Limbic scars: Functional and structural MRI reveal long-term consequences of childhood maltreatment

Harald Kugel[1], Anja Stuhrmann[2], Victoria Beutelmann[2], Peter Zwanzger[2], Thomas Lenzen[2], Dominik Grotegerd[2], Katharina Domschke[2], Christa Hohoff[2], Patricia Ohrmann[2], Jochen Bauer[2], Christian Lindner[2], Christian Postert[2,3], Carsten Konrad[4], Walter Heindel[1], Volker Arolt[2], Thomas Suslow[5], and Udo Dannlowski[2]

[1]Department of Clinical Radiology, University of Muenster, Muenster, NRW, Germany, [2]Department of Psychiatry, University of Muenster, Muenster, NRW, Germany, [3]Department of Child and Adolescent Psychiatry, University of Muenster, Muenster, NRW, Germany, [4]Department of Psychiatry, University of Marburg, Marburg, HE, Germany, [5]Department of Psychosomatic Medicine and Psychotherapy, University of Leipzig, Leipzig, SN, Germany

Introduction: Childhood maltreatment is a strong risk factor for the development of depression and posttraumatic stress disorder (PTSD) in later live (1). Endocrinological studies have shown that childhood maltreatment causes lasting changes in the hypothalamic-pituitary-adrenal (HPA) axis responsiveness to stress (2). In this study, the neurobiological bases of these associations were investigated with fMRI and voxel-based morphometry. Both, depression and PTSD have been associated with increased amygdala responsiveness to emotionally negative stimuli (3,4) as well as reduced hippocampal gray matter volume (5,6), therefore we speculated that childhood maltreatment results in similar functional and structural alterations in previously maltreated but now healthy adults.

Methods: 148 healthy subjects were enrolled via public notices without direct reference to childhood maltreatment and fully screened for psychiatric disorders. Amygdala responsiveness was measured using functional MRI with an emotional face-matching paradigm particularly designed to activate the amygdala in response to threat-related faces (7). During 4 blocks, the task was to view a trio of faces (angry or fearful (8)) projected onto a screen at the rear of the scanner and to select one of two faces at the bottom, which was identical to the face at the top. Alternating 5 control blocks were shown, depicting trios of geometric shapes. Each of the trios was presented for 4 s, with mean interstimulus interval of 4 s for the faces, and 2 s for the geometric shapes. Accuracy and reaction time was recorded. fMR data were acquired at 3 T (Philips Gyroscan 3.0T) with whole brain single shot EPI, cubic voxels with 3.6 mm edge length, TR/TE/FA = 2.1 s/30 ms/90 deg., tilted 25 deg. from the AC/PC line to minimize drop out artifacts in the orbitofrontal and mediotemporal region. Data were evaluated using SPM8 applying a mask created for the amygdala (9,10). First, activation in response to fear relevant faces in contrast to the shapes baseline was determined, resulting contrast images were then analyzed against CTQ scores. In addition, for voxel-based morphometry T1w high-resolution anatomical images were acquired using a 3D fast gradient-echo sequence ("TFE", TR/TE/FA = 7.4 ms/3.4 ms/9 deg., inversion prepulse every 815 ms, cubic voxels .5 mm edge length), normalized to MNI-space, using VBM8 and appropriate toolboxes. Childhood maltreatment was assessed by the 25-item childhood trauma questionnaire (CTQ, in German (11)).

Results: There was no association of CTQ-scores and any behavioral measure. We observed a strong association of CTQ-scores with amygdala responsiveness to threat related facial expressions, p = .001 (FWE-corrected), r = .46, cluster size k = 64 (Fig. 1). The morphometric analysis restricted to the hippocampus (9) showed reduced gray matter volumes with high CTQ-scores in the right hippocampus, p(FWE-corr.) .001, r = -.37, cluster size k = 102. In a supplementary whole brain analysis, also reduced gray matter of insula, orbitofrontal cortex, anterior cingulate gyrus, and caudate was found in subjects with high CTQ. These associations were not influenced by trait anxiety, depression level, age, intelligence, education, or more recent stressful life events.

Conclusions: Childhood maltreatment is associated with remarkable functional and structural changes even decades later in adulthood. These changes strongly resemble findings described in depression and PTSD. Therefore, the present results might suggest that limbic hyper-responsiveness and reduced hippocampal volumes could be mediators between the experiences of adversities during childhood and the development of emotional disorder.

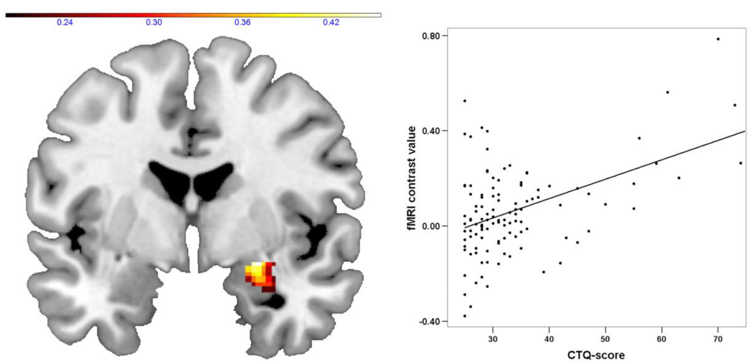

Fig. 1: Childhood maltreatment (CTQ-scores) is positively associated with right amygdala responsiveness to negative facial expressions. Left: Coronal view (y=-2) depicting amygdala responsiveness modulated by CTQ-scores. For display, threshold p < .01, uncorrected. Color bar indicates correlation coefficient **r**. Right: positive correlation (**r**=0.456, p<0.0001) of the mean cluster activation values (left panel) and CTQ scores.

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