Childhood maltreatment is associated with reduced volume in the hippocampal subfields CA3, dentate gyrus, and subiculum

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\textbf{AUTHOR SUMMARY}

Hippocampal vulnerability to the ravages of stress is one of the key translational neuroscience discoveries of the 20th century (1). Several studies have since reported smaller hippocampal size in a host of psychiatric conditions, including major depressive disorder and post-traumatic stress disorder (2). More recently, attention has been focused on the effects of childhood abuse, because consistent reports have emerged of diminished hippocampal volume in adults with maltreatment histories and maltreatment is a risk factor for all the psychiatric disorders associated with reduced hippocampal size. Hence, exposure to severe psychosocial stress during childhood may serve as a unifying mechanism.

Animal studies have shown that the effects of stress or glucocorticoid stress hormones on the hippocampal complex are localized to specific subfields. Stress suppresses neurogenesis in one subfield called the dentate gyrus and provokes the remodeling of parts of the neuron referred to dendrites in another portion called the cornu ammonis (CA), particularly the CA3 subfield (3). An unanswered critical question is whether exposure to childhood maltreatment (or any other stressor) is associated with alterations in the same hippocampal subfields in humans.

This has been a challenging problem. Delineating 3D subfield volumes by hand is an excruciatingly time-consuming and impractical process (4). Recently released FreeSurfer software, however, provides an automated solution (4). Using this method, we predicted a greater statistical relation to maltreatment scores in the CA4-dentate gyrus and CA2-CA3 subfields of the hippocampus than in other components of the hippocampus proper (CA1 or fimbria) or adjacent regions.

Unmedicated, right-handed subjects ($n = 193$, $38\%$ male, $21.9 \pm 2.1$ y of age) recruited from the community were imaged with a 3T Siemens Trio scanner using a high-resolution magnetic prepared rapid acquisition gradient echo sequence. All subjects provided written informed consent to participate in this McLean Hospital Institutional Review Board-approved study. Forty-six percent of the sample had no exposure to childhood adversity as assessed retrospectively by Adverse Childhood Experience (ACE) scores, whereas $16\%$ reported exposure to three or more forms of maltreatment. Clinically, $53\%$ of subjects with ACE scores $\geq 3$ met lifetime criteria for major depressive disorder and $23\%$ met criteria for posttraumatic stress disorder. ACE and Childhood Trauma Questionnaire scores were used to quantify exposure.

6.3% and 6.1% smaller, on average, in subjects with high vs. low maltreatment scores. Lesser but significant group differences were observed in the left subiculum, left presubiculum, and right CA1 regions.

These findings support the hypothesis that the most stress- or glucocorticoid-sensitive hippocampal subfields identified in translational studies are also the most sensitive subfields in maltreated humans. This suggests that early stress may also act in humans to suppress neurogenesis and to provoke remodeling of pyramidal cells (i.e., large neurons in the hippocampus that connect to other parts of the brain). The close anatomical and epigenetic parallels between animal models of early stress and childhood maltreatment support the validity of these models as a means of delineating the pathophysiology of maltreatment-related disorders, which also include substance abuse, psychosis, and personality disorders. This study provides evidence of the potential vulnerability of the subiculum region to childhood maltreatment. This is an interesting finding, given the role of the subiculum in modulating various responses to stress and its potential involvement in drug abuse and psychotic disorders (5).

Fig. P1 shows the percentage of variance in hippocampal subfield volumes accounted for by degree of maltreatment. The strongest and most consistent associations were seen in subfields containing the left dentate gyrus and CA3. Significant associations were also seen in adjacent regions called the left subiculum and presubiculum, and associations of marginal significance were seen in the CA1. The associations were nonsignificant in the fimbria (i.e., a portion of the hippocampus that consists of fiber tracts). Left CA2-CA3 and CA4-dentate gyrus volumes were

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Limitations of the present study include the retrospective assessment of maltreatment and dependence on automated segmentation software providing reproducible measures that are only in moderate agreement with hand measures (4).


