Reduced Cortical Thickness Mediates Prospective Associations between Early Life Stress and Externalizing Symptoms in School-Age Children

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BACKGROUND

- Early life stress (ELS) describes the exposure to environmental demands that challenge children's emotional and physical well-being beyond their coping abilities[1].
- Early adversity manifests as severe maltreatment, including physical and emotional abuse or neglect, as well as less severe forms of stress, such as poverty and parental psychopathology.
- While robust evidence supports the deleterious effects of severe ELS on children's neurological and behavioral development, leading to increased risk for chronic health problems in adulthood[1,2],little work has examined how less severe and more common forms of early stress "get under the skin" and impact the development of psychopathology.
- Although less severe forms of stress are often cumulative and chronic, few studies have examined neural mechanisms by which exposure to more common ELS predict higher risk for psychopathology.
- This study prospectively assessed whether 1) ELS predicts reduced brain volume, cortical thickness and increased internalizing and externalizing symptoms in children, controlling for current life stress, and 2) cortical thickness mediates the effects of ELS on behavioral outcomes.

METHODS

Participants: A subset of 63 children from a longitudinal study (32 female) that oversampled offspring of parents with a history of depression[3]; children were first assessed at Wave 1 (W1; ages 3-5 years) and again approximately 3 years later at Wave 2 (W2; 5-9 years).

Procedure: At W1, ELS was assessed and parents completed questionnaires about their child's behavior. At W2, parents completed questionnaires about their child's behavior and current life stress, followed by a neuroimaging assessment.

- Structural MPRRAGE (1mm^3) was collected at the Maryland Neuroimaging Center using a 12-channel coil in a Siemen's 3T scanner. Images were automatically segmented using Freesurfer Version 5.1.0[4]. Resulting segmentations were visually inspected and edited for major errors.

W1 assessment (3-5 years)

***Early life stress index*: scores range from 0 (no stress) to 6 (high stress)**

1. Single parent household (1=present)
2. Low parental education (1=neither parent with a four-year college degree)
3. Low family income (1=income< $40,000)
4. High levels of observed parental hostility (1=hostility score≥2 standard deviations above the mean)
5. Child exposure to parental depression (1=child exposed to parental depression from birth to the W1)
6. Child experienced ≥ 4 stressful life events in the 12 months prior to W1.

Child Behavior Checklist (CBCL) ages 1.5-5 years: Internalizing and externalizing symptom scales

W2 assessment (5-9 years)

Total brain volume: Total gray matter volume, Intracranial volume

Cortical thickness: Right and left fusiform and superior parietal cortical thickness *These regions were selected based on previous work demonstrating their relations to ELS and psychopathology[1,2].

CBCL 6-18 years: Internalizing and externalizing symptom scales

Preschool Age Psychiatric Assessment (PAPA): current life stress

Mediation analyses:

- Conducted using Andrew Hayes' PROCESS Macro in SPSS.
- Each model included: W1 ELS as the IV, ELS-predicted brain volume or thickness as the mediator, W2 behavior as the DV. Covariates included W1 behavior, child sex, W2 child age, W2 Intracranial volume, and W2 current stress.

RESULTS

Table 1. Sample characteristics (n=63)

	Wave 1		Wave 2	
Child mean age: years SD; range	4.23 (.84)	3-5.96	7.19 (.89)	5.57-10
Mother's mean age: years SD; range	35.65 (6.57)	21-50	39.14 (6.41)	24.98-53.38
Father's mean age: years SD; range	37.72 (6.97)	23-54	42.30 (6.08)	31.08-54.87
Child sex: female n (%)	32	(50.8)		
Child race: n (%)				
White	30	(47.6)		
Black/African-American	22	(35.9)		
Multi-racial/Other	9	(14.2)		
Child Hispanic/non-Hispanic ethnicity: n (%)	9	(14.3)		
Biological parents' marital status: n (%)				
Married	38	(60.3)		
Divorced, separated, or widowed	6	(9.5)		
Never married	19	(30.2)		
Early Life Stressors				
Mean early life stress Index: SD; range	1.52 (1.24)	0-6		
Single parent household: n (%)	16	(25.4)		
Neither parent attended college: n (%)	17	(27)		
Household income < $40,000: n (%)	7	(11.1)		
>4 stressors in past 12 months: n (%)	18	(28.6)		
Child exposure to parental depression: n (%)	31	(49.2)		
Mother	25	(39.7)		
Father	6	(9.5)		
Parental hostility ≥ 2 SDs above the mean: n (%)	7	(11.1)		

Table 2. Correlations among key study variables; *p<.05, **p<.01

Variables	1	2	3	4	5	6	7
1. Right fusiform thickness	-						
2. Right superior parietal thickness	.49**	-					
3. Left fusiform thickness	.70**	.53**	-				
4. Left superior parietal thickness	.58**	.79**	.60**	-			
5. Total gray volume	.51**	.45**	.55**	.36**	-		
6. W2 Externalizing symptoms	-.39**	-.26*	-.24	-.34**	-.17	-	
7. W2 Internalizing symptoms	-.05	-.09	-.01	.09	-.06	.46**	
8. Early life stress	-.41**	-.39**	-.28*	-.26*	-.33**	.09	-.04

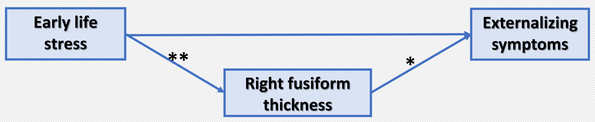

Figure 1. Mediation Model: Early life stress indirectly predicts externalizing symptoms through right fusiform cortical thickness, *b* [10,000 bootstrapped samples]=.38, *SE*=.24, 95% CI [.02, .94].

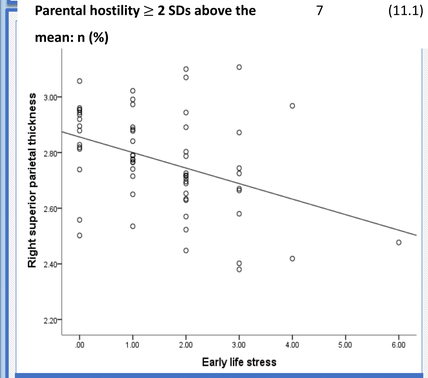

Figure 2. Early life stress predicted reduced right superior parietal thickness, controlling for child sex, W2 child age, and intracranial volume, *b*=-.04, *SE*=.017, *β*=-.289, *p*=.018 (with current stress: *p*=.052).

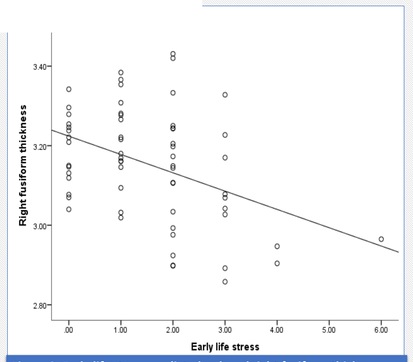

Figure 3. Early life stress predicted reduced right fusiform thickness, controlling for child sex, W2 child age, intracranial volume, and W2 current stress, *b*=-.035, *SE*=.013, *β*=-.310, *p*=.01.

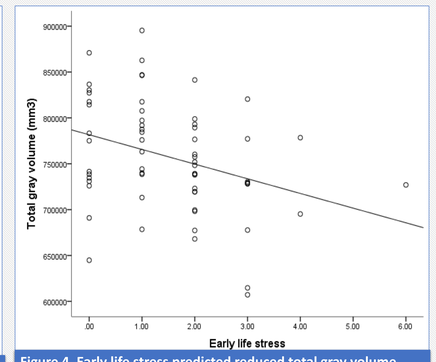

Figure 4. Early life stress predicted reduced total gray volume, controlling for child W2 age and current stress, *b*=-15953.02, *SE*=6194.70, *β*=-.33, *p*=.013.

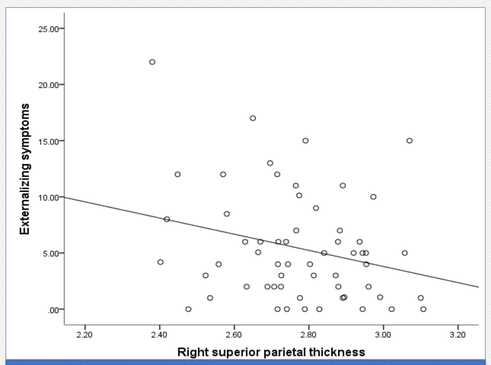

Figure 5. Right superior parietal thickness was concurrently negatively associated with W2 externalizing symptoms, *b*=-7.19, *SE*=3.53, *β*=-.26, *p*=.046. This result did not remain when controlling for covariates or current stress.

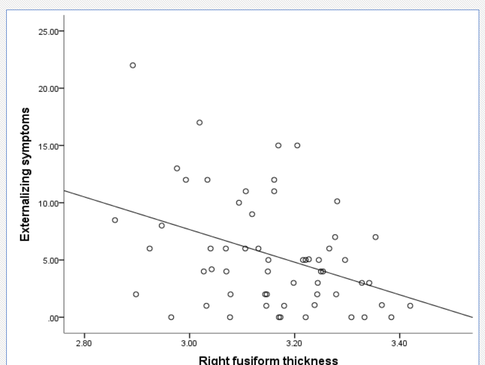

Figure 6. Right fusiform thickness was concurrently negatively associated with W2 externalizing symptoms, controlling for W1 externalizing symptoms, child sex, W2 child age, and intracranial volume, *b*=-10.59, *SE*=4.56, *β*=-.30, *p*=.024.

DISCUSSION

- ELS predicted reduced total gray volume and cortical thickness in the right fusiform and superior parietal cortex in school age children, over and above the influence of current stress.
- Reduced right fusiform thickness mediated the effects of ELS on externalizing symptoms 3 years later, over and above current stress.
- No other regions mediated the effects of ELS on externalizing or internalizing symptoms.
- This is the first study to examine the neural mechanisms, and specifically cortical thickness, linking a multifaceted combination of common early stressors and psychological symptoms in young children.
- Results highlight the important role that timing of stress exposure has on neural and behavioral development; specifically, that earlier stressors may predict poorer outcomes than later stressors, even within childhood.
- Findings suggest that the preschool years may be a particularly important time for early intervention efforts to mitigate the risks that early stressful environments pose on child development.

LIMITATIONS

- Brain data was only collected at W2; thus, we could not examine whether ELS predicted *changes* in neural outcomes.
- The subsample of participants who completed an MRI scan was relatively small, yet comparable to other published studies; results require replication.

FUTURE DIRECTIONS

- Future studies should examine whether common stressors predict changes in total brain volume and cortical thickness, as well as whether these changes in cortical thickness mediate the effects of ELS on psychological symptoms in children.
- Given that cortical thickness may serve as a widespread indicator of dysfunction resulting from ELS, this research should be expanded to other neural indicators such as large-scale brain networks at rest and during functional tasks to better understand the effects of ELS on the brain and behavior.

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