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## Sex differences in resilience to childhood maltreatment: Effects of trauma history on hippocampal volume, general cognition and subclinical psychosis in healthy adults



Erin Samplin <sup>a,b</sup>, Toshikazu Ikuta <sup>a,c</sup>, Anil K. Malhotra <sup>a,c,d,e,f</sup>, Philip R. Szeszko <sup>a,c,e,f</sup>, Pamela DeRosse <sup>a,c,\*</sup>

- <sup>a</sup> Center for Translational Psychiatry, The Feinstein Institute for Medical Research, Manhasset, NY, USA
- <sup>b</sup> Drexel University College of Medicine, Philadelphia, PA, USA
- <sup>c</sup> Division of Psychiatry Research, The Zucker Hillside Hospital, Division of the North Shore-Long Island Jewish Health System, Glen Oaks, NY, USA
- <sup>d</sup> Department of Psychiatry and Behavioral Science, Albert Einstein College of Medicine, Yeshiva University, Bronx, NY, USA
- <sup>e</sup> Hofstra North Shore LIJ School of Medicine, Department of Psychiatry, Hempstead, NY, USA
- <sup>f</sup>Hofstra North Shore LIJ School of Medicine, Department of Molecular Medicine, Hempstead, NY, USA

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#### ABSTRACT

Recent data suggests that a history of childhood maltreatment is associated with reductions in hippocampal volume in healthy adults. Because this association is also evident in adults with psychiatric illness, it has been suggested that reductions in hippocampal volume associated with childhood maltreatment may be a risk factor for psychiatric illness. Such an interpretation suggests that healthy adults with a history of childhood maltreatment are more resilient to the effects of maltreatment. Current models of resilience suggest, however, that resiliency should be measured across multiple domains of functioning. The present study sought to investigate childhood maltreatment in relationship to hippocampal volumes in healthy adults and to address the question of whether the putative resiliency extends to other domains of functioning. Sixty-seven healthy Caucasian adults were assessed for a history of childhood emotional abuse, emotional neglect and physical abuse and received high resolution structural MR imaging scans. Participants with and without histories of abuse or neglect were compared on measures of total hippocampal volume, general cognitive ability and subclinical psychopathology. Our results suggest that childhood emotional abuse is associated with reduced hippocampus volume in males, but not in females. However, emotional abuse was associated with higher levels of subclinical psychopathology in both males and females. These data suggest that while females may be more resilient to the neurological effects of childhood maltreatment, they are not more resilient to the psychiatric symptoms associated with childhood maltreatment. Further research is needed to elucidate the mechanisms involved in these different levels of resilience.

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Stress has been shown to have a substantial impact on the structure and function of limbic structures, particularly the hippocampus. In rodents, early work found that elevating stress-related hormone levels for an extended period reduced the number of neurons in the hippocampus (Sapolsky, 1987) and subsequent work demonstrated that this effect is particularly pronounced during early postnatal development (Brunson et al., 2001; Chen et al., 2004). In humans, evidence for the relation between early-life stress and hippocampal volume derives from studies

E-mail address: pderosse@lij.edu (P. DeRosse).

demonstrating reduced hippocampus volume in adults with a history of childhood maltreatment compared to controls. In most of these studies, however, the study samples were comprised of adults with a psychiatric disorder.

Recently, Teicher et al. (2012) examined the relation between childhood maltreatment and hippocampal volumes in a large, general community sample and found a strong negative correlation between severity of childhood maltreatment and volume of several hippocampal subfields. However, participants in this study were selected without regard to psychiatric history and a large percentage of the sample was found to have a diagnosable psychiatric illness. Specifically, approximately 25% of the sample met criteria for major depressive disorder (MDD), 7% met criteria for posttraumatic stress disorder (PTSD) and approximately 25% met

 $<sup>^{*}</sup>$  Corresponding author. The Zucker Hillside Hospital, North Shore-Long Island Jewish Health System, 75-59 263rd Street, Glen Oaks, NY 11004, USA. Tel.: +17184708601; fax: +17183431659.

criteria for another mood or anxiety disorder. Due to the high percentage of the sample having a diagnosis of a mood or anxiety disorder, it was unclear if the findings indicated a direct relation between childhood maltreatment and reduced hippocampal volumes or between childhood maltreatment and psychiatric illness. The authors attempted to address this issue by conducting a followup analysis using structural equation modeling to evaluate whether a diagnosis of MDD or PTSD mediated the association between childhood maltreatment and subfield volumes. Although the authors found no evidence to suggest that a diagnosis of MDD or PTSD mediated the association between childhood maltreatment and reduced hippocampal volumes, this interpretation could not be entirely ruled out because approximately 25% of the sample that had a diagnosis other than MDD or PTSD were excluded from the mediation analysis. Despite this limitation, however, the authors concluded that the reductions in hippocampal volumes they observed were a consequence of maltreatment and a risk factor for the development of psychiatric illness.

To date only a single study has assessed the relation between a history of childhood maltreatment and hippocampal volume in adult subjects with no history of psychiatric illness. Dannlowski et al. (2012) used voxel-based morphometry to study morphological alterations of the hippocampus in 148 adults with no history of psychiatric illness. These authors found significant negative correlations between right hippocampal gray matter volume and total score, as well as all subscale scores, on the Childhood Trauma Questionnaire (CTQ). These results suggest a direct relation between childhood maltreatment and reduced hippocampal volumes even in individuals with no history of a psychiatric illness. Similar to the conclusions drawn by Teicher et al. (2012), Dannlowski et al. (2012) concluded that reductions in hippocampal volumes in response to childhood maltreatment were likely risk factors for, rather than a feature of psychiatric illness. Such an interpretation suggests that some individuals may be resilient to the long-term consequences of reductions in hippocampal volume resulting from childhood maltreatment.

Generally, resilience refers to an individual's ability to successfully adapt to acute or chronic stress (Feder et al., 2009). A growing literature has recently begun to focus on understanding resilience among people with a history of childhood maltreatment. Among the key developments in this area of research is the recognition that resilience defined by a single outcome measure is inadequate (Afifi and Macmillan, 2011). Current definitions of resilience suggest that it is a dynamic process that may be observed in some domains of functioning but not in others (Walsh et al., 2010) and should be measured across many different phenotypic levels (Feder et al., 2009). Thus, examining the effects of childhood maltreatment on measures of hippocampal volume concurrently with other potential measures of resilience could contribute to a more integrative model of resilience to psychiatric illness.

The present study sought to examine the relationship between childhood maltreatment and hippocampal volume in an adult sample with no history of psychiatric illness. Moreover, we also sought to specifically address whether individuals with a history of childhood maltreatment would show evidence of resilience in other domains of functioning. Specifically, in addition to examining the relation between childhood maltreatment and hippocampal volume, we also assessed the relation between childhood maltreatment and other key domains of functioning, including cognition and subclinical levels of positive, negative and depressive symptoms. Moreover, because resilience often shows robust sex-differences, we sought to assess differences between males and females in all of these domains.

Although the relation between childhood maltreatment and cognitive deficits has not been widely studied in healthy

populations, data suggest that exposure to trauma during childhood may lead to significant deficits in memory and executive function (Majer et al., 2010; Spann et al., 2012). Similarly, although a limited number of studies have examined the relation between childhood maltreatment and subclinical positive, negative and depressive symptoms in healthy populations, a recent metaanalysis indicated that individuals exposed to childhood stress or trauma were 2 times more likely to report subclinical psychotic experiences (including positive, negative and depressive symptoms) than those without such histories (Linscott and van Os, 2010). Combined with data demonstrating significant relations between childhood maltreatment and cognitive deficits in patients with psychiatric illness (Aas et al., 2012) and the plethora of data demonstrating the relation between childhood maltreatment and psychiatric illness, these domains are ideal candidates for the present study. Finally, a considerable body of data suggests that females may be more resilient to the effects of stress than their male counterparts. Several studies conducted in PTSD suggest that maltreated males may show more evidence of adverse brain development than maltreated females (De Bellis et al., 1999, 2002; De Bellis and Keshavan, 2003). Thus, the present study also sought to assess whether sex differences could be observed in any of our primary dependent measures.

#### 1. Method

#### 1.1. Participants

Caucasian healthy volunteers (30 males, 37 females,  $M_{\rm age} = 36.94 \pm 14.77$ ) were recruited from the general population via word of mouth, newspaper and internet advertisements and posted flyers. All participants provided written informed consent to a protocol approved by the Institutional Review Board of the North Shore-Long Island Jewish Health System. Participants were excluded from the study if they had an Axis I diagnosis, active or recent substance abuse, a first-degree relative with a known or suspected Axis I disorder, based on family history questionnaire, contraindications to magnetic resonance imaging, prior psychosurgery and pregnancy. The sample used in the present study represents a subset of a larger healthy volunteer sample and were selected based on the availability of MRI data.

#### 1.2. Clinical assessments

#### 1.2.1. Diagnostic rule-out

Participants were initially administered the Structured Clinical Interview for DSM-IV, Non-Patient edition (SCID-I/NP) to rule out a past or present Axis I psychiatric disorder (First et al., 2002). Information obtained from the SCID was compiled into a narrative case summary and absence of pathology was determined by two expert diagnosticians from the ZHH faculty.

#### 1.2.2. History of childhood maltreatment

To assess the history of childhood maltreatment we utilized the 28-item Childhood Trauma Questionnaire (CTQ; Bernstein et al., 2003). The CTQ is a 5-point Likert-type self-report questionnaire that measures several dimensions of abuse and neglect during childhood including physical abuse (PA), emotional abuse (EA) and sexual abuse (SA) as well as emotional neglect (EN) and physical neglect (PN). Examination of the CTQ scores in the present sample revealed that none of the dimensional scores were normally distributed and thus, not amenable to investigation using parametric tests. Therefore, participants were dichotomized into maltreatment positive and negative groups on each subscale. Group assignment was based on whether or not they endorsed any

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