Hippocampal volume changes in healthy subjects at risk of unipolar depression

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1. Introduction

Unipolar depression is moderately heritable. It is unclear whether structural brain changes associated with unipolar depression are present in healthy persons at risk of the disorder. Here we investigated whether a genetic predisposition to unipolar depression is associated with structural brain changes. A priori, hippocampal volume reductions were hypothesized. Using a high-risk study design, magnetic resonance imaging brain scans were obtained from 59 healthy high-risk subjects having a co-twin with unipolar depression, and 53 healthy low-risk subjects without a first-degree family history of major psychiatric disorder. High-risk twins had smaller hippocampal volumes than low-risk twins (p < 0.04). The finding was most pronounced in DZ twins. Groups did not differ on global brain tissue volumes or regional tissue volumes assessed in exploratory voxel-wise whole cerebrum analyses. In conclusion, hippocampal volume reduction may index a predisposition to develop depression and thus may be predictive of future onset of the disorder. Further studies are needed to elucidate the role of (shared) environmental and genetic factors.

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2. Methods and materials

2.1. Participants

In the present study 112 participants were included (Table 1): 59 healthy twins at risk of unipolar depression (high-risk – HR – twins) and 53 healthy twins without known personal or co-twin
history of hospital contact with affective disorder (low-risk—LR—twins). The healthy high-risk and low-risk twins were identified through record linkage between the Danish Twin Registry, the Danish Psychiatric Research Register and the Danish Civil Register (the registers are described in more detail in Section 2.3). This linkage identified same sex twin pairs in which one twin had been treated in a psychiatric hospital setting for a depressive episode (the proband) and one had not been treated for depressive disorder, the high-risk healthy co-twin. Probands were identified as twins who on their first admission, in the period between 1968 and 2005, were discharged from a psychiatric hospital with a diagnosis of depression or recurrent depression (the proband) and lifetime life events = Number of adverse lifetime life events. Discordance time = Number of months between the date a healthy high-risk twin was scanned and the date that the ill co-twin was discharged from a psychiatric hospital with a diagnosis of depression or recurrent depression.

Table 1
Demographic and clinical data.a

<table>
<thead>
<tr>
<th></th>
<th>High-risk</th>
<th>Low-risk</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>59</td>
<td>53</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>45.0 (13.5)</td>
<td>38.8 (12.1)</td>
<td>0.01</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>27/32</td>
<td>21/32</td>
<td>0.51</td>
</tr>
<tr>
<td>Zygosity (MZ/DZ)</td>
<td>18/41</td>
<td>22/31</td>
<td>0.23</td>
</tr>
<tr>
<td>Education (years)</td>
<td>12.3 (3.3)</td>
<td>14.1 (2.7)</td>
<td>0.01</td>
</tr>
<tr>
<td>Weight</td>
<td>71.5 (11.9)</td>
<td>71.7 (11.4)</td>
<td>0.96</td>
</tr>
<tr>
<td>Height</td>
<td>171.2 (8.9)</td>
<td>173.2 (8.5)</td>
<td>0.22</td>
</tr>
<tr>
<td>Handedness (R/L)</td>
<td>50/9</td>
<td>44/9</td>
<td>0.81</td>
</tr>
<tr>
<td>Symptoms 12b</td>
<td>3.00 (0–7)</td>
<td>2.00 (0–5)</td>
<td></td>
</tr>
<tr>
<td>Symptoms 14c</td>
<td>1.35 (2.07)</td>
<td>0.70 (1.28)</td>
<td>0.154</td>
</tr>
<tr>
<td>Lifetime life eventsd</td>
<td>7.24 (2.82)</td>
<td>1.55 (1.67)</td>
<td>0.031</td>
</tr>
<tr>
<td>Lifetime life eventsd</td>
<td>2.00 (0–11)</td>
<td>1.00 (0–8)</td>
<td></td>
</tr>
<tr>
<td>Discordance time</td>
<td>7.12 (7.60)</td>
<td>1.71 (1.38)</td>
<td>0.001</td>
</tr>
<tr>
<td>Age of proband at first discharge</td>
<td>37.87 (12.33)</td>
<td>34.08 (13.68)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

a Values for the demographic data are mean (SD) or median (range) respectively. M = male; F = female; MZ = monozygotic; DZ = dizygotic; R = right; L = left; HAM-D = Hamilton Depression Scale; BDI-21 = 21-item Beck Depression Inventory; BDI-14 = 14-item Beck Depression Inventory Anxiety Subscale; Life events 12 = Number of adverse life events in the 12 months preceding the MR scan; Lifetime life events = Number of adverse lifetime life events. Discordance time = Number of months between the date a healthy high-risk twin was scanned and the date that the ill co-twin was discharged from a psychiatric hospital with a diagnosis of depression or recurrent depression.

b Information on BDI-21, BDI-14, Life events 12 was missing for the same 2 high-risk subjects.

c Information on lifetime life events was missing for 2 low-risk and 3 high-risk subjects.

d Two of the latter were the same as under footnote "b".

2.2. Clinical assessment

Participants were rated by a trained psychiatrist in a face-to-face interview using semi-structured interviews: diagnoses were obtained using Schedules for Clinical Assessment in Neuropsychiatry (SCAN) version 2.1 (Wing et al., 1990). All persons with a lifetime (current or past) diagnosis of affective disorder, schizofrontic disorder or schizophrenia according to SCAN interviews were excluded from the study. Lifetime minor psychiatric diagnoses defined as non-organic, non-schizophrenic or non-affective SCAN diagnoses were not exclusion criteria. The Hamilton Depression Scale HAM-D, 17-item (Hamilton, 1960, 1967) was used to assess depressive symptoms. At the end of the interview, participants were interviewed about lifetime family psychiatric psychiatric history of first-degree relatives (their biological parents, co-twin, siblings and offspring) based on the Brief Screening for Family Psychiatric History questionnaire (Weissman et al., 2000). They were asked specifically about depression, mania and schizophrenia among their first-degree relatives and questioned whether probands had been admitted to psychiatric hospital or received medical treatment for any psychiatric disorder. An additional exclusion criterion was any significant brain disease.

Further self-rating of psychopathology was assessed using Symptom Rating Scale for Depression and Anxiety including assessment of depressive symptoms using the 21-item Beck Depression Inventory (BDI-21) (Beck et al., 1961), manic symptoms using the 6-item Mania Subscale and anxiety symptoms using the 14-item Anxiety Subscale (BDI-14) (Beck et al., 1988). Life events in the last 12 months preceding the MR scan and lifetime were recorded using a Danish version (translated to Danish after permission from the author) of the questionnaires used by (Kendler et al., 1995; Vinberg et al., 2007). Participants were asked about 9 ‘personal’ events, i.e. events that happened to the participant, and 22 ‘network’ events, i.e. events that occurred primarily to, or in interaction with, an individual in the participant’s social network. The ‘personal’ events, included assault, serious marital problems, divorce/break-up, job loss, and loss of a confidant, serious illness, major financial problem, being robbed, and serious legal problems. The ‘network’ events included death or severe illness of the participant’s spouse, child, parent, co-twin, other sibling, other relative or other individuals close to the participant and serious trouble getting along with the participant’s parent, child, co-twin, sibling, in-laws, other relative, neighbor, or close friend. The number of months between the dates that a healthy high-risk twin was MR scanned and the ill co-twin was discharged from a psychiatric hospital with a diagnosis of depression or recurrent depression defined the time of discordance. Zygosity was determined from anamnesis and/or from photographs of the twin pair. Disagreement in relation to the information from the Danish Twin Registry was found in 17 cases (7.2%), a slightly higher rate than the described error rate of 5% (Hauge, 1981). In case of doubt blood samples from both twins was taken for DNA-analyses.

2.3. The registers

The Danish Civil Registration System assigns a unique personal identification number for all Danish residents. This number is linked to information on name, address, and date of birth. All other Danish registers use the same unique identifier and thus Danish residents can be tracked in all the public registers through record linkage. The Danish Psychiatric Central Research Register is nationwide, with registration of all psychiatric admissions and (from 1995) outpatient hospital contacts in Denmark for the country’s 5.3 million inhabitants (Munk-Jorgensen and Mortensen, 1997). From April 1969 to December 1993, diseases were classified according to the International Classification of Diseases, “8th
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