Relationship Between Early Life Stress and Pubertal Development in Structural Brain Development of Post-Institutionalized Adolescents

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Introduction

How do early life stress and puberty jointly impact brain development in children adopted internationally from institutional care?

Recent studies have highlighted the relationship between variation in pubertal timing and structural brain development in typically developing children and adolescents.

- *Sex steroid receptors* are present widely through the brain, including in the *prefrontal cortex* and *limbic areas* (Finley & Kritzer, 1999; Simerly et al., 1999)
- Reductions in *prefrontal cortex* gray matter volume occur earlier for females than males and are related to hormone levels and pubertal status (Giedd et al, 1999; ; Peper & Bower et al., 2009; Pepper & Schnack et al., 2009; Shaw et al., 2008; Sowell et al., 2003; Sowell et al., 2004)
- Changes in *limbic system* regions, including *amygdala* and *hippocampal* volumes, are correlated with hormone levels and pubertal status, although this may be sex-specific and results have varied across studies (Blanton et al., 2012; Bramen et al., 2011; Hu et al., 2013; Neufang et al., 2009; Nguyen et al., 2013)

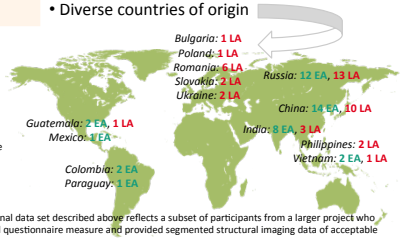
Both pubertal timing and structural brain development are altered as a result of early life stress, including in post-institutionalized (PI) children.

- PI children are *at risk for earlier puberty* and shorter final height in comparison to their non-adopted peers (e.g. Parent et al., 2003)
- Altered white matter organization in *prefrontal cortex* and changes in metabolism and volume of *limbic system* regions are associated with early deprivation (Behen et al., 200; Chugani et al., 2001; Eluvathingal et al., 2006; Govindan et al., 2010; Mehta et al., 2009; Tottenham et al., 2010)

Participants

12-14 year old children either adopted internationally from institutional care or raised in Minnesota with their biological family

Controls	Early Adopted (PI-EA)	Late Adopted (PI-LA)
N = 38 *(18 females)*	N = 42 *(29 females)*	N = 42 *(22 females)*
Not adopted	Adopted before 12 months	Adopted between 13-72 months
• No developmental, neurological, or psychiatric disorders	• No FAS or developmental disorders • At least 50% of pre-adoptive care spent in an institution • Diverse countries of origin	



Demographics: Both PI and control children lived primarily in two-parent families, with most households having at least one parent who had completed college or a graduate level degree. Unlike PI children, control children were predominantly Caucasian.

Excluded Participants: The final data set described above reflects a subset of participants from a larger project who completed both the pubertal questionnaire measure and provided segmented structural imaging data of acceptable quality.

Methods

Puberty Measure: Petersen Self-Rating Scale for Pubertal Development (Petersen et al., 1988)

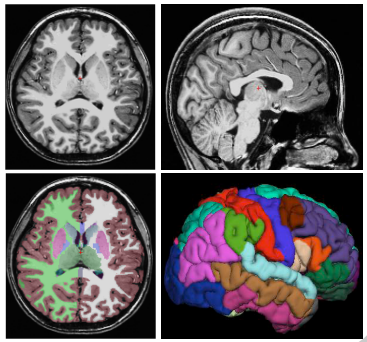
- *Self-report measure* completed by the adolescent, assessing growth in height, growth of body hair, changes in skin, changes in voice (males), growth of facial hair (males), breast development (females) along a 4 point Likert-scale and presence of menstruation (females)
- Reflects changes in adrenal, gonadal, and growth hormones
- Used to create both *continuous and categorical measures of pubertal development* (Petersen et al., 1988)

Structural MRI Scan: T1-weighted 3D MPRAGE anatomical series acquired on a Siemens 3T Trio Scanner

- TR = 2530 ms, TE = 3.56 ms, FOV = 256 mm, flip angle = 7 degrees
- slice thickness = 1 mm, 240 sagittal slices

MRI Analyses: Freesurfer Image Analysis Suite was used to obtain automated, volumetric segmentation data for subcortical and cortical structures

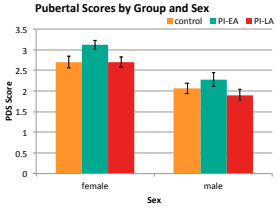
- Segmentations were visually inspected for quality
- Volumetric analyses adjusted for total intracranial volume
- All analyses included age and gender as covariates

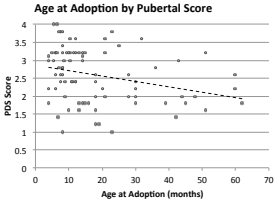


Pubertal Development

PI children report altered pubertal timing.

- *Sex effects?* Females reported more advanced puberty
- *Group effects?* EA children reported more advanced puberty
- *Interaction?* Sex differences were equivalent across groups
- Within the PI group, older age at adoption was associated with less advanced pubertal status, $r = -.29$, $p < .01$





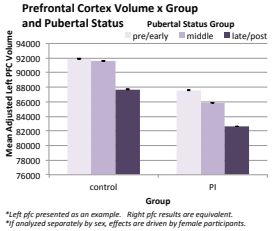
Structural Brain Development

Previously, our group has reported alterations in structural brain development in a similar sample of PI youth, including…

- *Reduced prefrontal cortex gray matter volume* in PI children
- *Reduced hippocampal volume*, especially in LA children
- No group differences in amygdala volume

Stress, Puberty & Brain Development

Prefrontal Cortex Gray Matter Volume



*Left pfc presented as an example. Right pfc results are equivalent.
*If analyzed separately by sex, effects are driven by female participants.

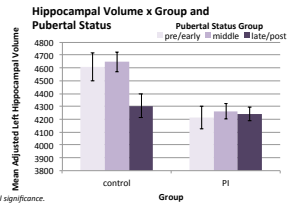
PI and control children both show decreases in prefrontal cortex volume as pubertal status increases.

- *Group effects?* PI children show reduced volume
- *Pubertal effects?* Volume decreases with puberty
- *Interaction?* Effects of puberty are equivalent across groups

Hippocampal Volume

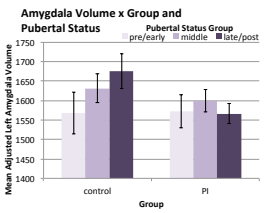
Only control children show puberty-related changes in hippocampal volume.

- *Group effects?* PI children show reduced volume
- *Pubertal effects?* Volume decreases with puberty
- *Interaction?* Only control children show puberty-related changes



*Left hippocampus presented as an example. Right hippocampus at trend level significance.
*If analyzed separately by sex, effects are driven by male participants.

Amygdala Volume



Joint effects of pubertal and/or group status were not present in the amygdala.

- *Group effects?* Non-significant
- *Pubertal effects?* Non-significant trend toward increasing volume with pubertal status, driven by control children

*Left amygdala shown as example. Right amygdala results are also non-significant.
*If analyzed separately by sex, still no significant effects.

Conclusion

Early life stress may alter the trajectory of normative, puberty-specific changes in brain development for PI youth.

Reports of altered pubertal timing in PI children were replicated in this diverse sample of PI children.

- *More advanced pubertal development* was present in adoptees who spent less time (<12 months) in institutional care

We expanded on previous literature reporting differences in structural brain development of PI youth.

- Although *PI youth have smaller prefrontal cortices*, they show *normative decreases in volume* associated with pubertal development
- *PI youth do not show normative, pubertal related changes in hippocampal volume*

Future directions. A better understanding of *catch-up growth*, *ethnicity* effects, and *longitudinal change* will help explain how early life stress, pubertal timing, and brain development are related in this sample, and how **these factors may relate to the heightened risk of behavioral and emotional problems in PI adolescents**.

Acknowledgments This research was supported by a NIMH Grant to Megan R. Gunnar and Kathleen M. Thomas (P50-MH79513, Project II), a University of Minnesota Graduate School Fellowship Award (Amanda S. Hodel), the NIH under a Ruth L. Kirschstein National Research Service Award (T32-HD007151 to Amanda S. Hodel), the University of Minnesota Center for Neurobehavioral Development (T32-MH73129), and the University of Minnesota Center for Magnetic Resonance Research (P41-RR008079, P30-NS057091, MIND Institute). The authors thank collaborators at the Center for Brain, Gene, and Behavioral Research Across Development located at the Sackler Institute for Developmental Psychobiology, as well as members of Kathleen M. Thomas' Cognitive Developmental Neuroimaging Lab and Megan R. Gunnar's Human Developmental Psychobiology Lab for assistance with participant recruitment, scheduling, and testing.