Journal of Psychiatric Research 44 (2010) 655–662

Contents lists available at ScienceDirect

Journal of Psychiatric Research

journal homepage: www.elsevier.com/locate/jpsychires

Hippocampal volume changes in healthy subjects at risk of unipolar depression

William F.C. Baaré [a,b,*], Maj Vinberg [c], Gitte M. Knudsen [b,d], Olaf B. Paulson [a,b,d], Annika R. Langkilde [a], Terry L. Jernigan [a,b,e], Lars Vedel Kessing [c]

[a] Danish Centre for Magnetic Resonance, MR Department, Hvidovre Hospital, University Hospital of Copenhagen, Hvidovre, Denmark
[b] Center for Integrated Molecular Brain Imaging, Copenhagen, Denmark
[c] Department of Psychiatry, Rigshospitalet, University Hospital of Copenhagen, Copenhagen, Denmark
[d] Neurobiology Research Unit, Rigshospitalet, University Hospital of Copenhagen, Copenhagen, Denmark
[e] Department of Psychiatry, University of California, San Diego, United States

ARTICLE INFO

Article history:
Received 18 July 2009
Received in revised form 30 November 2009
Accepted 17 December 2009

Keywords:
Depression
Hippocampus
Twins
High-risk
MRI
Imaging

ABSTRACT

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.

1. Introduction

Unipolar depression is heritable with concordance rates from 0.23 to 0.67 for monozygotic (MZ) twins and from 0.14 to 0.43 for dizygotic (DZ) twins (Sullivan et al., 2000). Structural brain imaging studies in unipolar depression have reported increased prevalence of white matter hyperintensities and volume decreases/changes in hippocampus, amygdala, caudate, putamen and frontal cortex (for reviews see Sheline, 2003; Lorenzetti et al., 2009; Koolschijn et al., 2009). The presence of hippocampal volume reduction in patients with unipolar depression is underscored in recent meta-analyses (Videbech and Ravnkilde, 2004; Koolschijn et al., 2009). Familial major depressive disorder has been associated with subgenual frontal volume reduction (Drevets et al., 1997). Moreover, a recent study of young psychotropic-naive patients with familial major depressive disorder, showed that the 22 included patients had significantly smaller left and right hippocampal volumes than the 35 matched controls (MacMaster et al., 2008). It is at present unclear whether structural brain changes associated with unipolar depression can also be observed in healthy persons at risk of the disorder.

In the present study we examined healthy individuals who never experienced depressive episodes to look for neuroanatomical correlates of a genetic predisposition to unipolar depressive disorder. Identification of high and low-risk individuals was accomplished by linking records of the Danish Psychiatric Central Research Register and the Danish Twin Registry. High resolution magnetic resonance (MR) scans of the brain were obtained in healthy MZ and DZ twins with a co-twin diagnosed with unipolar depression, and healthy MZ and DZ twins with a co-twin never diagnosed with an affective disorder. That is, the present study is a *high-risk* study, not a "classical" twin study, as it was not possible to investigate the (ill) co-twins. A priori we hypothesized that high-risk twins would have smaller hippocampal volumes than low-risk twins. Additionally, we performed exploratory voxel-wise whole cerebrum analyses.

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

* Corresponding author. Address: Danish Centre for Magnetic Resonance, MR Department, Hvidovre Hospital, University Hospital of Copenhagen, Kettegaard Allé 30, 2650 Hvidovre, Denmark. Tel.: +45 3632 2978; fax: +45 3647 0302.
E-mail address: wimb@drcmr.dk (W.F.C. Baaré).
URLs: http://www.drcmr.dk, http://www.cimbi.dk (W.F.C. Baaré).

0022-3956/$ - see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.jpsychires.2009.12.009

Table 1
Demographic and clinical data.[a]

	High-risk	Low-risk	*p*
Number	59	53	
Age	45.0 (13.5)	38.8 (12.1)	*0.01*
Sex (M/F)	27/32	21/32	0.51
Zygosity (MZ/DZ)	18/41	22/31	0.23
Education (years)	12.3 (3.3)	14.1 (2.7)	*0.01*
Weight	71.5(11.9)	71.7 (11.4)	0.96
Height	171.2 (8.9)	173.2 (8.5)	0.22
Handedness (R/L)	50/9	44/9	0.81
HAM-D	2.81 (1,61)	1.71 (1.38)	*0.001*
	3.00 (0–7)	2 .00 (0–5)	
BDI-21[b]	2.11 (2.88)	0.96 (1.47)	0.07
	1.00 (0–10)	0 (0–6)	
BDI-14[b]	1.35 (2.07)	0.70 (1.28)	0.154
	0 (0–9)	0 (0–6)	
Life events 12[b]	2.74 (2.82)	1.55 (1.67)	*0.031*
	2.00 (0–11)	1.00 (0–8)	
Lifetime life events[c]	2.07 (1.48)	1.59 (1.36)	0.08
	2.00 (0–6)	1.00 (0–5)	
Discordance time	7.12 (7.60)		
	4.5 (1–32.5)		
Age of proband at first discharge	37.87 (12.33)		
	34.08 (19.3–68.3)		

[a] Values for the demographic data are mean (SD) or frequency; Values for the clinical data are mean (SD) and 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. Two of the latter were the same as under footnote "b".

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 (ICD-8-codes: 296.09, 296.29, 296.89, 296.99; ICD-10-codes: F32-33.9). Low-risk healthy control twins were identified as twins without known personal or co-twin history of hospital contact with affective disorder, and were matched on age, sex and zygosity to a high-risk twin.

The participants are a subsample of a larger cohort included in a high-risk study on affective disorders. Participants and non-participants in the latter study have been described in detail elsewhere (Vinberg et al., 2007). The current study is the first report on structural MRI findings. The selection procedure identifying the 112 participants in the current study is detailed in the Section 2.4.

The study was approved by the Danish Ministry of Health, The Danish Regional Scientific Ethical Committee [(KF)-12-122/99 and (KF)-01-001/02], and the Data Inspection Agency. The study was conducted in accordance with the latest version of the Declaration of Helsinki. All procedures were carried out with adequate understanding and written informed consent of the participants.

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, schizoaffective 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 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"