Research report

Life events and hippocampal volume in first-episode major depression

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Abstract

Background: There are many studies on life events in depression and also several studies examining brain structural changes in the hippocampus of depressed patients. However, only few studies have focused on the association of life events and hippocampal volume in depression. The hypothesis of a significant negative association between life events and hippocampal volumes in first episode depression was examined.

Methods: 28 in-patients with a first episode of major depression were examined with high-resolution magnetic resonance imaging measuring hippocampal volumes. The precourse of depression was assessed with the Interview for the Retrospective Assessment of the Onset and Course of Schizophrenia and Other Psychoses (IRAOS) and life events by using the Munich Interview for the Assessment of Life Events and Conditions (MEL).

Results: A significant negative correlation between major life events three month before the onset of depression and the left hippocampal volume was found for male patients. In female patients no significant association between major life events and hippocampal volumes could be found.

Conclusions: The results support the hypothesis that the hippocampus plays a crucial role in the pathogenesis of major depression in the early phase of the disorder particularly for male patients.

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1. Introduction

Structural cerebral abnormalities in limbic-thalamic-cortical networks have repeatedly been found in patients with unipolar depression (Soares and Mann, 1997; Campbell and MacQueen, 2003, 2006). A core
area within these networks is the hippocampus which is involved in memory and emotional regulation deficits that often accompany depression. In meta-analyses, a reduction of the left as well as of the right hippocampal volume could be shown (Videbech and Ravnkilde, 2004; Campbell et al., 2004). Although the hippocampus has been found to be smaller in patients with depression, results are heterogeneous regarding the factors associated with this reduction in hippocampal volumes. One important factor often discussed as associated with the reduction of hippocampal volume in depressed patients is the occurrence of major life events.

Stressful life events are among the major predisposing risk factors for developing depression (Kendler et al., 2000). Depressed patients report higher rates of stressful life events especially affecting interpersonal interactions (Hammen, 2003). Whereas the accumulation of stressful life events before the first onset of depression is undisputed, it is controversially discussed whether the number of life events in patients with recurrent depression decreases as the kindling or sensitization hypothesis states (Post, 1992; Kendler et al., 2000) or whether the number of life events increases, as the stress generation concept (Hammen, 2006) suggests. Therefore, we examined the association of life events and hippocampal volumes in a homogeneous group of patients with a first episode of depression.

Hypercortisolemia has been frequently reported to be associated with life events as well as with major depressive disorder (Young et al., 2001). There are also findings of an association between stress and cortisol-induced damage of hippocampal structures in animal studies (Sapolsky, 2000). This concept suggests that a loss of hippocampal volume might occur as a consequence of repeated stress with associated glucocorticoid excess (Lucassen et al., 2006). Accumulating evidence predominantly from animal models implicates hippocampal neurogenesis in the pathophysiology of depression and that psychosocial stress reduces neurogenesis (Dranovsky and Hen, 2006). Other studies have recently begun to address the hypothesis that structural changes might predispose to depression, because hippocampal size has been found to be highly genetically determined (Schatzberg, 2002a,b; Gilbertson et al., 2002; Frodl et al., 2007).

There are many studies on life events in depression and also several studies examining brain structural changes in the hippocampus of depressed patients. However, only very few studies exist regarding the association of both, life events and hippocampal volumes in depression. Vythilingam and Heim (2002) found a reduction in hippocampal volume only in women with prepubertal abuse whereas postpubertal abuse was not associated with a reduction in volume. Besides these studies on early adverse events, Inagaki et al. (2004) examined first major depressive episodes after breast cancer diagnosis in women. Here, first major depressive episodes after this life event did not appear to be associated with hippocampal volumes. In the studies on the association of depression, life events and hippocampal volumes carried out to date, only women and mainly early adverse life events were examined. The aim of the present study therefore was to examine the relationship between life events and hippocampal volume in first episode depression. The hypothesis was that there is a significant negative correlation between the number of life events before the onset of depression and hippocampal volumes. Additionally, gender effects were examined.

2. Method

2.1. Subjects

Twenty-eight inpatients with DSM-IV (APA, 1994) first episode major depression treated in the Department of Psychiatry of the University in Heidelberg were recruited. The diagnoses were made using a structured clinical interview (SCID) (Wittchen et al., 1997). The mean age of the 16 female and 12 male patients at initial assessment was 45.84 (SD=12.20, 19–64) (see Table 1). Fourteen (50.0%) patients were married. Eight (28.57%) had a high and 20 (71.43%) a low level of school education. Mean score in the 17-item Hamilton Depression Rating Scale (HDRS) (Hamilton, 1960) was 23.97 (SD=6.65) at admission to treatment and 28.23 (SD=11.96) in the Beck Depression Inventory (BDI) (Beck et al., 1961). All patients were receiving an antidepressant medication at the time of the MRI examination. Patients had been

| Table 1: Sociodemographic and clinical characteristics of the sample (N=28) |
|-----------------|-----------------|-----------------|
| **Sex**         | **Female (57%)**| **Male (43%)**  |
| **Age (in years)** | 45.84±12.20 | 45.84±12.20 |
| **Family status**: married | 14 (50.0%) | 14 (50.0%) |
| **Educational level** | 20 (71%) | 8 (29%) |
| **Duration of depression (in weeks)** | 44.81±71.04 | 44.81±71.04 |
| **Psychopathology** | 17-item Hamilton Depression Rating Scale (HDRS) 23.97±6.65 | 23.97±6.65 |
| | Beck Depression Inventory (BDI) 28.23±11.96 | 28.23±11.96 |
| | Antidepressant medication, actual 28 (100%) | 28 (100%) |
| | Psychopharmacological comedication 16 (57.1%) | 16 (57.1%) |
| | Duration of antidepressant medication (in weeks) 22.15±45.61 | 22.15±45.61 |

Note: values are means±standard deviations.
treated with antidepressants for 22.15 weeks (SD=45.61) on average. All the participants were screened for comorbid medical and psychiatric conditions by means of clinical, physical, and neurological examinations. After a complete description of the study was given to the patients, written informed consent was obtained. The study protocol was approved by the local ethics committee and was prepared in accordance with the ethical standards laid down in the Declaration of Helsinki.

2.2. Clinical assessments

For the assessment of the precourse of depression the Interview for the Retrospective Assessment of the Onset and Course of Schizophrenia and Other Psychoses (IRAOS) (Häfner et al., 2003) was used. The IRAOS provides information on prodromal signs, symptoms, functional impairment, social disability and the patient’s social development by means of a time matrix based on anchoring events. Interrater reliability of the IRAOS symptom scale and the onset of depression was satisfactory with intraclass correlation coefficient (ICC) between .73 und 1.00. Life events were assessed by the Munich Interview for the Assessment of Life Events and Conditions, respectively ‘Munich Event List’ (MEL) (Wittchen et al., 1989). The MEL consists of 85 single items including negative as well as positive life events and life situations from many different social areas. Each item was rated regarding duration and severity. Major events are defined as life events rated as severe or very severe on a 5 point scale according to subjective impact (Wittchen et al., 1989; Mundt et al., 2000). By means of the time matrix established with the IRAOS, the number of major events within 3 months prior to the first signs of depression, within 3 months prior to the onset of depression and within 3 months prior to admission to hospital were assessed. Interrater reliability for two independent raters was between .83 and .95.

2.3. MRI procedures and definition of the hippocampus formation

MRI scans of the whole brain were obtained by using a Siemens 1.5-Tesla MR scanner (Siemens Medical Systems, Inc., Erlangen, Germany). T1-weighted three-dimensional magnetization-prepared rapid gradient echo sequences (3D-MPRAGE) were acquired with the following parameters: 124 1.5-mm coronal slices, TR= 11.6 ms, TE=4.9 ms, total acquisition time=9 min, FOV=260 mm, number of acquisitions=1, matrix = 512*512. T2-weighted images were acquired with the following parameters: 2-mm coronal slices, TR=7840 ms, TE=54 ms, total acquisition time=4 min, number of acquisitions=1, FOV=260 mm, matrix = 256×192. Image processing was performed on a computer workstation (Silicon Graphics Inc, Mountain View, Calif) using the BRAINS (Brain Research: Analysis of Images, Networks, and Systems) software package (Andreasen et al., 1992). As part of the segmentation procedure of BRAINS, intracranial volume (ICV), computed as the volume of tissue and CSF contained under the pia matter, was determined semi-automatically. In this study, hippocampal volume was measured by using a reliable and validated method which was previously described in detail by Pantel et al. (2000). The anatomical landmarks and boundaries used for this volumetric method were based on the concise and extensive morphological description given by H.M. Duvernoy in his Atlas of Applied Hippocampal Anatomy (Duvernoy, 1988). The hippocampal formation was traced manually on the continuous segmented image (stereo image) provided by BRAINS. A detailed description of boundary definition is provided at: http://iowa-mhcrc.psychiatry.uiowa.edu/mhcrc/IPLpages/manual_tracing.htm. Interrater reliability for two independent raters was determined using the intraclass correlation coefficient (ICC) for volumetric assessments of the hippocampus in a subgroup of 16 randomly selected subjects. The ICCs were 0.97 for the left hippocampus and 0.98 for the right hippocampus.

2.4. Statistical analysis

Morphometric data of the hippocampus were normally distributed whereas major events and duration of depression were not. Partial correlations (Spearman coefficients) were used to explore the relationship between hippocampal volumes and clinical variables by using age and intracranial volume as covariates. ANOVAs were performed to examine the relationship between gender, course of illness and life events. Results were considered statistically significant if at or below 5% probability level (two-tailed). Analyses were performed with SAS Version 9.12 (SAS Institute, Cary, N.C.).

3. Results

3.1. Early course of depression and major events

The average duration of depression before admission to hospital was 44.81 weeks (SD=71.04) with a median of 15.43 weeks. The average time interval from the first prodromal signs to admission to hospital was 203.91 weeks (SD=416.99) with a median of 51.64 weeks. Twenty-four (85.71%) patients had at
least had one major life event 3 months prior to the first prodromal signs of depression until admission to hospital. On average, patients had 3.18 (SD=2.80) major life events within this time interval. For the number of major life events, no significant differences for male and female patients and no significant age effects were found. Twenty (71.43%) patients had had 1.32 (SD=1.47) major life events on average within 3 months prior to first prodromal signs. Twenty-two (78.57%) patients had had 2.11 (SD=2.41) major life events on average within 3 months prior to admission to hospital. There were no significant age or sex effects for the precourse of depression and the number of major life events. There was also no significant association between severity of depression and the number of major life events.

3.2. Major life events and hippocampal volumes

The average hippocampal volumes for the whole sample were 2.81 cm³ (SD=0.31) for the left and 2.95 cm³ (SD=0.40) for the right hippocampus. No significant differences between female and male patients were found and the cofactors age and intracranial volume were also not significant. No significant correlation between duration of depression and hippocampal volumes was found either. The spearman correlations between the number of major life events and hippocampal volumes are shown in Table 2. In these analyses, partial correlations were computed using intracranial volume and age as covariates. No significant correlations between hippocampal volumes and the number of major life events were found for the total sample and for the female subsample. For male patients however, a significant correlation between the number of major life events 3 months prior to the onset of depression and left hippocampal volume could be found. For the right hippocampus no significant correlations were found for male patients either.

Testing the correlation coefficients for differences between male and female patients revealed significantly different associations of the number of major life events and left hippocampal volume for the time interval 3 months prior to the onset of depression (z=2.27, p=0.02).

4. Discussion

The aim of the study was to examine the relationship between life events and hippocampal volumes in first episode depression. The duration of the illness precourse found in the present study is very heterogeneous but still comparable to that found in other studies (Häfner et al., 2002) and with those of Inagaki et al. (2004) who did not find a change in hippocampal volumes in women with postpubertal life events. Also, in the meta-analyses on hippocampal volume in depression (Videbech and Ravnkilde, 2004; Campbell et al., 2004) it was shown that more studies found a reduction in left than in right hippocampal volume. The authors assumed that changes in left hippocampal volume start earlier in the course of the disorder than changes in right volume. The present results also support the stable finding of life event research that life events taking place within 3 months prior to the onset of depression are more significant than life events in other time intervals. To our knowledge, the present study is the first to show an association between life events and reduction of left hippocampal volume in male patients with first episode depression.

Regarding gender effects, results of structural imaging studies are heterogeneous (Videbech and Ravnkilde, 2004; Campbell et al., 2004; Campbell and MacQueen, 2003, 2006). However, it is well known that the

<table>
<thead>
<tr>
<th>Hipocampal volume</th>
<th>Sample</th>
<th>Major events 3 months before first prodromal signs</th>
<th>Major events 3 months before onset of depression</th>
<th>Major events 3 months before admission to hospital</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total</td>
<td>$r^*$ -0.15 0.45</td>
<td>$r^*$ -0.24 0.25</td>
<td>$r^*$ -0.32 0.11</td>
</tr>
<tr>
<td></td>
<td>Men</td>
<td>$r^*$ -0.28 0.44</td>
<td>$r^*$ -0.51 0.13</td>
<td>$r^*$ -0.25 0.49</td>
</tr>
<tr>
<td></td>
<td>Women</td>
<td>$r^*$ -0.04 0.88</td>
<td>$r^*$ 0.11 0.71</td>
<td>$r^*$ -0.33 0.25</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>$r^*$ -0.17 0.41</td>
<td>$r^*$ -0.27 0.18</td>
<td>$r^*$ -0.33 0.10</td>
</tr>
<tr>
<td></td>
<td>Men</td>
<td>$r^*$ -0.37 0.29</td>
<td>$r^<em>$ -0.67 0.03</em></td>
<td>$r^*$ -0.27 0.45</td>
</tr>
<tr>
<td></td>
<td>Women</td>
<td>$r^*$ -0.03 0.93</td>
<td>$r^*$ 0.17 0.56</td>
<td>$r^*$ -0.26 0.37</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>$r^*$ -0.19 0.36</td>
<td>$r^*$ -0.23 0.27</td>
<td>$r^*$ -0.24 0.24</td>
</tr>
<tr>
<td></td>
<td>Men</td>
<td>$r^*$ -0.21 0.56</td>
<td>$r^*$ -0.42 0.23</td>
<td>$r^*$ -0.20 0.58</td>
</tr>
<tr>
<td></td>
<td>Women</td>
<td>$r^*$ -0.11 0.71</td>
<td>$r^*$ 0.14 0.64</td>
<td>$r^*$ -0.21 0.46</td>
</tr>
</tbody>
</table>

*Intracranial volume and age were used as covariates in partial correlations.
hippocampus volume of healthy men is greater than that of healthy women and that the decrease over the life span is more prominent in men than in women (Pruessner et al., 2001; Lupien et al., 2007). Some recent studies found smaller hippocampal volumes more often in depressive men than in depressive women (Frodal et al., 2002; MacMaster and Kusumakar, 2004). Also for the studied sample a smaller left hippocampal volume compared to a healthy control group was found only for men with a first episode of depression (Kronmüller et al., 2008).

On the basis of the present results it could also be assumed that the reduction in hippocampal volume is increased by life events. Another explanation for the results could be that men have a more stress-sensitive hippocampus compared to women because male patients with a first episode go into treatment later than women do (Piccinelli and Wilkinson, 2000; Möller-Leimkühler, 2002). It can be hypothesised that men have longer periods of untreated depression which could also account for smaller hippocampal volume since treatment of depression may stop hippocampal atrophy and stimulates neurogenesis (Lucassen et al., 2006; Dranovsky and Hen 2006; Sheline et al., 2003).

However, what can only be differentiated by longitudinal data is the question whether the hippocampus volume decreases or increases over the course of depression in relation to life events or whether there are different subgroups of patients that premorbidity differ in hippocampal volumes. It is also possible that differences in brain morphometry are due to genetic influences that simultaneously shape the way people response to stress and their brain structure and function (Gilbertson et al., 2002). In several meta-analyses on posttraumatic stress disorder (PTSD) (Smith, 2005; Kitayama et al., 2005; Karl et al., 2006) it could also be shown that healthy persons without PTSD have a smaller hippocampal volume after a traumatic event when compared to non-traumatized persons. Even smaller hippocampal volumes were found in patients who had developed PTSD after a traumatic event. Thus, critical life events seem to have an influence on hippocampal volume which is independent from the disorder but which is perhaps modified by the illness. Contrary to these result, Cohen et al. (2006) could not find an association of early life events and hippocampal volume in a large sample of healthy persons. Perhaps a depression specific vulnerability is responsible for the effects of life events on hippocampal volume. Also, findings of recent studies challenge the implicit assumption that a smaller hippocampus is associated with several dysfunctions (Van Petten, 2004; Pruessner et al., 2007). Altogether, these results point to a much more complicated association of life events, hippocampus and depression than the neurodevelopmental or the degeneration model of hippocampal volume changes in depression suggested.

The retrospective analysis of the course of depression and life events can not, however, substitute prospective longitudinal studies. Also, the definition of life events might influence the results. Another limitation of the present study is the sample, which is relatively small and includes only in-patients. Moreover, the study did include only patients receiving psychotropic medications. What could also explain the results is the fact that only a linear association of life events and hippocampal volume was examined. However, it is imaginable that the association is a linear one in men but much more complex in women. Nevertheless, the results do support the hypothesis that the hippocampus plays a crucial role in the pathogenesis of major depression especially in the early phase of the disorder and especially in male patients. The results could also contribute to the reformulation of neuroanatomic models of the pathophysiology of depression in a more gender-specific conceptualisation. Possibly, a stress and hypercortisolism related reduction in hippocampal volume is more typical for male patients with first episodes than for female patients for whom other biological mechanisms are maybe more relevant. In future studies the mechanisms behind decreased hippocampal volumes, life events and depression should be addressed.

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Conflict of interest
No conflict declared.

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