Hippocampal atrophy in major depression – rather a function of childhood maltreatment?

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Introduction: Reduced hippocampal volumes are probably the most frequently reported structural neuroimaging finding associated with major depressive disorder (MDD)[1,2]. It remains unclear, however, whether altered hippocampal structure represents a risk factor for or a consequence of MDD[3]. There is an ongoing discussion about the influence of traumatic events like maltreatment during childhood on structural alterations of the limbic system. Reduced hippocampal volumes were consistently reported in subjects affected by childhood maltreatment[4,5]. Since the prevalence of childhood maltreatment is highly elevated in MDD populations, previous morphometric findings regarding hippocampal atrophy in MDD therefore might have been confounded by maltreatment experiences. The aim of this study was to differentiate the impact of childhood maltreatment from the influence of MDD diagnosis on hippocampal morphometry.

Methods: 85 depressed patients (DSM-IV criteria[6]; 34 m, 51 f, 37.2±11.8 yrs) as well as 85 age- and sex-matched healthy controls (31 m, 54 f, 37.6±12.0 yrs) underwent structural MRI at 3 T (Gyroscan Intera 3.0T, Philips, Best, NL) (T1w high resolution anatomical images: 3D Turbo-Field Echo, TR/TE/FA 7.4 ms/3.4 ms/9°, inversion prepulse every 814.5 ms, 2 signal averages, FOV 256 mm (fh) x 204 mm (ap) x 160 mm (lr), phase encoding in ap and rl direction, reconstructed to cubic voxels of .5 mm edge length). The Childhood Trauma Questionnaire (CTQ)[7] was administered to estimate experiences of childhood maltreatment. Hippocampal volume and surface structure was examined by the use of two independent methods, automated segmentation (FSL-FIRST) and voxel-based morphometry (VBM8). The first method uses pre-defined anatomical landmarks to delineate the hippocampus boundaries to obtain volume and shape information[8], while the latter focuses on gray matter structure after segmentation of gray matter across the whole brain and normalization to a template[9-11]. Both methods are highly reliable and sensitive for hippocampus morphometry[12].

Results: In line with existing studies, MDD patients showed reduced hippocampal volumes both evaluated with FSL-First (and ANCOVA with patients vs. controls as between-subjects factor) and VBM8 (Group statistics using SPM8). In addition, as expected, childhood maltreatment was consistently associated with hippocampal volume loss in both, patients and healthy controls (e.g. FSL-FIRST; patients: left, r=-.297, p=.007/right, r=-.283, p=.01; controls: left, r=-.245, p=.025/right, r=-.252, p=.021). However, when additionally controlling for CTQ scores (CTQ-score as additional covariate in ANCOVA with FSL-FIRST data, CTQ-score added as nuisance regressor to the design in SPM8), group differences could no longer be observed (Fig. 1).

Conclusion: While comparing patients with healthy controls resulted in a smaller hippocampal volume in patients, no significant morphological differences between patients and controls could be analyzed if maltreatment experience was regressed out. Regarding the strong morphometric impact of childhood maltreatment and its distinctly elevated prevalence in MDD populations, this study provides an alternative explanation for frequently observed limbic structural abnormalities in depressed patients. Our results suggest that hippocampal alterations in MDD patients may at least partly be traced back to traumatic experiences occurring in early-life, and this effect can be also detected in volunteers, who are healthy at the time of examination.

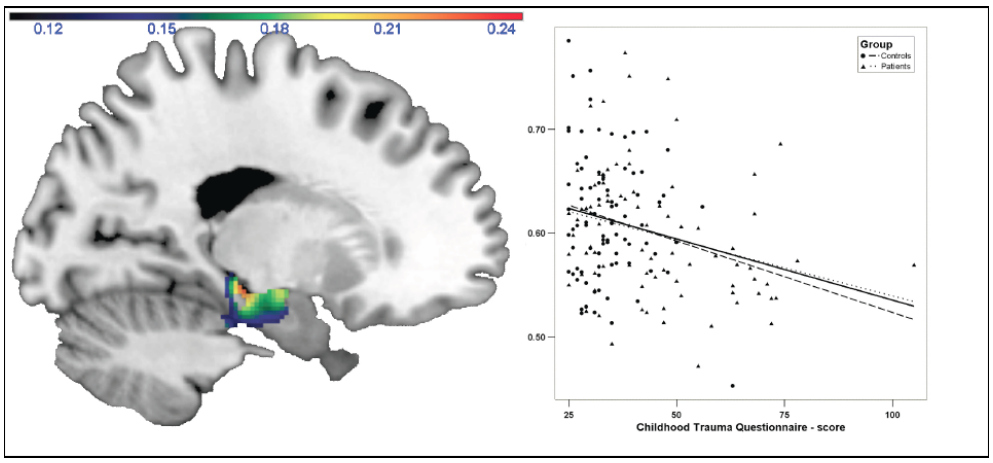

Fig 1: Effect of childhood maltreatment on hippocampal gray matter volume in the entire study sample.
Left: Coronal view (x=-14) depicting left hippocampus gray matter volume negatively associated with CTQ-scores; color bar, negative correlation coefficient *r*.
Right: Scatter plot depicting gray matter volume at x=-14, y=-10, z=-24 correlated with CTQ-scores; dotted line, regression slope of controls; dashed line, regression slope of patients; solid line, regression slope of both groups combined (r=-.26, p=.0003 (result from VBM)).

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