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. While most individuals recover following TSE, a substantial subset develop chronic pain.1,2 In a previous study, we showed that early life adversity (ELA) substantially increased vulnerability to a related type of chronic pain.1,2 Functional changes to neurochemical stress pathways (e.g., glucocorticoid signaling) are also purported to play a significant role in risk for pain development and chronic pain.3 Functional changes to brain connectivity are also related to pain experience.4 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 and pain.5

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)1,2 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 preventive. 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 and chronic pain.

METHODS

Data Collection (Figure 1): Human cohort study: We used MRI and pain data from the AURORA (n=2942), a longitudinal study that enrolled participants in the emergency department in the children’s hospital in 72 hours of TSE. ELA was assessed at the ED timepoint via the childhood trauma questionnaire (CTQ).6 and two SCID-I/IV bullying questions. Pain (0-10 NRS)7 was assessed in the ED and six months following TSE. A subset of study participants (n=131) completed a 3T MRI scan 2 weeks following enrollment.

Rat study: At birth, Sprague Dawley pups were assigned to neonatal limited bedding (NLB)1,2 or control groups. At postnatal day 100, n=10 controls and n=10 NLB rats were snared 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 ELA.5,8

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 predictor of chronic pain (Figure 1).

Rats: We conducted right hippocampal seed-based resting 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 describes the characteristics of the full AURORA cohort (n=2942) and the subset of participants with MRI data (n=131) (n=189). CTQ total scores were associated with increased pain intensity 6 months after TSE. Those with the top 1/3 of CTQ scores, report significantly greater pain compared to those in the bottom or middle 1/3 of CTQ scores (Table 1).

Table 2 shows the average pain intensity (PI) values by CTQ subscore and bullying. Each subscore was tested as a continuous variable indicating the frequency of exposure and as a dichotomous variable indicating whether the subtype was ever experienced. Bullying, Physical, and Emotional Abuse were top 3 factors 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.

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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