Early Life Adversity Increases Risk for Posttraumatic Chronic Pain via Enduring Hippocampal Changes: Preliminary Evidence from the AURORA Cohort and a Reverse-Translated Rodent Model

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INTRODUCTION

Traumatic stress exposures (TSE) affect >90% of individuals in their lifetime. [1] While most individuals recover following TSE, a substantial subset develop chronic pain. [2, 3] In a previous study, we showed that early life adversity (ELA) substantially increased vulnerability to a related type of chronic pain.[4]

Functional changes to neurochemical stress pathways (e.g. glucocorticoid signaling) are also purported to play a significant role in risk for pain development follow ELA and TSE.[5]. Our previous work has shown that the relationship between ELA and chronic pain is dependent on both hippocampal volume and *FKBP5* (a regulator of glucocorticoid signaling) risk alleles.[4]

AIMS

We conducted preliminary analyses to A) replicate our previous results connecting early life stress and chronic pain development using a large longitudinal cohort study of TSE survivors (the AURORA study[6]) and to B) establish a back-translated animal model of chronic pain following ELA in which we could later test FKBP5 inhibition as a pain preventative. For the analysis of rat function MRI data, we hypothesized that the hippocampus would show altered connectivity with the prefrontal cortex and amygdala, like previous reports in ELA[7-9] and pain[10].

METHODS

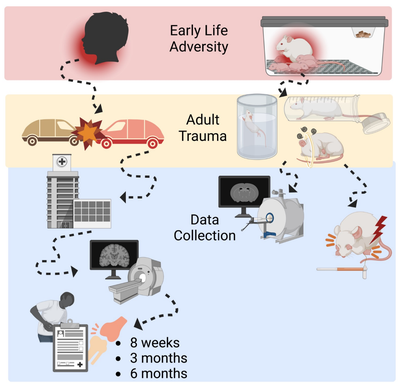


FIGURE 1 Overview of data collection. left panel: humans; right panel: rats.

Data Collection(**Figure 1**).

Human cohort study: We used MRI and pain data from the AURORA[6] (n=2942), a longitudinal study that enrolled participants in the emergency department within 72 hours of TSE. ELA was assessed at the ED timepoint via the childhood trauma questionnaire (CTQ) [11] and two SCID-IV[12] bullying questions. Pain (0-10 NRS[13]) was assessed in the ED and six months following TSE. A subset of study participants (n=413) completed a 3T MRI scan 2 weeks following enrollment.

Rat study: At birth, Sprague Dawley pups were assigned to neonatal limited bedding (NLB)[14] or control groups. At postnatal day 100, n=10 controls and n=10 NLB rats were scanned in a Bruker 9T MRI. On postnatal day 125, we tested paw withdrawal threshold (n=18 controls and n=24 NLB) using von Frey before and after exposing the animals to the single prolonged stress (SPS) model of TSE.[15]

Data analysis. Humans: A repeated measures linear mixed model tested for main effects and interactions between CTQ and hippocampal structure on chronic pain severity (8 weeks, 3 months, and 6 months after TSE) . We used multiple regression to test which CTQ subscore was the strongest (β) predictor of chronic pain development.

Rats: We conducted right hippocampal seed-based functional connectivity analysis. A two-sample t-test identified significantly different voxels between control and NLB animals. A threshold of 40 voxels was used to identify significant regions of connectivity. The effect of NLB and SPS on paw withdrawal was tested using two-way ANOVA.

RESULTS

TABLE 1. Baseline characteristics of the full AURORA cohort (n=2942) and the subset of participants with MRI data (n=413).

	Full AURORA Cohort	AURORA MRI Cohort
Female	**n**=1818/2942 (61.79%)	**n**=256/413 (61.98%)
Age	**mean**=35.90 (**sd**=13.29)	**mean**=34.49 (**sd**=13.06)
Race	**n (%)**	**n (%)**
Hispanic	342 (11.67%)	67 (16.30%)
Non-Hispanic White	1020 (35.00%)	138 (33.60%)
Non-Hispanic Black	1458 (50.00%)	188 (46.00%)
Other	111 (3.80%)	18 (40.00%)
Education (Highest Grade)	**n (%)**	**n (%)**
Less than HS	339 (11.60%)	30 (7.30%)
HS Graduate	778 (26.50%)	115 (28.00%)
Some college	1194 (40.70%)	167 (40.00%)
College graduate	623 (21.23%)	101 (24.00%)
Early life adversity	**mean (SD)**	**mean (SD)**
CTQ Total Score (out of 52)	9.90 (10.20)	9.50 (9.79)
Physical Abuse (out of 8)	1.58 (2.31)	1.71 (2.47)
Sexual Abuse (out of 12)	1.95 (3.37)	1.88 (3.22)
Emotional Abuse (out of 8)	2.59 (2.64)	2.64 (2.67)
Physical Neglect (out of 8)	1.54 (2.14)	1.66 (2.16)
Emotional Neglect (out of 8)	1.95 (2.36)	2.06 (2.33)
Bullying (out of 8)	2.99 (2.37)	2.96 (2.34)

SD=standard deviation, HS=high school, CTQ=childhood trauma questionnaire

TABLE 2. β estimates and significance values for each CTQ subscore and bullying. Each subscore was tested as a continuous variable indicating frequency of the experience and as a dichotomous variable indicating whether the subtype was ever experienced. Bullying, Physical, and Emotional Abuse were top 3 predictors of pain intensity. Only Bullying (SCID-IV "how often did other kids call you names or say mean things" and "how often did other kids threaten to hurt you") was significant in the MRI cohort.

		Full AURORA Cohort		MRI AURORA Cohort	
CTQ Subscore	variable type	β	*p*	β	*p*
Physical Abuse	frequency	***1.620***	***<0.001****	0.819	*0.287*
	dichotomous	0.468	*0.007**	0.389	*0.408*
Sexual Abuse	frequency	1.069	*0.003**	1.450	*0.125*
	dichotomous	0.460	*0.024**	0.054	*0.913*
Emotional Abuse	frequency	***1.603***	***<0.001****	0.868	*0.164*
	dichotomous	0.490	*0.004**	0.849	*0.052*
Physical Neglect	frequency	0.118	*0.730*	0.520	*0.552*
	dichotomous	0.670	*<0.001**	0.677	*0.121*
Emotional Neglect	frequency	0.374	*0.245*	1.167	*0.158*
	dichotomous	0.376	*0.041**	0.075	*0.868*
Bullying	frequency	***2.010***	***<0.001****	***2.105***	***0.002****
	dichotomous	0.097	*0.612*	0.207	*0.676*

* represents a significant result, p<0.05, bold values are the top 3 predictors of pain

FIGURE 2. Pain intensity 6 months after a traumatic event by CTQ tertile Higher self-reported CTQ scores were associated with increased pain intensity 6 months after TSE. Those with the top 1/3 of CTQ scores, report significantly greater pain when compared to either the bottom or middle 1/3 of CTQ scores.

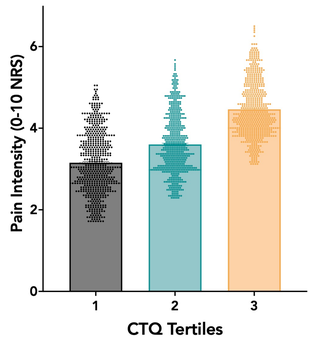
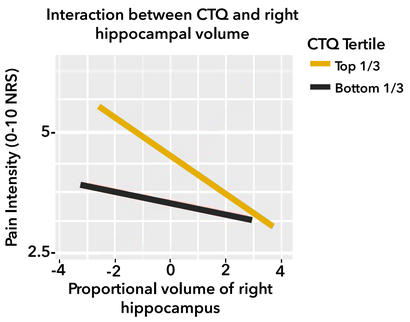


FIGURE 3. Interaction between CTQ and right hippocampal volume on pain intensity. Right hippocampal volume significantly moderates the effect of CTQ on pain intensity (t=-2.416, *p*=0.016). Individuals reporting the most ELA (i.e. top 1/3) exhibit a stronger negative relationship between pain intensity and hippocampal volume, as compared to those who reported the least ELA (i.e. bottom 1/3).



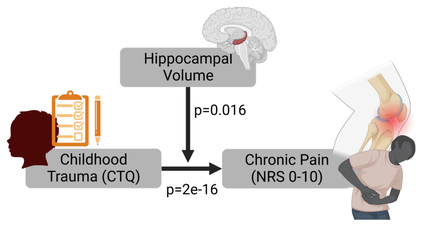


FIGURE 4. von Frey measurement of paw withdrawal threshold (PWT) at baseline and following single prolonged stress (SPS) in neonatal limited bedding (NLB) and control rats. At baseline NLB male animals have a lower PWT, though it was not a significant difference (t (13.75)=1.76, *p*=0.101). A traumatic event (i.e. SPS) causes the same magnitude of change in PWT regardless of NLB, but NLB animals exhibit significantly reduced PWT for a longer duration. Female animals exhibit a similar pattern of PWT though NLB females recover to baseline more quickly than males.

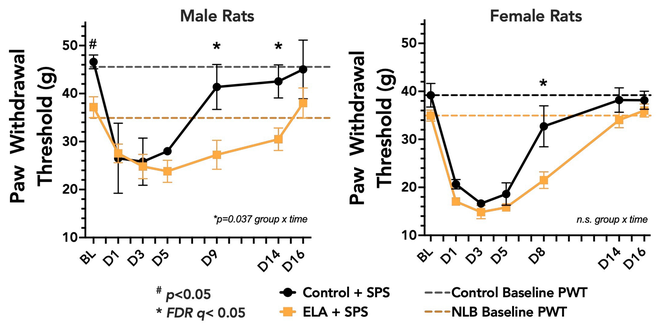
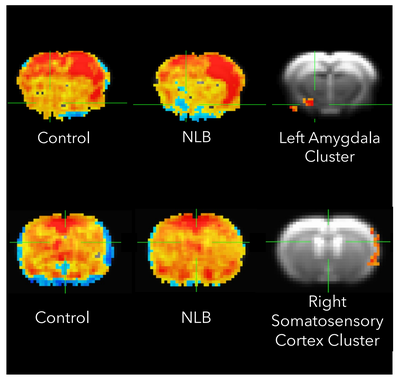


FIGURE 5. Hippocampal seed-based resting state functional connectivity in rats with and without NLB. NLB rats exhibit decreased connectivity between the right hippocampus and left amygdala (41 voxels, p<0.05), and they exhibit increased functional connectivity between the right hippocampus and right secondary somatosensory cortex (75 voxels, p<0.05).



RESULTS SUMMARY:

- In men and women from the AURORA study (n=2,942, **Table 1**), we found that exposure to ELA increases vulnerability to chronic pain after trauma (β=0.99, p<0.001, **Figure 2**).
- Bullying in childhood was the strongest predictor of chronic pain (**Table 2**, β=2.010 p<0.001).
- There was a significant interaction (t=-2.416, p=0.0159) between hippocampal volume and CTQ (**Figure 3**) such that those with the highest reported levels of CTQ exhibited a stronger negative relationship between hippocampal volume and pain intensity than those with the lowest CTQ.
- In rats, ELA + subsequent TSE exposure in adulthood (PND 125) led to a prolonged period of hyperalgesia vs TSE alone (F(6,42)>2.50, p=0.0370, **Figure 4**).
- Preliminary analysis of hippocampal-specific resting state functional MRI data indicated decreased functional connectivity between the hippocampus and amygdala (41 voxels, p<0.05) in ELA exposed rats (consistent with previous ELA literature) and increased connectivity between the hippocampus and the secondary somatosensory cortex (75 voxels, p<0.05) in ELA exposed rats **(Figure 5).**

CONCLUSIONS

- ELA, especially childhood bullying, is a strong predictor of post-TSE pain and hippocampal volume is an important moderator of the relationship between ELA and post-TSE chronic pain.
- In our rodent model, we replicated previously reported functional connectivity alterations involving the hippocampus and extended previous findings by identifying an additional ELA-altered connection to pain processing brain centers.

FUTURE DIRECTIONS

Future studies will explore the role of *FKBP5* changes in the development of chronic pain following ELA as is mediated by changes in the hippocampus.

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