)	-.40	**.002**

Note. DD = Depressive Disorder, including Major Depressive Disorder or Dysthymic Disorder

Supplementary Table 16

Interactions between cortisol reactivity and maternal depression on left hippocampal head volume.

	β	**b (SE)**	***pr***	***p***
Model 1				
T1 AUCg	-.02	-7.16(82.16)	-.01	.931
Maternal Lifetime Depressive Disorder	.19	113.38(76.60)	.20	.145
Gender	-.27	-155.82(76.46)	-.27	.046
T1 AUCg x Maternal DD	.13	42.16(91.87)	.06	.648
Model 2				
T1 AUCg	.09	25.16(38.70)	.09	.518
Percent Exposure to Maternal DD	.04	11.35(40.52)	.04	.781
Gender	-.29	-170.37(78.25)	-.29	.034
T1 AUCg x Exposure to Maternal DD	-.07	-24.05(45.47)	.07	.599
Model 3				
T1 AUCi	.20	143.83(143.69)	.14	.321
Maternal Lifetime Depressive Disorder	.20	119.61(76.40)	.21	.123
Gender	-.27	-155.80(77.97)	-.26	.051
T1 AUCi x Maternal DD	-.12	-115.61(193.31)	-.08	.552
Model 4				
T1 AUCi	.12	85.62(95.88)	.12	.376
Percent Exposure to Maternal DD	.05	15.87(40.43)	.05	.696
Gender	-.26	-153.50(77.39)	-.26	.053
T1 AUCi x Exposure to Maternal DD	.12	112.88(127.33)	.12	.379
Model 5				
T2 AUCg	<.01	-0.05(59.81)	<.01	.999
Maternal Lifetime Depressive Disorder	.15	91.95(75.41)	.16	.228
Gender	-.28	-165.15(74.30)	-.28	.030
T2 AUCg x Maternal DD	-.13	-45.42(72.96)	-.08	.536
Model 6				
T2 AUCg	-.15	-41.49(36.23)	-.15	.257
Percent Exposure to Maternal DD	.01	3.03(37.35)	.01	.936
Gender	-.32	-185.21(75.37)	-.31	.017
T2 AUCg x Exposure to Maternal DD	.10	31.02(41.76)	.10	.461
Model 7				
T2 AUCi	<-.01	-1.17(64.69)	<-.01	.986
Maternal Lifetime Depressive Disorder	.16	92.40(75.31)	.16	.225
Gender	-.27	-159.31(72.51)	-.28	.032
T2 AUCi x Maternal DD	-.21	-103.33(87.57)	-.15	.243
Model 8				
T2 AUCi	-.15	-54.57(44.39)	-.16	.224
Percent Exposure to Maternal DD	-.06	-15.66(35.57)	-.06	.661
Gender	-.27	-161.15(72.50)	-.29	.030
T2 AUCi x Exposure to Maternal DD	-.21	-83.06(48.86)	-.22	.095

Note. DD = Depressive Disorder, including Major Depressive Disorder or Dysthymic Disorder

Supplementary Table 17

Interactions between cortisol reactivity and maternal depression on left hippocampal body volume.

	β	**b (SE)**	***pr***	***p***
Model 1				
T1 AUCg	.21	43.67(58.73)	.10	.460
Maternal Lifetime Depressive Disorder	-.16	-66.88(53.34)	-.16	.224
T1 AUCg x Maternal DD	.03	8.00(65.93)	.02	.904
Model 2				
T1 AUCg	.25	51.97(26.31)	.26	.053
Percent Exposure to Maternal DD	-.24	-51.86(27.84)	-.25	.068
T1 AUCg x Exposure to Maternal DD	.05	12.07(31.23)	.05	.701
Model 3				
T1 AUCi	-.37	-189.02(98.46)	-.25	.060
Maternal Lifetime Depressive Disorder	-.17	-71.65(52.34)	-.18	.177
T1 AUCi x Maternal DD	.01	4.97(129.68)	.01	.970
Model 4				
T1 AUCi	-.38	-192.92(63.20)	-.38	.004
Percent Exposure to Maternal DD	-.27	-58.20(26.75)	-.28	.034
T1 AUCi x Exposure to Maternal DD	<-.01	-2.86(83.98)	-.01	.973
Model 5				
T2 AUCg	.13	26.98(45.08)	.08	.552
Maternal Lifetime Depressive Disorder	-.12	-53.33(56.46)	-.12	.349
T2 AUCg x Maternal DD	-.10	-24.39(55.48)	-.06	.662
Model 6				
T2 AUCg	.05	10.06(27.09)	.05	.712
Percent Exposure to Maternal DD	-.05	-11.22(28.11)	-.05	.691
T2 AUCg x Exposure to Maternal DD	.04	8.95(31.45)	.04	.777
Model 7				
T2 AUCi	-.04	-9.51(49.11)	-.03	.847
Maternal Lifetime Depressive Disorder	-.14	-58.19(56.59)	-.13	.308
T2 AUCi x Maternal DD	.20	71.07(66.75)	.14	.291
Model 8				
T2 AUCi	.11	27.29(34.40)	.10	.431
Percent Exposure to Maternal DD	-.05	-9.35(27.52)	-.05	.735
T2 AUCi x Exposure to Maternal DD	.05	15.04(37.71)	.05	.691

Note. DD = Depressive Disorder, including Major Depressive Disorder or Dysthymic Disorder

Supplementary Table 18

Interactions between cortisol reactivity and maternal depression on left hippocampal tail volume.

	β	**b (SE)**	***pr***	***p***
Model 1				
T1 AUCg	.12	13.75(34.70)	.05	.693
Maternal Lifetime Depressive Disorder	.01	1.12(32.10)	.01	.972
T1 AUCg x Maternal DD	.06	7.97(38.95)	.03	.839
Model 2				
T1 AUCg	.16	18.83(15.34)	.17	.225
Percent Exposure to Maternal DD	.06	7.26(16.23)	.06	.657
T1 AUCg x Exposure to Maternal DD	-.22	-30.17(18.21)	-.22	.103
Model 3				
T1 AUCi	-.22	-64.50(60.61)	-.14	.292
Maternal Lifetime Depressive Disorder	-.01	-1.21(32.22)	-.01	.970
T1 AUCi x Maternal DD	.08	30.58(79.83)	.05	.703
Model 4				
T1 AUCi	-.13	-39.37(38.91)	-.14	.316
Percent Exposure to Maternal DD	.06	7.24(16.47)	.06	.662
T1 AUCi x Exposure to Maternal DD	.19	75.41(51.70)	.20	.150
Model 5				
T2 AUCg	-.24	-28.02(25.98)	-.14	.285
Maternal Lifetime Depressive Disorder	-.05	-12.90(32.54)	-.05	.693
T2 AUCg x Maternal DD	-.04	-5.28(31.97)	-.02	.869
Model 6				
T2 AUCg	-.28	-32.68(15.37)	-.27	.038
Percent Exposure to Maternal DD	.06	7.46(15.95)	.06	.642
T2 AUCg x Exposure to Maternal DD	.02	2.30(17.84)	.02	.898
Model 7				
T2 AUCi	-.23	-35.10(27.50)	-.17	.207
Maternal Lifetime Depressive Disorder	-.07	-17.34(31.69)	-.07	.586
T2 AUCi x Maternal DD	-.18	-37.23(37.37)	-.13	.323
Model 8				
T2 AUCi	-.34	-51.44(18.75)	-.34	.008
Percent Exposure to Maternal DD	<.01	0.39(15.00)	<.01	.979
T2 AUCi x Exposure to Maternal DD	-.15	-25.09(20.56)	-.16	.227

Note. DD = Depressive Disorder, including Major Depressive Disorder or Dysthymic Disorder

Supplementary Table 19

Interactions between cortisol reactivity and maternal depression on left total hippocampal volume.

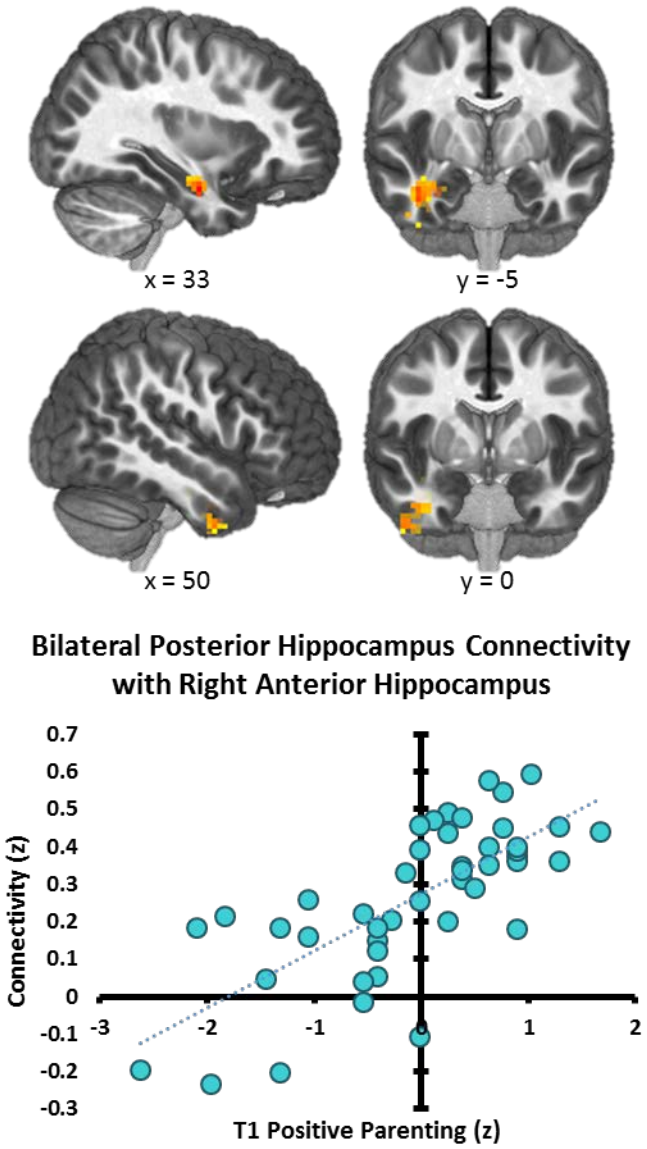
	β	**b (SE)**	***pr***	***p***
Model 1				
T1 AUCg	.06	19.14(87.13)	.03	.827
Maternal Lifetime Depressive Disorder	.12	74.41(80.62)	.12	.360
T1 AUCg x Maternal DD	.23	81.15(97.81)	.11	.410
Model 2				
T1 AUCg	.27	81.27(38.84)	.27	.041
Percent Exposure to Maternal DD	-.10	-31.65(41.10)	-.10	.445
T1 AUCg x Exposure to Maternal DD	-.16	-56.63(46.10)	-.17	.225
Model 3				
T1 AUCi	-.16	-126.07(156.15)	-.11	.423
Maternal Lifetime Depressive Disorder	.12	73.48(83.01)	.12	.380
T1 AUCi x Maternal DD	-.03	-32.08(205.66)	-.02	.877
Model 4				
T1 AUCi	-.18	-132.25(98.51)	-.18	.185
Percent Exposure to Maternal DD	-.10	-32.33(41.70)	-.11	.442
T1 AUCi x Exposure to Maternal DD	.22	222.86(130.89)	.23	.094
Model 5				
T2 AUCg	.13	38.79(66.09)	.08	.560
Maternal Lifetime Depressive Disorder	.11	68.83(82.76)	.11	.409
T2 AUCg x Maternal DD	-.29	-105.66(81.32)	-.17	.199
Model 6				
T2 AUCg	-.15	-45.29(39.17)	-.15	.252
Percent Exposure to Maternal DD	-.01	-4.19(40.65)	-.01	.918
T2 AUCg x Exposure to Maternal DD	.12	39.84(45.47)	.12	.385
Model 7				
T2 AUCi	-.03	-10.43(72.93)	-.02	.887
Maternal Lifetime Depressive Disorder	.10	61.54(84.04)	.10	.467
T2 AUCi x Maternal DD	-.17	-91.46(99.13)	-.12	.360
Model 8				
T2 AUCi	-.16	-59.99(48.38)	-.16	.220
Percent Exposure to Maternal DD	-.08	-25.28(38.70)	-.09	.516
T2 AUCi x Exposure to Maternal DD	-.24	-96.54(53.04)	-.23	.074

Note. DD = Depressive Disorder, including Major Depressive Disorder or Dysthymic Disorder

Hippocampal Functional Connectivity

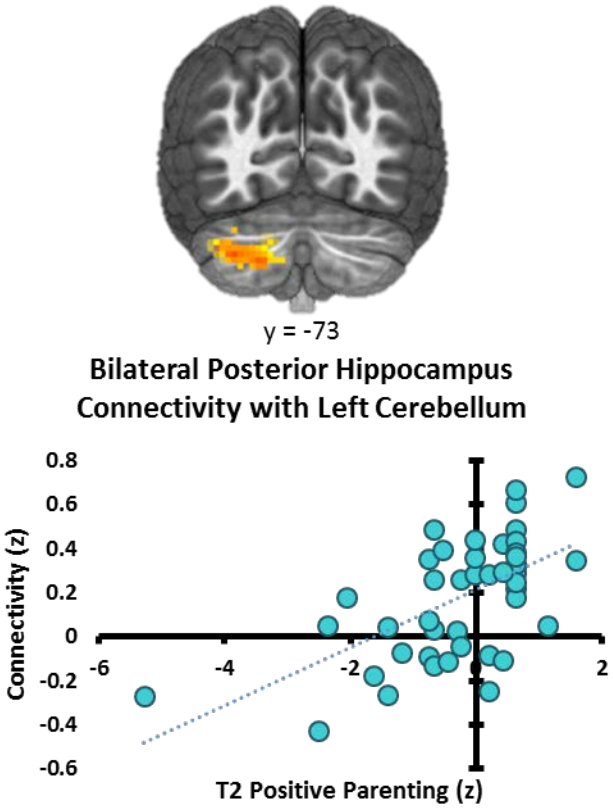
Aim 1: Associations between Parenting and Children's Hippocampal Connectivity

Greater T1 Positive Parenting was associated with increased bilateral posterior hippocampus connectivity with a region spanning the right anterior hippocampus into the right inferior temporal gyrus and temporal pole (k=110, [32 -8 -24], *t*=3.59; Supplementary Figure 2). T1 Negative Parenting was not significantly associated with anterior or posterior hippocampus connectivity.

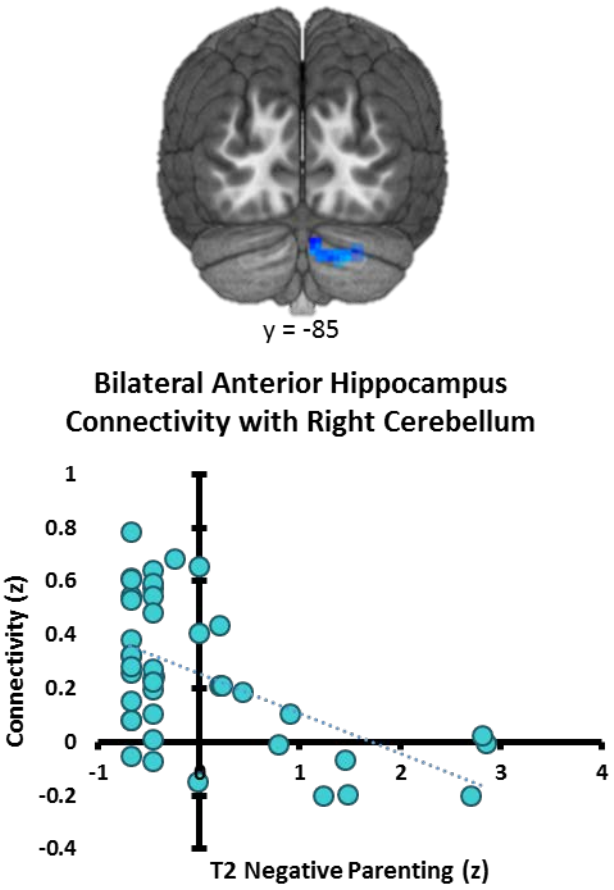


Supplementary Figure 2. Regions demonstrating significant associations between T1 Positive Parenting and posterior hippocampus connectivity.

Greater T2 Positive Parenting predicted increased bilateral posterior hippocampus connectivity with left cerebellum (k=161, [-40 -71 -39], *t*=3.58; Supplementary Figure 3). Greater T2 Negative Parenting was associated with reduced bilateral anterior hippocampus connectivity with the right cerebellum (k=87, [8 -89 -30], *t*=-3.34; Supplementary Figure 3) and reduced bilateral posterior hippocampus connectivity with the left cerebellum and a region of bilateral posterior cingulate gyrus (Supplementary Table 20, Supplementary Figure 5).



Supplementary Figure 3. Regions demonstrating significant posterior hippocampus connectivity that varies as a functional of T2 Positive Parenting.

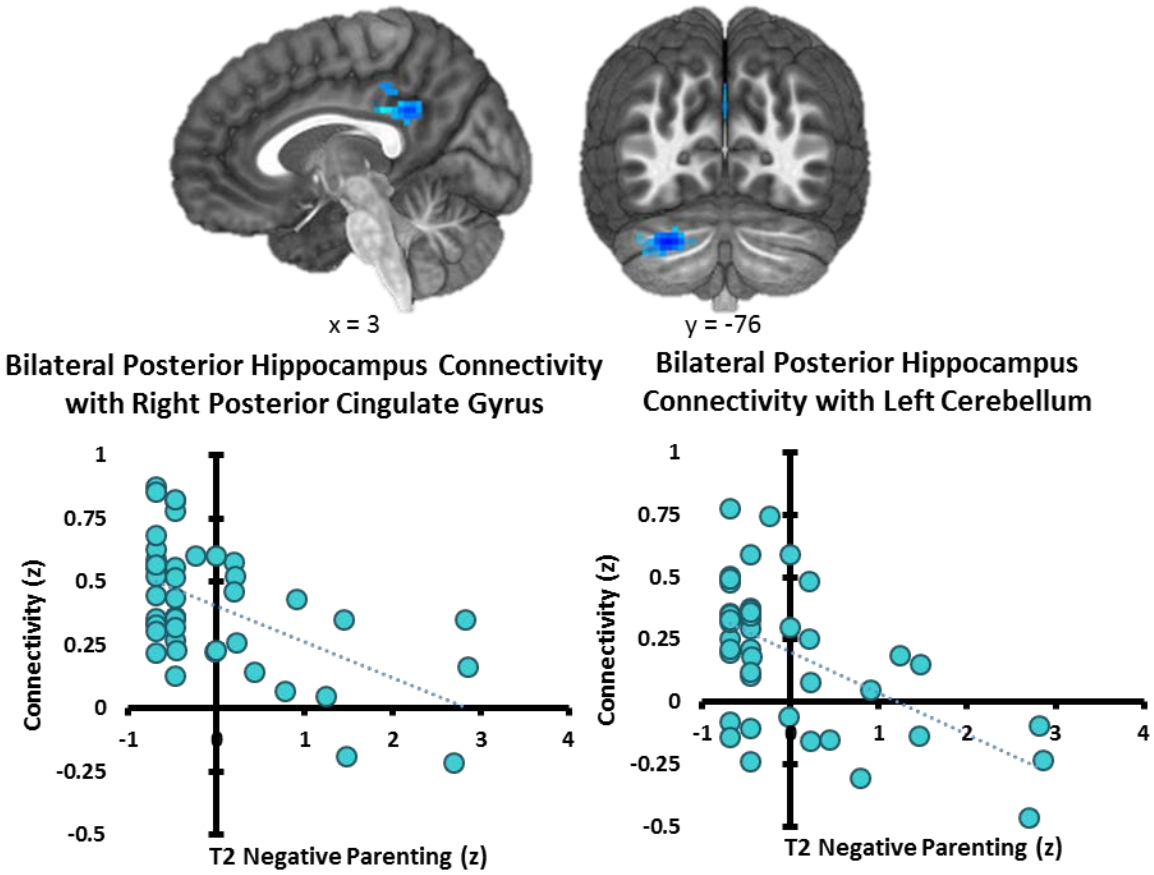


Supplementary Figure 4. Region where bilateral anterior hippocampus connectivity significantly varies as a function of T2 Negative Parenting.

Supplementary Table 20

Regions where bilateral posterior hippocampus connectivity significantly varied as a function of T2 Negative Parenting.

Region	k	x	y	z	*t*
Left Cerebellum	111	-28	-77	-36	-3.43
Right Posterior Cingulate Cortex	81	5	-47	27	-3.38
Left Posterior Cingulate Cortex					



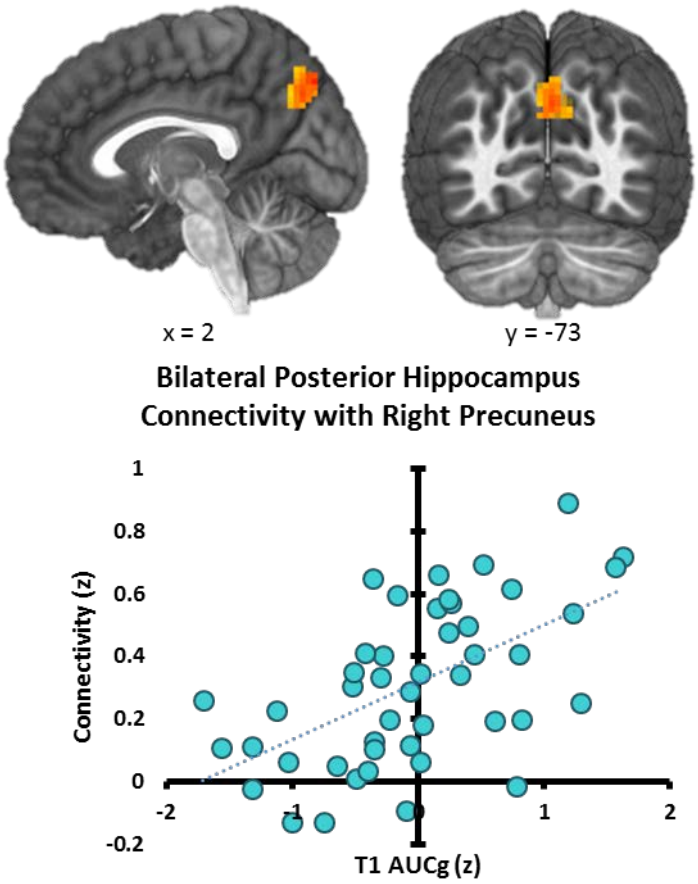
Supplementary Figure 5. Regions demonstrating significant associations between T2 Negative Parenting posterior hippocampus connectivity.

Aim 2: Associations between Children's Cortisol Reactivity and Hippocampal Connectivity

Greater T1 AUCg significantly predicted increased bilateral posterior hippocampus connectivity with a region of bilateral precuneus (Supplementary Table 21, Supplementary Figure 6). T1 AUCi was not significantly associated with anterior or posterior hippocampus connectivity.

Supplementary Table 21. *Regions where bilateral posterior hippocampus connectivity significant varied as a function of T1 AUCg.*

Region	k	x	y	z	*t*
Right Precuneus	99	2	-80	45	3.50
Left Precuneus					



Supplementary Figure 6. Regions where T1 AUCg was significantly associated with posterior hippocampus connectivity.

Neither T2 AUCg or AUCi was significantly associated bilateral anterior or posterior hippocampus connectivity.

Aim 3: Mediation of Associations between Parenting and Hippocampal Connectivity by Cortisol Reactivity

There were five regions where parenting significantly predicted hippocampal connectivity. Neither T2 AUCg or T2 AUCi significantly mediated the association between parenting and hippocampal connectivity in any of these regions (Supplementary Table 22).

Supplementary Table 22

Mediation of the association between parenting and hippocampal resting-state functional connectivity by cortisol reactivity.

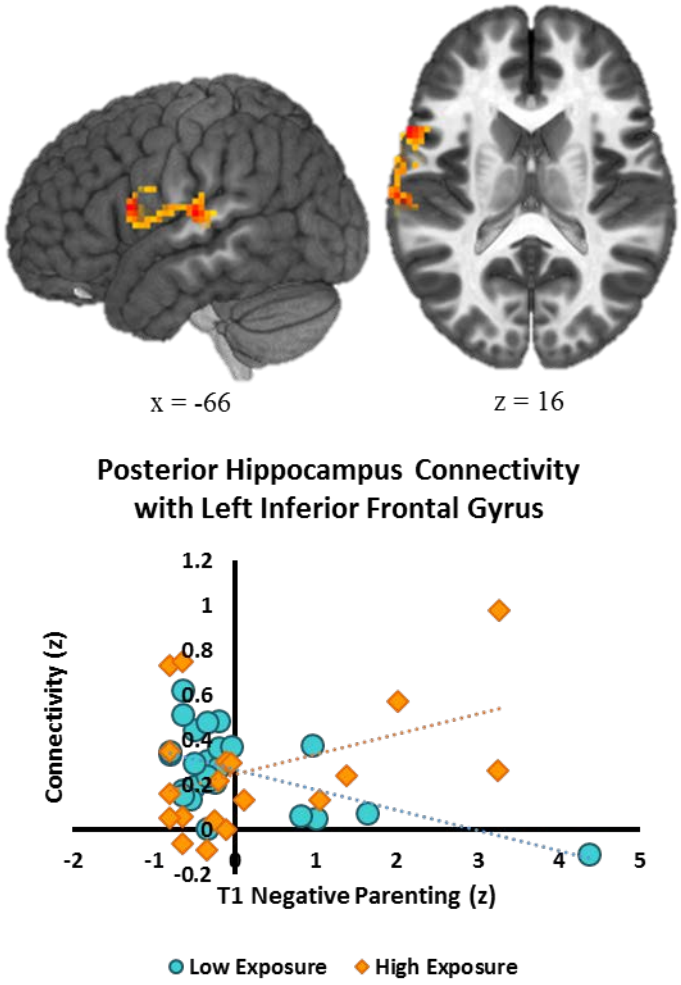
Predictor	Dependent Variable	Mediator	Covariates	Total Effect	Direct Effect	Indirect Effect	SE	CI	*p*
T2 Positive Parenting	Posterior Connectivity with Left Cerebellum	T2 AUCg	Age, Mean FD	-0.11	-0.10	<-0.01	0.06	[-0.18, 0.08]	.929
		T2 AUCi	Age, Mean FD	-0.11	-0.16	0.05	0.08	[-0.03, 0.40]	.630
T2 Negative Parenting	Anterior Connectivity with Right Cerebellum	T2 AUCg	Age, Mean FD	-0.32	-0.39	0.07	0.12	[-0.06, 0.54]	.596
		T2 AUCi	Age, Mean FD	-0.32	-0.36	0.04	0.08	[-0.02, 0.42]	.696
	Anterior Connectivity with Left Cerebellum	T2 AUCg	Age, Mean FD	-2.05	-1.95	-0.10	0.21	[-0.82, 0.17]	.579
		T2 AUCi	Age, Mean FD	-2.05	-2.06	0.01	0.09	[-0.12, 0.19]	.933
	Posterior Connectivity with Left Cerebellum	T2 AUCg	Age, Mean FD	0.26	0.27	-0.02	0.14	[-0.38, 0.23]	.898
		T2 AUCi	Age, Mean FD	0.26	0.25	0.01	0.06	[-0.04, 0.20]	.898
	Posterior Connectivity with Right Cerebellum	T2 AUCg	Age, Mean FD	-0.18	-0.10	-0.08	0.19	[-0.72, 0.15]	.647
		T2 AUCi	Age, Mean FD	-0.18	-0.20	0.02	0.07	[-0.05, 0.27]	.888

CI = Confidence Interval; SE = Standard Error; FD = Framewise Displacement

Exploratory Aim: Role of Maternal Depression

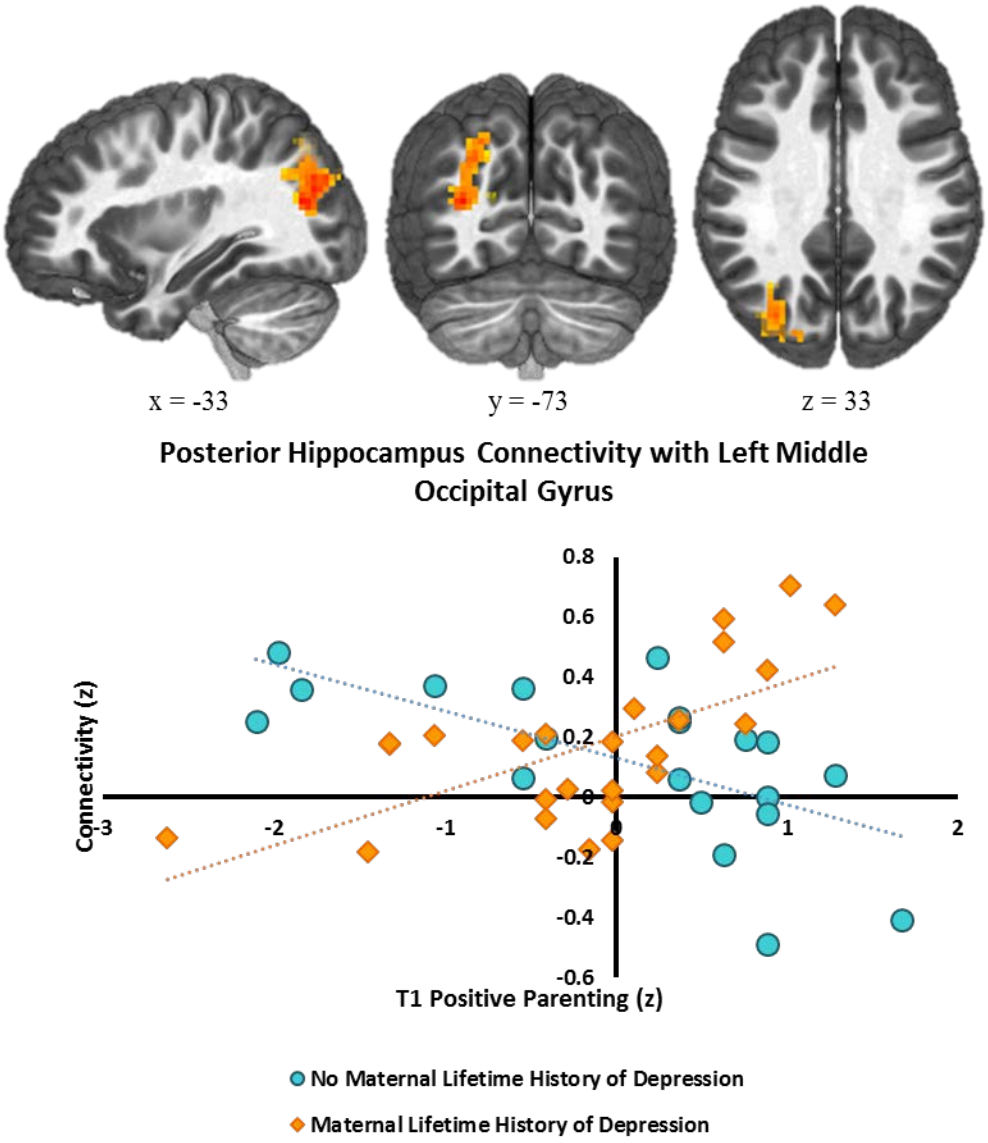
Interactions between Parenting and Maternal Depression.

Lifetime exposure to maternal depression moderated the association between T1 Negative Parenting and posterior hippocampus connectivity with left inferior frontal gyrus (pars Opercularis) (k=107, [-61 13 15], *t*=3.50; Supplementary Figure 7). In individuals with low exposure to maternal depression, greater T1 Negative Parenting was associated with reduced hippocampal connectivity with left inferior frontal gyrus. In individuals with high exposure to maternal depression, greater T1 Negative Parenting was associated with increased hippocampal connectivity with this region.



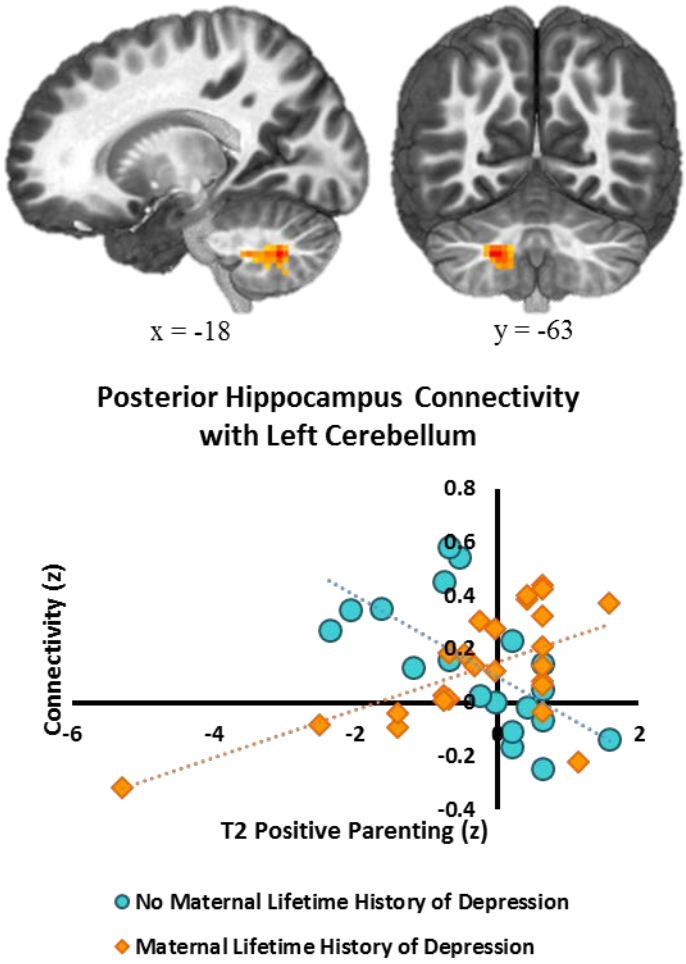
Supplementary Figure 7. Regions where proportion lifetime exposure to maternal depression moderated the association between posterior hippocampus connectivity with T1 Negative Parenting. Note: Scatterplot depicts bivariate correlations between the predictor and connectivity and is not adjusted for covariates included in the statistical model.

Maternal lifetime depression status significantly moderated the association between T1 Positive Parenting and posterior hippocampus connectivity with left middle occipital gyrus (k=219, [-37 -80 24], *t*=3.62; Supplementary Figure 8). Specifically, in children with no maternal lifetime history of depressive disorders, greater T1 Positive Parenting was associated with reduced posterior hippocampus connectivity with the left middle occipital gyrus. In contrast, in offspring with a maternal lifetime history of depression, greater T1 Positive Parenting was associated with increased posterior hippocampus connectivity with this region.



Supplementary Figure 8. Regions where maternal lifetime history of depressive disorders moderated the association between T1 Positive Parenting and posterior hippocampus connectivity. Note: Scatterplots depict bivariate correlations between the predictor and connectivity and are not adjusted for covariates included in the statistical models.

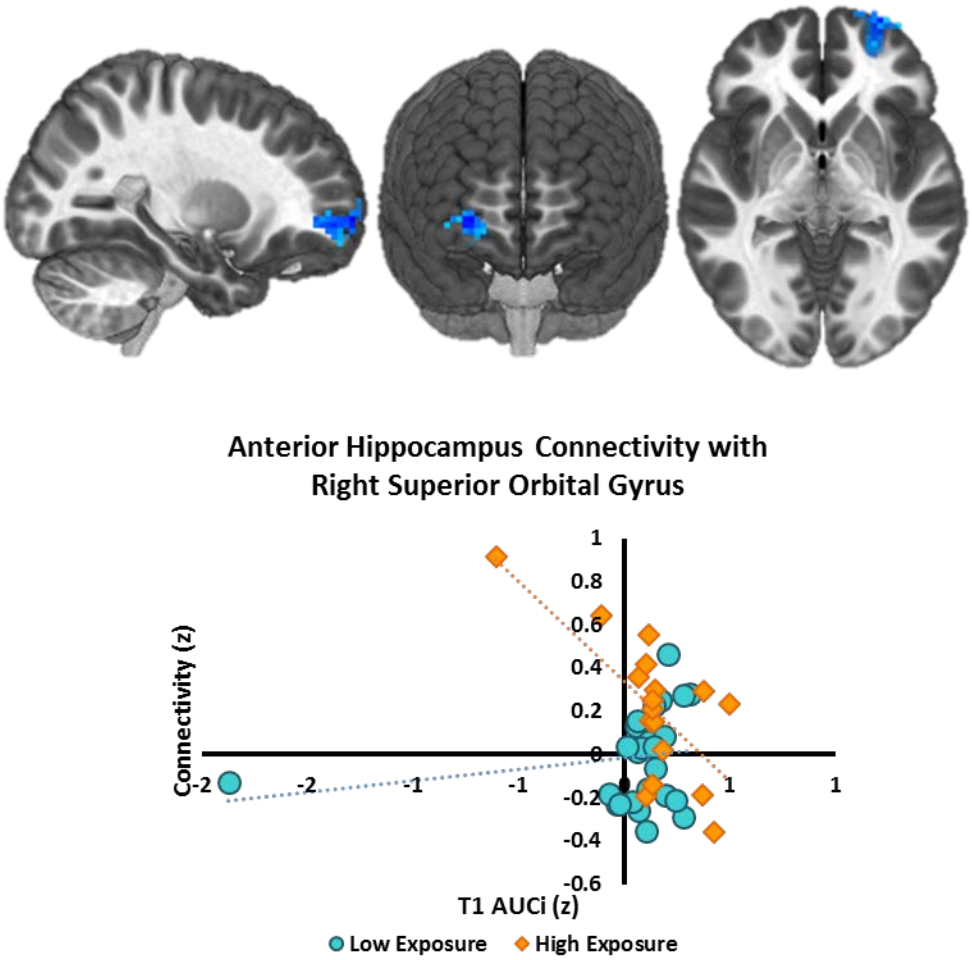
Maternal lifetime history of depressive disorders moderated the association between T2 Positive Parenting and posterior hippocampus connectivity with left cerebellum (k=77, [-19 -62 -37], *t*=3.49; Supplementary Figure 9). Specifically, in offspring without a maternal lifetime history of depression, greater T2 Positive Parenting was associated with decreased posterior hippocampus connectivity with the left cerebellum while in offspring with a maternal lifetime history of depression, greater T2 Positive Parenting was associated with reduced posterior hippocampus connectivity in this region.



Supplementary Figure 9. Regions where maternal lifetime history of depressive disorders significantly moderated the association between T2 Positive Parenting and posterior hippocampal connectivity. Note: Scatterplot depicts bivariate correlations between the predictor and connectivity and is not adjusted for covariates included in the statistical model.

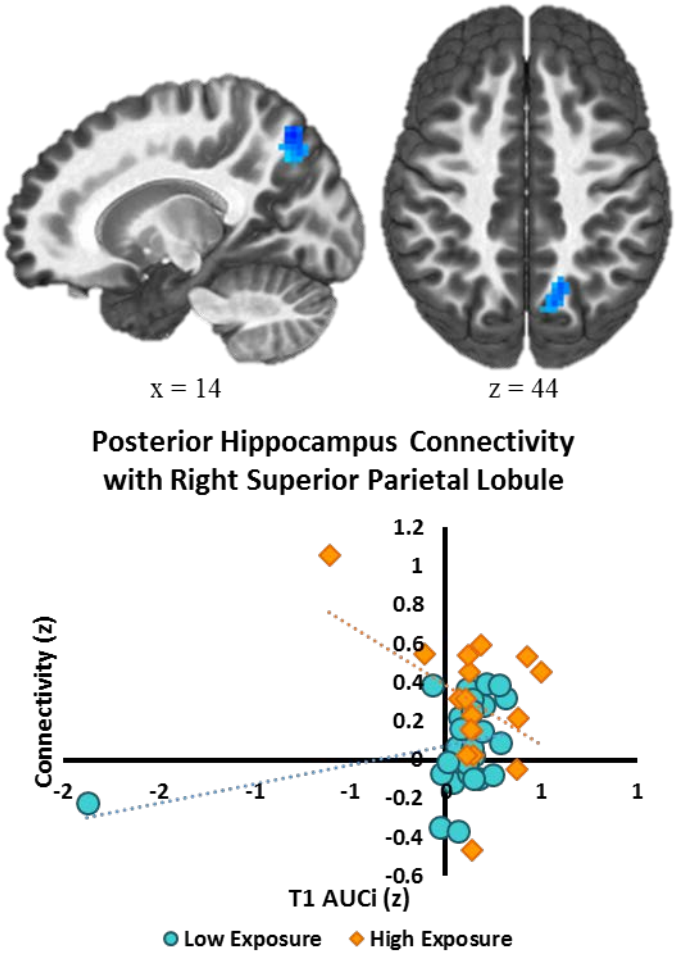
Interactions Between Maternal Depression and Cortisol Reactivity.

The association between T1 AUCi and anterior hippocampus connectivity was moderated by lifetime exposure to maternal depression. Specifically, in offspring with low exposure, greater T1 AUCi predicted increased anterior hippocampus connectivity with the right superior orbital gyrus (k=70, [29 64 -3], *t*=-3.31; Supplementary Figure 10). In offspring with high exposure, greater T1 AUCi was associated with reduced anterior hippocampal connectivity with the right superior orbital gyrus.



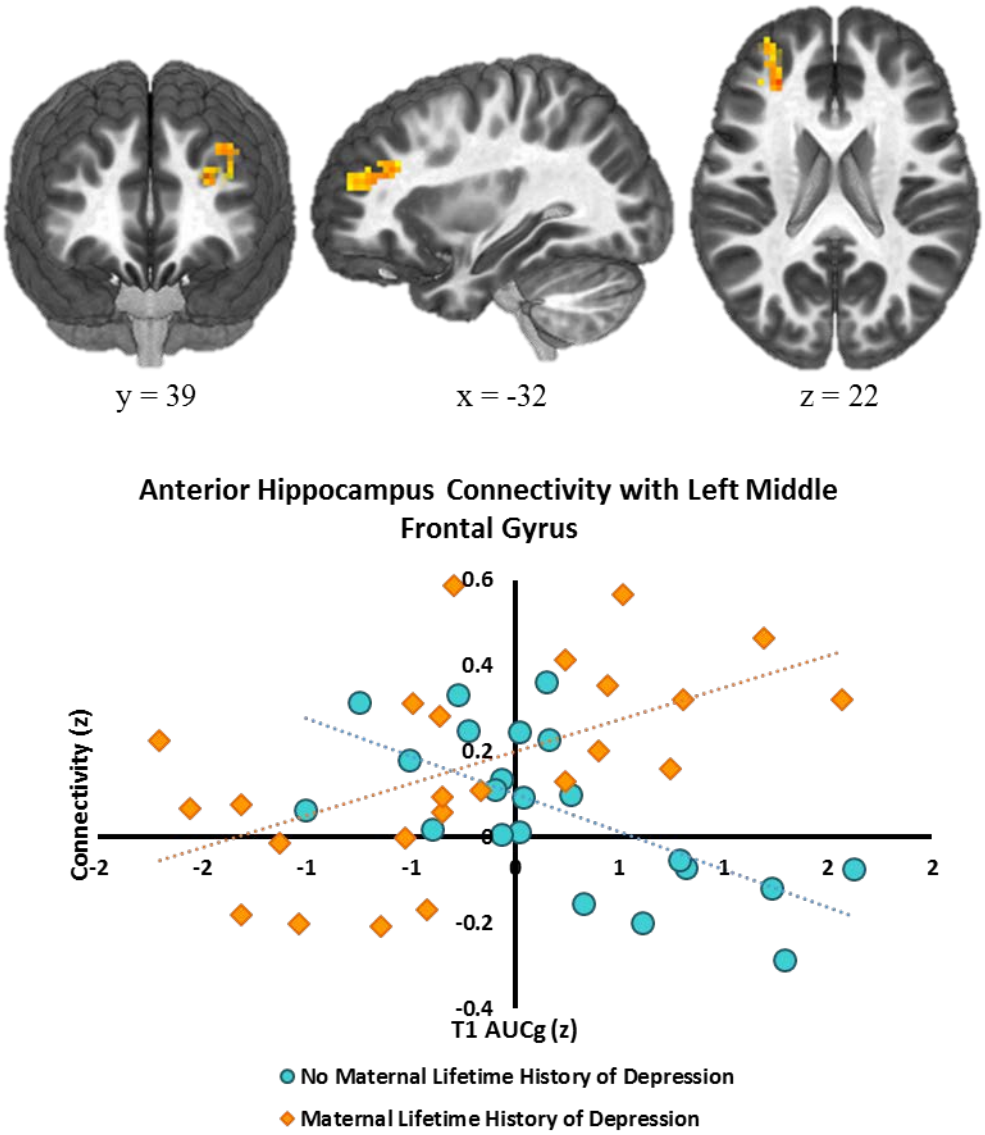
Supplementary Figure 10. Regions where the association between T1 AUCg and anterior hippocampus connectivity was significantly moderated by lifetime exposure to maternal depressive disorders. Note: Scatterplot depicts bivariate correlation between the predictor and connectivity and is not adjusted for covariates included in the statistical model.

Lifetime exposure to maternal depression significantly moderated the association between T1 AUCi and posterior hippocampus connectivity with right superior parietal lobule (k=75, [14 -71 51], *t*=-3.42; Supplementary Figure 11). In children with low exposure, greater T1 AUCg was associated with increased posterior hippocampus connectivity with right superior parietal lobule while children with high exposure demonstrated reduced posterior hippocampus connectivity with this region as T1 AUCi increased.



Supplementary Figure 11. Regions where the association between T1 AUCi and anterior hippocampus connectivity was significantly moderated by proportion lifetime exposure to maternal depression. Note: Scatterplot depicts bivariate correlation between the predictor and connectivity and is not adjusted for covariates included in the statistical model.

Maternal lifetime depression status moderated the associated with T1 AUCg and anterior hippocampus connectivity with left middle frontal gyrus (k=88, [-28 37 21], *t*=-3.31; Supplementary Figure 12). Specifically, in offspring without a maternal lifetime history of depression, greater T1 AUCg was associated with decreased anterior hippocampus connectivity with the left middle frontal gyrus. In offspring with a maternal lifetime history of depression, greater T1 AUCg was associated with increased anterior hippocampal connectivity in this region.

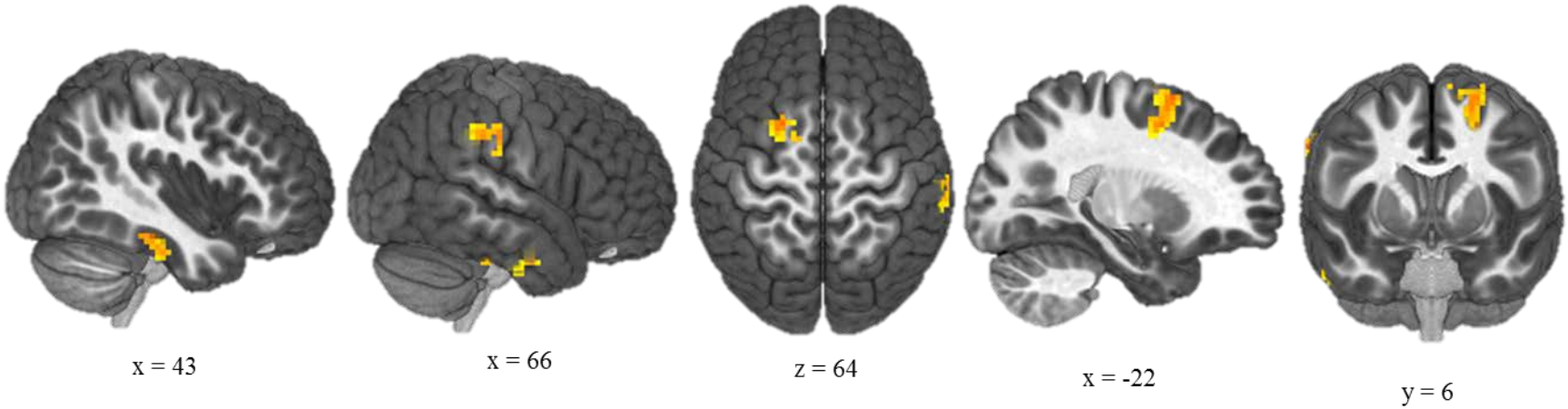


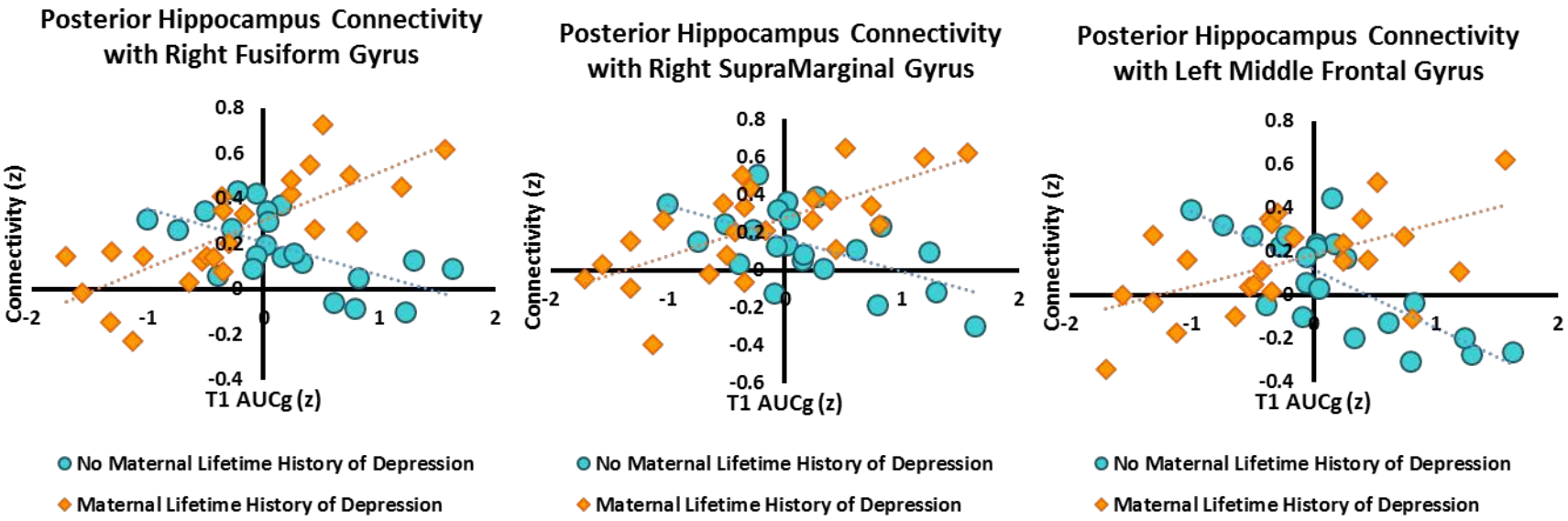
Supplementary Figure 12. Regions where the association between T1 AUCg and anterior hippocampus connectivity was significantly moderated by a maternal lifetime history of depressive disorders. Note: Scatterplot depicts bivariate correlation between the predictor and connectivity and is not adjusted for covariates included in the statistical model.

Maternal lifetime depression status moderated the association between T1 AUCg and posterior hippocampus connectivity with a region of the right fusiform gyrus, the right supramarginal gyrus, and the left middle frontal gyrus (Supplementary Table 23, Supplementary Figure 13). In all regions, the same trend was evident: in offspring without a maternal lifetime history of depressive disorders, greater T1 AUCg was associated with reduced connectivity while in offspring with a maternal lifetime history of depressive disorders greater T1 AUCg predicted increased connectivity with these regions.

Supplementary Table 23
Regions where the association between T1 AUCg and posterior hippocampus connectivity was significantly moderated by a maternal lifetime history of depressive disorders.

Region	k	x	y	z	*t*
Right Fusiform Gyrus	109	38	-23	-21	3.42
Right Inferior Temporal Gyrus					
Right Middle Temporal Gyrus					
Left Middle Frontal Gyrus	82	-22	10	63	3.58
Right SupraMarginal Gyrus	72	68	-23	36	3.46


x = 43
x = 66
z = 64
x = -22
y = 6

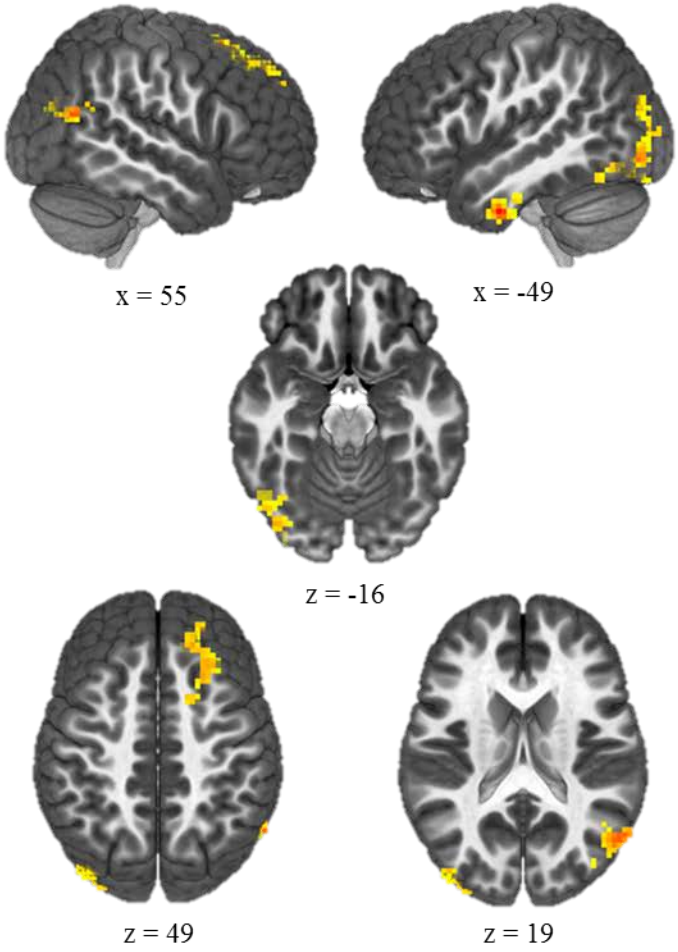

Posterior Hippocampus Connectivity with Right Fusiform Gyrus
Connectivity (z)
T1 AUCg (z)
Posterior Hippocampus Connectivity with Right SupraMarginal Gyrus
Connectivity (z)
T1 AUCg (z)
Posterior Hippocampus Connectivity with Left Middle Frontal Gyrus
Connectivity (z)
T1 AUCg (z)
No Maternal Lifetime History of Depression
Maternal Lifetime History of Depression

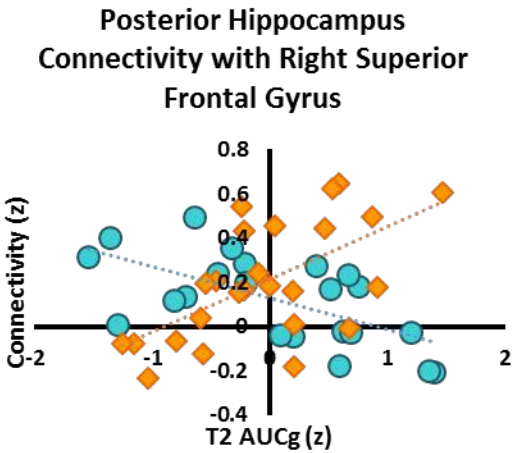
Supplementary Figure 13. Regions where the association between T1 AUCg and posterior hippocampus connectivity was significantly moderated by a maternal lifetime history of depressive disorders. Note: Scatterplots depict bivariate correlations between the predictor and connectivity and are not adjusted for covariates included in the statistical models.

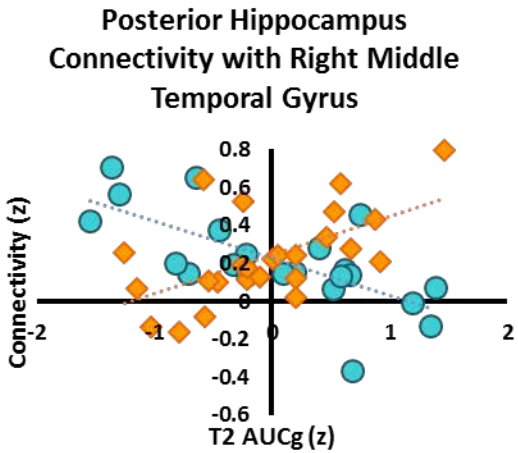
Maternal lifetime history of depression also moderated the association between T2 AUCg and posterior hippocampus connectivity with four regions: left inferior temporal gyrus, left inferior occipital gyrus, right superior frontal gyrus, and right middle temporal gyrus (Supplementary Table 24, Supplementary Figure 14). As at T1, all regions demonstrated the same direction of effects: in offspring without a maternal lifetime history of depression, greater T2 AUCg was associated with reduced hippocampus connectivity in these regions while in offspring with a maternal lifetime history of depression, greater T2 AUCg was associated in increased posterior hippocampus connectivity in these regions.

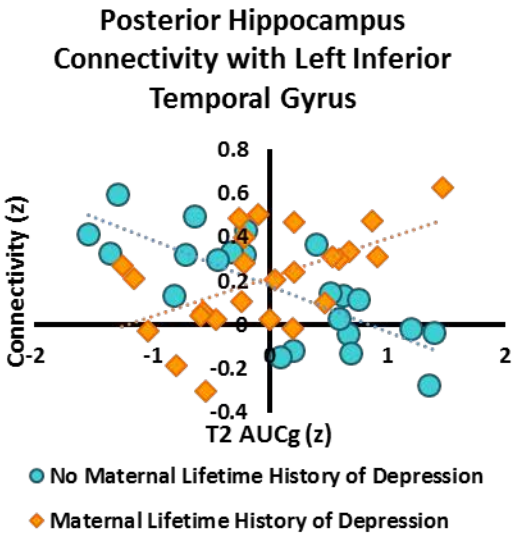
Supplementary Table 24
Regions where the association between T2 AUCg and posterior hippocampus connectivity was significantly moderated by a maternal lifetime history of depressive disorders.

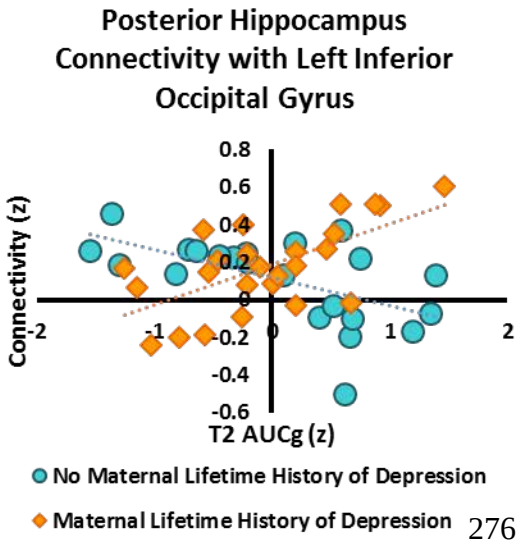
Region	k	x	y	z	*t*
Right Superior Frontal Gyrus	172	20	43	45	3.48
Left Inferior Occipital Gyrus	128	-46	-86	-9	3.38
Left Fusiform Gyrus					
Left Inferior Temporal Gyrus	99	-49	-5	-39	3.64
Right Middle Temporal Gyrus	78	62	-62	21	3.5


x = 55
x = -49
z = -16
z = 49
z = 19


Posterior Hippocampus Connectivity with Right Superior Frontal Gyrus
Connectivity (z)
T2 AUCg (z)
No Maternal Lifetime History of Depression
Maternal Lifetime History of Depression


Posterior Hippocampus Connectivity with Right Middle Temporal Gyrus
Connectivity (z)
T2 AUCg (z)
No Maternal Lifetime History of Depression
Maternal Lifetime History of Depression


Posterior Hippocampus Connectivity with Left Inferior Temporal Gyrus
Connectivity (z)
T2 AUCg (z)
No Maternal Lifetime History of Depression
Maternal Lifetime History of Depression

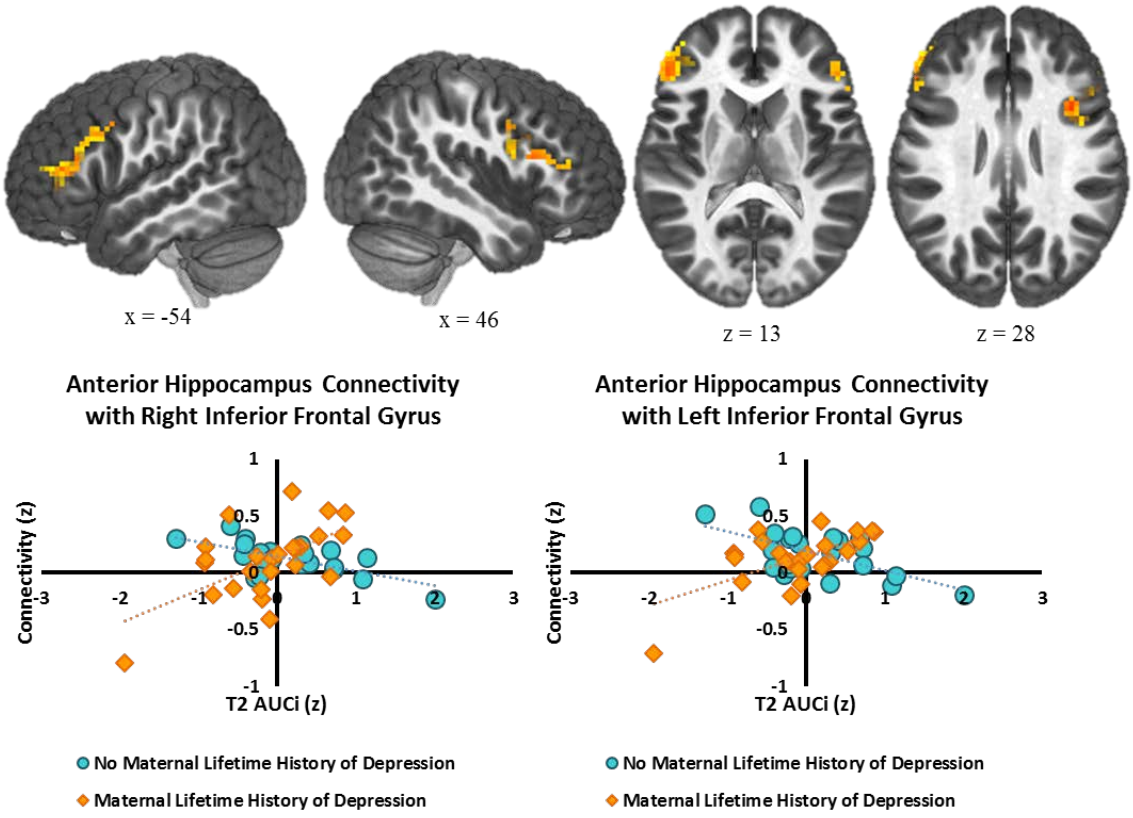

Posterior Hippocampus Connectivity with Left Inferior Occipital Gyrus
Connectivity (z)
T2 AUCg (z)
No Maternal Lifetime History of Depression
Maternal Lifetime History of Depression

Supplementary Figure 14. Regions where the association between T2 AUCg and posterior hippocampus connectivity was significantly moderated by a maternal lifetime history of depressive disorders. Note: Scatterplots depict bivariate correlations between the predictor and connectivity and are not adjusted for covariates included in the statistical models.

There was a significant interaction between maternal lifetime depression status and T2 AUCi in predicted anterior hippocampus connectivity with regions of right and left inferior frontal gyrus (Supplementary Table 25, Supplementary Figure 15). For both regions, in offspring with no maternal lifetime history of depressive disorders, greater T2 AUCi was associated with reduced anterior hippocampus connectivity and in offspring with a maternal lifetime history of depressive disorders, greater T2 AUCi was associated with increased anterior hippocampus connectivity with these regions.

Supplementary Table 25
Regions where the association between T2 AUCi and anterior hippocampus connectivity was significantly moderated by a maternal lifetime history of depressive disorders.

Region	k	x	y	z	*t*
Right Inferior Frontal Gyrus (p. Opercularis)	93	38	13	24	3.37
Left Inferior Frontal Gyrus (p. Triangularis)	91	-52	37	9	3.50

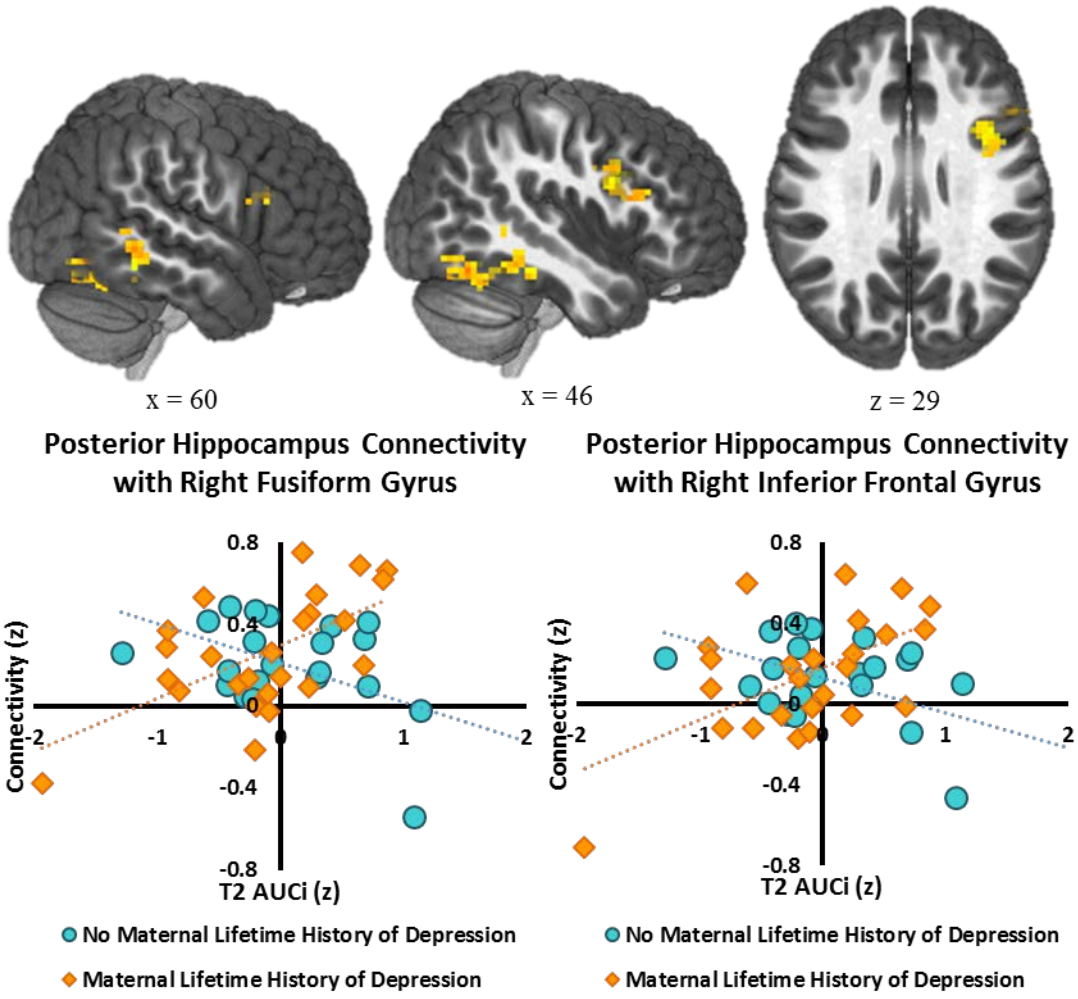


Supplementary Figure 15. Regions where the association between T2 AUCi and anterior hippocampus connectivity was significantly moderated by a maternal lifetime history of depressive disorders. Note: Scatterplots depict bivariate correlations between the predictor and connectivity and are not adjusted for covariates included in the statistical models.

Maternal lifetime history of depression significantly moderated the association between T2 AUCi and posterior hippocampus connectivity with the right fusiform gyrus and the right inferior frontal gyrus (Supplementary Table 26, Supplementary Figure 16). Specifically, in offspring with a maternal lifetime history of depression, greater T2 AUCi predicted increased posterior hippocampus connectivity with right fusiform gyrus and right inferior frontal gyrus while in offspring without a maternal lifetime history of depression, greater T2 AUCi was associated with reduced posterior hippocampal connectivity with these regions.

Supplementary Table 26
Regions where the association between T2 AUCi and posterior hippocampus connectivity was significantly moderated by a maternal lifetime history of depressive disorders.

Region	k	x	y	z	*t*
Right Fusiform Gyrus	171	38	-74	-18	3.40
Right Inferior Temporal Gyrus					
Right Middle Temporal Gyrus					
Right Inferior Frontal Gyrus (p. Opercularis)	97	47	16	18	3.42



Supplementary Figure 16. Regions where the association between T2 AUCi and posterior hippocampus connectivity was significantly moderated by a maternal lifetime history of depressive disorders. Note: Scatterplots depict bivariate correlations between the predictor and connectivity and are not adjusted for covariates included in the statistical models.