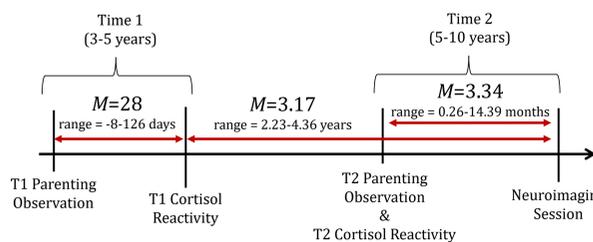


Introduction

- Rodent models indicate that perturbations in the early parenting environment epigenetically program the hypothalamic-pituitary-adrenal (HPA) axis, ultimately leading to elevated levels of cortisol in response to stress and structural changes in the hippocampus (e.g., Liu et al., 1997; Weaver et al., 2004).
- Examination of these pathways in humans is only emerging. Previous studies have demonstrated:
 - Parenting predicts hippocampal volume (Rao et al., 2010; Luby et al., 2012)
 - Cortisol reactivity predicts hippocampal volume (e.g., Frodl & O'Keane, 2013)
 - Parenting predicts cortisol reactivity (e.g., Taylor et al., 2013)
- No study to date has tested the full model of parenting acting through cortisol reactivity to modify hippocampal structure in a young, longitudinal sample

The present study attempts to extend the rodent literature by examining the effects of early parenting on later hippocampal structural development in a longitudinal sample of children ($n=63$), with a specific goal of exploring the mediating role of cortisol reactivity.

Methods



Participants

- 63* children from a longitudinal dataset ($N=175$) of offspring of depressed mothers and a non-depressed community comparison group who provided useable scan data at Time 2 (T2) *n's vary for each analysis

Observational Parenting Assessments

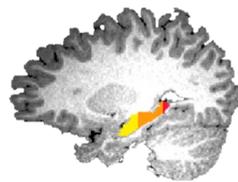
- Children and their parents worked together to complete six tasks modified from the Teaching Tasks Battery (Egeland et al., 1995). Different age-appropriate tasks were completed at T1 and T2
 - Each task was rated on measures of Maternal Intrusiveness*, Hostility*, Support*, Negative Affect*, and Positive Affect*. Measures were averaged across episodes and converted to z-scores. 5-point scales *3-point scales
 - Negative Parenting Composite: Average of z-scored Maternal Intrusiveness, Maternal Hostility, and Maternal Negative Affect
 - Positive Parenting Composite: Average of z-scored Maternal Support and Maternal Positive Affect

Cortisol Reactivity

- At T1 and T2, children completed an age-appropriate laboratory stressor
 - T1 Stressor: timed shame-inducing matching task (Tolep & Dougherty, 2014).
 - T2 Stressor: modified Trier Social Stress Test (TSST-C; Buske-Kirschbaum et al., 1997) followed by an unsolvable puzzle
- Salivary cortisol samples were collected at baseline (after 30 minutes of quiet play) and 20-, 30-, 40-, and 50-minutes post-stressor
- Cortisol reactivity measures were derived from the 5 samples
 - AUCg: measure of the magnitude of total cortisol secretion
 - AUCi: measure of total cortisol change

Neuroimaging

- Structural MPRAGE (1mm³) was collected at the Maryland Neuroimaging Center using a 12-channel coil in a Siemens 3T scanner. Images were automatically segmented using Freesurfer v5.1. Resulting segmentations were visually inspected. Gross over- or under- hippocampal inclusions were manually edited ($n=7$).
- Segmentations were split into head, body, and tail (Weiss et al., 2005). The posterior boundary of the head was determined to be the last slice at which the uncus apex was visible. The anterior boundary of the tail was determined to be the slice where the fornix separates from the hippocampus.
- Final volumes were adjusted for total intracranial volume (Raz et al., 2005).

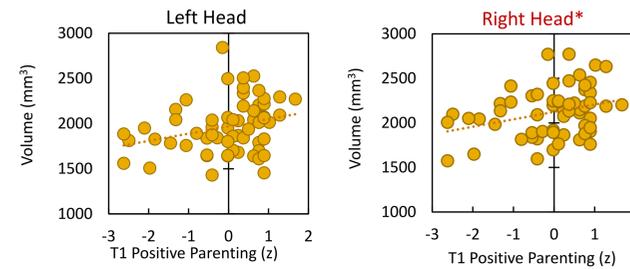


Analysis

- Individual multiple regressions were run to test associations between T1/T2 parenting (positive or negative) and T1/T2 cortisol reactivity (AUCg, AUCi) with unilateral hippocampal head, body, tail, and total volumes.
- Gender was entered as a covariate in all analyses of left or right head. Scan Age was included as a covariates in analyses of right body.

Time 1 Parenting ($n=60$)

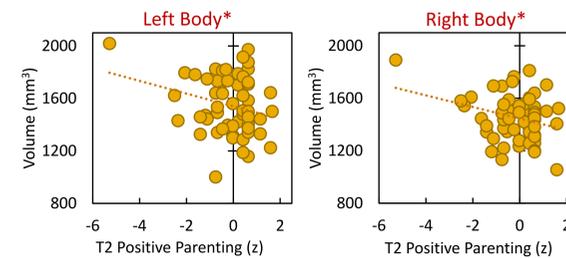
T1 Positive Parenting



- Greater T1 Positive Parenting predicted larger left ($b=76.48$, $SE=35.16$, $pr=0.28$, $p=.034$) and right ($b=79.80$, $SE=33.53$, $pr=0.30$, $p=.021$) head volumes.
- T1 Negative Parenting was not associated with any left or right whole or segmented hippocampal volume ($ps>0.214$)

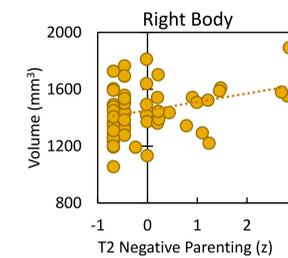
Time 2 Parenting ($n=59$)

T2 Positive Parenting



- Greater T2 Positive Parenting predicted smaller left body ($b=-48.42$, $SE=24.15$, $pr=-0.26$, $p=.050$) and right body ($b=-47.39$, $SE=18.61$, $pr=-0.31$, $p=.014$) volumes.

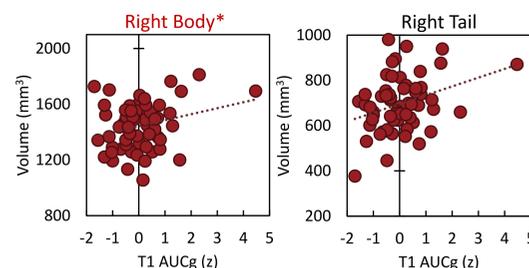
T2 Negative Parenting



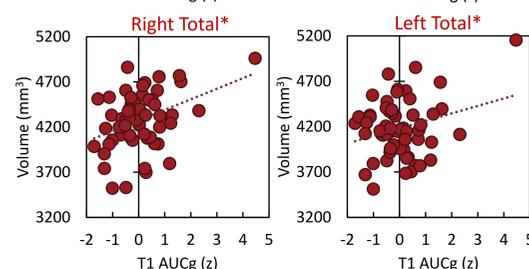
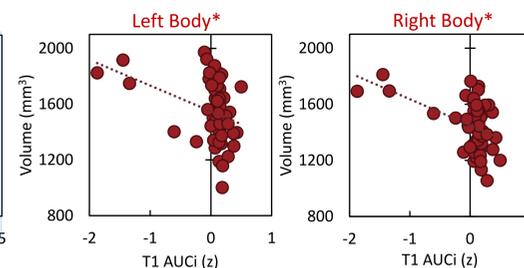
- Greater T2 Negative Parenting predicted larger right hippocampal body volume ($b=56.49$, $SE=23.88$, $pr=0.30$, $p=.021$).

Time 1 Cortisol Reactivity ($n=59$)

T1 AUCg



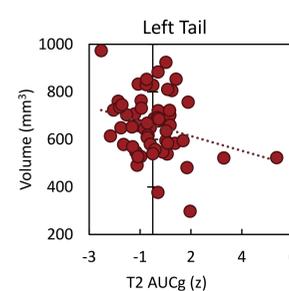
T1 AUCi



- Greater T1 AUCg predicted larger right body ($b=52.29$, $SE=20.14$, $pr=0.33$, $p=.012$), right tail ($b=38.75$, $SE=14.77$, $p=.011$), right total ($b=116.91$, $SE=37.46$, $p=.003$), and left total ($b=82.74$, $SE=39.45$, $p=.040$) hippocampus volumes.
- Greater T1 AUCi predicted smaller left body ($b=-184.51$, $SE=64.00$, $p=.006$) and right body ($b=-207.05$, $SE=45.31$, $pr=-0.52$, $p<.001$) volumes.

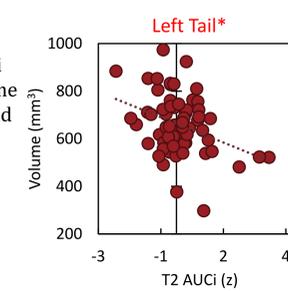
Time 2 Cortisol Reactivity ($n=62$)

T2 AUCg

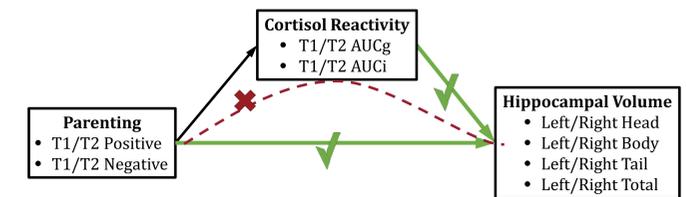


- Greater T2 AUCg and T2 AUCi predicted smaller left tail volume ($b=-30.94$, $SE=14.85$, $p=.041$ and $b=-53.22$, $SE=18.31$, $p=.005$, respectively).

T2 AUCi



Mediation ($ns=56-59$)



Mediation was tested within a multiple regression framework using Hayes' SPSS Process macro for mediation (Hayes, 2013). Separate mediation models were performed with T1 or T2 Positive or Negative Parenting as the predictor, T1 or T2 AUCg or AUCi entered as the mediator, and left or right hippocampal head, body, or tail volume entered as the dependent measure of interest. Significant mediation was not observed for any model.

Discussion

Parenting

- Results suggest both timing-dependent and regionally-specific associations between hippocampal volume and parenting
 - The hippocampal head appears to be more sensitive to early parenting and the hippocampal body may be more sensitive to later, concurrent parenting
 - Greater T1 Positive Parenting is associated with increased head volumes, but greater T2 Positive Parenting is associated with reduced body volumes
 - Moreover, T2 Positive and Negative Parenting appear to be complimentary dimensions, with greater positive parenting associated with decreased body volumes and greater negative parenting associated with increased volumes. This similarity of effects is not evident at Time 1.
- This may suggest that the parenting environment may alter or delay specific regionally-specific developmental mechanisms during this period

Cortisol Reactivity

- At T1, different metrics of cortisol reactivity demonstrate unique associations with regional hippocampal volumes
 - The more cortisol secreted during a stressful event (AUCg) is associated with increased volumes, while larger changes in cortisol secretion at T1 (AUCi) are associated with reduced volumes
- At T2, both AUCg and AUCi are associated with decreased volumes in left hippocampal tail: a finding consistent with what has been proposed in the rodent literature (e.g., Woolley et al., 1990)
- Bilateral hippocampal tails appear to be more sensitive to concurrent (T2) versus early (T1) cortisol reactivity while early (T1) versus concurrent (T2) cortisol reactivity appears to more selectively affect hippocampal body volumes

Limitations & Future Directions

- This study, although longitudinal, only obtained neuroimaging data at Time 2, was underpowered, and was lacking significant variability in many of the independent variables
- Larger longitudinal samples with multiple points of neuroimaging data collection are necessary to replicate and expand upon the present findings
- Future investigations should explore the potential cognitive and affective implications of the observed associations between parenting and cortisol reactivity with hippocampal structure

Acknowledgements

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