



## Hippocampal shape alterations in healthy young women with familial risk for unipolar depression

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### ARTICLE INFO

Available online xxxx

### ABSTRACT

**Background:** Although reduced hippocampal volume (HCV) is a common finding in depression, it is unclear whether the structural alterations leading to reduction of HCV are pre-existing risk factors before the onset of clinical symptoms or a cumulative process that begins with the onset of clinical symptoms. The aim of the present study was to understand the anatomical status of the hippocampus prior to the clinical symptoms in subjects with high familial risk for depression.

**Methods:** Twenty-seven young women (mean age:  $22.3 \pm 2.1$  years) who were at high risk for familial unipolar depression and 26 age- and gender-matched healthy controls (mean age:  $22.1 \pm 2.1$  years) with low familial risk for depression were included in the study. Total hippocampal volumes were measured by manual tracing. For 3D shape differences, the spherical harmonic basis functions (SPHARM) software was used. The segmented images were parameterized, and the point-to-point based group difference was compared by the Hotelling's T-squared test with total brain volume and Beck Depression Scale as covariates.

**Results:** Although there was no difference in overall HCVs, shape analyses revealed a contracted area on the Cornu Ammonis (CA) 1 region of the right hippocampus head in the high-risk group compared to the low-risk group. Cross-sectional design and small sample size, including only females, were the main limitations of this study.

**Conclusion:** This study with shape analyses provided data suggesting that local structural hippocampal alterations in the CA1 region might be associated with depression vulnerability in women at high risk.

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### 1. Introduction

Major depressive disorder (MDD) is one of the most debilitating and common psychiatric diseases with a lifetime prevalence estimated at 4–17% in the general population [1]. Although there are effective treatments for depression, only fewer than half of the patients reach remission and nearly 80% of patients have at least one relapse in the following 5 years [2]. Improved treatment interventions are needed,

but ultimate achievement would be the prevention of the disease before its onset. These goals can be reached by extending our current understanding of MDD pathophysiology, by focusing on neurobiological alterations not only during the disease but also before its clinical appearance. Studying populations at high risk for MDD can help us for this purpose. Although the definition of high-risk groups for MDD is not clear, the risk factors have been studied rigorously. The best-known risk factors that increase the odds for depression were positive familial history and female gender [3, 4]. First-degree family members of depressed patients have a 2–3-fold increase in the risk for developing MDD, and if the proband's depression is early onset (e.g., during teenage years) or recurrent, the risk for offspring increases up to 4–5 fold [5, 6]. Beyond genetics, negative behavioral effects of maternal depression add risk for depression in the offspring living in the same household [7]. Thus, with these high odds, family history is one of the most reliable risk

**Abbreviations:** MDD, Major depressive disorder; HPA, Hypothalamic–pituitary–adrenal; HCV, Hippocampal volume; HRFD, High familial risk for depression; LRFD, Low familial risk for depression; WM, White matter; GM, Gray matter; CSF, Cerebral spinal fluid; TBV, Total brain volume.

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factors for depression [8]. It is well known that by adolescence, the risk is two-fold higher among women than among men [6, 9]. Both sex hormones and gender-related environmental experiences (e.g., more traumatic experiences for females) contribute to the difference in prevalence between genders [10]. (For a detailed discussion, see Kuehner, 2016).

The hippocampus has long been at the center of depression studies because it has widespread functional connections to the structures that regulate mood and the stress related to the hypothalamic–pituitary–adrenal (HPA) axis. Furthermore, it is the core region for neurogenesis in the adult mammalian brain that might be related to antidepressant response, as some studies suggested [11–14]. A large number of MRI studies investigated the hippocampi volume in MDD. Some of those studies reported no hippocampus volume (HCV) difference between MDD patients and controls, but others reported smaller HCV in depression. The combination of MRI studies revealed an 8–10% smaller HCV of patients in meta-analyses [15–17]. It is unclear whether the HCV reduction, when it is observed, is a cumulative process that begins with the onset of clinical symptoms and continues over the many years of illness (i.e., the neurotoxicity with the illness onset hypothesis) [17–19] or a pre-existing risk factor before the onset of the clinical symptoms (i.e., the vulnerability hypothesis) [20]. The neurotoxicity with illness onset hypothesis is based on hypercortisolemia-induced neurotoxicity due to HPA dysfunction with the disease [21, 22]. It further proposes that high levels of glucocorticoids suppress neurogenesis and exert detrimental effects on the dentate gyrus (DG) as well as other hippocampal sub-regions [23–25]. This effect is most prominent during the state of depression despite the evidence suggesting that antidepressants might help reverse this effect [26, 27]. Thus, as long as these unfavorable processes persist, further HCV reduction is expected. This hypothesis finds support in the association between reduced HCV and the patient's lifetime duration of illness or number of episodes [17, 19, 28]. On the other hand, studies finding reduced HCV in euthymic subjects carrying susceptibility genes or subjects with a history of childhood trauma (another risk factor for depression) support the vulnerability hypothesis, which suggests that hippocampal atrophy is a result of a faulty developmental process before the disease onset and might be a vulnerability factor that influences the development and course of the illness [29–32]. Based on the vulnerability hypothesis, studying the pre-disease state of the hippocampus would help to understand how the disease breaks through in the risk populations.

Few studies assessed HCV in healthy individuals at high risk for depression, and their results support the vulnerability hypothesis indicating that HCV reduction is present before the illness onset [33–36]. One caveat of the many existing studies might be accepting the hippocampus as functionally and histologically one uniform structure by measuring overall volume. Besides, due to technical limitations, the studies used voxel based approach either did not specify the exact location of the cluster or did additional manual tracing for increasing validity of the results [33, 34]. Hippocampal subfields have distinct neurochemical, cytoarchitectonic, and functional properties [37]. For example, the ventral part of the hippocampus is mostly related to episodic memory and functionally integrated with the limbic system, whereas the posterior part of the hippocampus is associated with spatial memory [38]. Moreover, adult neurogenesis takes place in particular hippocampal sub-regions such as the dentate gyrus [39, 40].

Local small changes within the sub-regions of the hippocampus can be captured by surface mapping, a sensitive method with current imaging techniques, yet the inward gyrfication of the hippocampal shape precludes the assessment of deeper structures [41]. At least four studies reported local hippocampal shape alterations in depressed patients, even though three of them could not show an overall HCV difference between patients and controls [42–45]. Three of the studies showed shape alteration in the ventral subiculum and Cornu Ammonis (CA) 1 sub-region at the head of the hippocampus [42, 44, 45]. The reported local shape alterations were in line with post-mortem studies reporting

morphological abnormalities in those regions of depressed patients [46, 47]. The CA1 and subiculum are the origins of many outputs from the hippocampus projecting to the striatum, thalamus, and limbic system, including the amygdala, insula, and orbitofrontal cortex. The networks that are formed by these structures are generally reported as functionally impaired in depressed patients [48, 49].

The aim of the present study was to compare the overall HCV and hippocampal shape in young women who were at high risk for familial unipolar depression to those of age-matched women with low familial risk for depression. Based on the previous findings in depressed patients and considering functional and anatomical connections within the hippocampal subfields and limbic regions, we expected structural alterations in the ventral subiculum and CA1 of the high-risk group for depression.

## 2. Material and Methods

### 2.1. Participants

We recruited a cohort of healthy young women, who were between 18 and 26 years old and had no personal history of current or lifetime psychiatric disorder, through an advertisement on the Internet and social media. From this cohort, two samples were drawn; the first one was composed of 27 subjects who had a mother with a diagnosis of recurrent depression (at least two depressive episodes) and at least one second-degree relative diagnosed with MDD. The subjects who had mothers with any other comorbid axis I diagnosis except anxiety disorders were excluded from the study. This sample was accepted as the high familial risk for depression (HRFD). The second sample (low familial risk for depression; LRFD) was composed of 26 subjects without any family history (first- or second-degree relatives) of depressive disorders, including dysthymia. Exclusion criteria for both groups included a history of previous head injury with loss of consciousness; hydrocortisone or any psychotropic drug treatment in their medical history; alcohol or substance abuse; and any neurological disease or chronic medical disease, including hypertension or diabetes mellitus. Subjects with a first- or second-degree relative diagnosed with bipolar or psychotic disorders were also excluded from the study. Finally, a history of serious childhood trauma (parental loss before age of 14, severe physical or any sexual abuse) was an exclusion criterion for the LRFD group.

All the candidate subjects and their mothers were assessed by a psychiatrist or an experienced clinical psychologist through a semi-structured interview focused on personal and familial medical and psychiatric history. This semi-structured interview included explorative open-ended questions related to childhood trauma modified from the Turkish Version of Childhood Trauma Questionnaire [50]. Those eligible for inclusion were further evaluated by an experienced clinical psychologist with the SCID-I (Structured Clinical Interview for DSM-IV) [51] to exclude any Axis I disorder, including substance abuse. The severity of subclinical symptoms was assessed by the HAM-D-17 (Hamilton Depression Assessment Scale) [52], the BDI (Beck Depression Inventory) [53], and the STAI (State-Trait Anxiety Inventory) [54]. Trait and state anxiety scores obtained from the STAI were reported independently. Handedness was determined by the Edinburgh Handedness Inventory [55]. The mothers of the subjects underwent the same screening procedure to confirm their MDD diagnoses for the HRFD group or the absence of any psychiatric disease for the LRFD group.

The local ethics committee approved the study protocol, and written informed consent was obtained from all subjects after the description of the study.

### 2.2. MRI procedure

MR scans were performed within the same week as clinical assessment. Three dimensional T1 weighted, sagittal magnetization prepared rapid gradient echo (MPRAGE) scans of the head (*repetition time (TR)*/

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