Chapter 3

Hippocampal volume and subcortical white matter lesions in late-life depression: comparison of early- and late-onset depression

Joost Janssen[1,4], Hilleke E. Hulshoff Pol[1], Frank-Erik de Leeuw[2], Hugo G. Schnack[1], Indrag K. Lampe[3], Rob M. Kok[4], Rene S. Kahn[1], Thea J. Heeren[1,5]

[1]Rudolf Magnus Institute of Neuroscience, University Medical Centre Utrecht, Department of Psychiatry, Utrecht, The Netherlands

[2]University Medical Centre St Radboud Nijmegen, Department of Neurology, Nijmegen, The Netherlands

[3]University Medical Centre St Radboud Nijmegen, Department of Psychiatry, Nijmegen, The Netherlands

[4]Department of Old Age Psychiatry, Altrecht, Zeist, The Netherlands

[5]Symfora Group, Centres of mental health care, Amersfoort, The Netherlands

ABSTRACT

Introduction: Reduced hippocampal volume and increased prevalence of subcortical white matter lesions are associated with both recurrent early-onset depression (EOD) and late-onset depression (LOD). It is not clear whether these two factors differentially affect the age of first depression onset. Therefore we want to investigate the relationship between age of first depression onset and hippocampal volume with adjustment for subcortical white matter lesions.

Methods: Magnetic Resonance Imaging (MRI) brain scans were used to compare hippocampal volumes and white matter lesions in age-matched female older patients (> 60 years) with recurrent early-onset depression and late-onset depression and healthy controls.

Results: When comparing the three groups and adjusting for age, total brain volume and Mini-Mental Status Examination score, total hippocampal volume was significantly smaller in patients with EOD compared to controls (5.6 ml versus 6.1 ml, p=0.04). Prevalence of larger subcortical white matter lesions was higher in patients with LOD compared to patients with EOD (47% versus 8%, p=0.002). Adding larger subcortical white matter lesions as a covariate did not change the results. Patients with LOD did not differ in hippocampal volume from patients with EOD and from controls.

Conclusions: In late-life depression, age of first depression onset may distinguish between different independent neuropathologic mechanisms. A small hippocampus volume may be a neuranatomic marker of EOD depression and larger subcortical white matter lesions could be an intermediate between cerebrovascular disease and LOD.

INTRODUCTION

Late-life depression (depression in people aged ≥ 60 years) is associated with a smaller hippocampal volume when compared to age-matched controls. [1-5] The decrease in hippocampal volume may be related to a chronic intermittent illness course in aged depressed patients. [3,6-9] Accordingly, older patients with recurrent early-onset depression (EOD, first onset of depression before 60 years) would therefore have smaller hippocampal volumes compared to patients with late-onset depression (LOD, first onset of depression at age 60 years or after) due to a longer duration of the disease. However, two recent studies showed smaller hippocampal volumes in patients with LOD compared with EOD. [10,11]

The latter observation could have been confounded by the increased prevalence of subcortical white matter lesions among patients with LOD [12-16] since these lesions may be related to hippocampal atrophy. [17-20] Therefore, in the current study we want to investigate the relationship between age of onset of the depression and hippocampal volume with adjustment for subcortical white matter lesions in elderly (≥ 60 years) patients with chronic recurrent EOD and patients with LOD.

METHODS

Participants

We investigated 13 patients with early-onset depression, 15 patients with late-onset depression and 22 healthy controls. All study participants were female and aged 60 years or older. For patients with early-onset depression, age at onset of the first depressive episode had to be before 45 years of age. They were recruited from the mental health

clinics of the University Medical Center Utrecht and Altrecht, a large mental health care center in the Utrecht area. The exclusion criteria for these patients were a history of central nervous system disease, dementia, substance dependence within the last year, terminal somatic illness, and a Mini-Mental State Examination [21] (MMSE) score below 15. The number of previous depressive episodes of the patients with early-onset depression was assessed in an interview by a geriatric psychiatrist (IKL) using life-chart methodology. Healthy controls were recruited within the community from general practitioners´ practices situated in the city of Utrecht and from advertisements in regional newsletters. For the healthy controls, exclusion criteria were similar to the patient group, with the addition of excluding those with any current or past Axis I psychiatric diagnosis. All patients with late-onset depression (n=15) were inpatients from the geriatric psychiatry unit of Altrecht. All patients in the current study met the criteria for major depression according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) and did not have contra-indications for MRI acquisition. Patients were excluded if they met DSM-IV criteria for dementia, alcohol or drug abuse in the last year, or had a MMSE score < 15. Patients with late-onset depression had an age of onset of the first depressive episode at age 60 years or older. The Montgomery-Åsberg Depression Rating Scale (MADRS) (Montgomery et al 1979) [22] was assessed at the time of the scan to measure the severity of any present depressive symptoms at that particular moment. All patients and controls were screened for their medical and psychiatric history by two experienced geriatric psychiatrists (IKL and RMK), through a self-report health- questionnaire and by inspection of their medical records. To approximate a representative sample of the population, patients and controls with the

cerebrovascular risk factors hypertension, diabetes, and smoking were not excluded. At the time of the MRI acquisition, 4 (14%) patients were taking lithium. Two independent clinical neuroradiologists examined the MRI brain scans; no gross brain abnormalities were reported in any of the participants. The Ethics Committee of the University Medical Center of Utrecht approved the study. A signed written informed consent was obtained from all subjects after information about the study was provided.

MRI Acquisition

Magnetic resonance images were acquired using a scanner (Philips Gyroscan; Philips Medical Systems, Best, the Netherlands) operating at 1.5 T in all subjects. All subjects had a T1-weighted, 3-dimensional, fast field echo scan with 160 to 180 1.2-mm contiguous coronal slices (echo time [TE], 4.6 ms; repetition time [TR], 30 ms; flip angle, 30°; field of view [FOV], 256 mm; in-plane voxel size, 1 x 1 mm^2) and a T2-weighted, dual echo turbo spin echo scan (DTSE) with 120 1.6-mm contiguous coronal slices (TE1, 14 ms; TE2, 80 ms; TR, 6350 milliseconds; flip angle, 90°; FOV, 256 mm; in-plane voxel size, 1 x 1 mm^2) of the whole head were used for quantitative measurements. In addition, a T2-weighted, DTSE scan with 19 axial 6-mm slices and a 1.2-mm gap (TE1, 30 ms; TE2, 90 ms; TR, 2377 ms, flip angle, 90°; FOV, 256 mm; in-plane voxel size, 0.89 x 0.89 mm^2) was used for clinical neurodiagnostic evaluation and all 19 axial 6-mm slices (1.2 mm gap) of the DTSE scan were inspected for white matter lesion rating. Prior to quantitative assessments and white matter lesion rating 10 MRIs were randomly chosen and cloned to test intrarater reliability. All MRIs were coded to ensure masking for subject identification and diagnosis. The MRI datasets were transformed (no scaling) to fit Talairach coordinates [23] with software developed in house. The transformation used

information gathered from the placement of a midline in coronal and axial views and the marking of the superior edge of the anterior commissure and the inferior edge of the posterior commissure in the sagittal view. Additionally, MRI scans were corrected for inhomogeneities in the magnetic field. [24]

Brain volumes

Intracranial volume was segmented on the DTSE scans, with the foramen magnum being used as inferior boundary. Total brain volumes were automatically segmented from the 3D-FFE (T1-weighted) scans using histogram analysis algorithms and a series of mathematical morphological operators to connect all voxels of interest. [25] The total brain segments contained gray and white matter tissue only. All segments were checked after the measurements and corrected manually if necessary. Quantitative measurement of the hippocampus was done with the software package DISPLAY developed at the Montreal Neurological Institute. This program allows simultaneous viewing in coronal, sagittal and axial sections. Neuroanatomic borders of the hippocampus have been previously described. [4] Segmentation of the hippocampus started in the coronal slice in which the mamillary bodies were visible and stopped when the fornix was visible as a continuous tract. [26]

White matter lesions

Subcortical white matter lesions were counted and categorized according to their largest diameter in small (<3 mm) and large (>3 mm) lesions in each slice. Periventricular white matter lesions adjacent to the frontal, lateral or occipital wall of the ventricle were rated semi-quantitatively (0-3) per region. This rating scale has been used previously. [15]

Furthermore, highly comparable findings between this rating scale and volumetric assessment of white matter lesions has been reported. [27]

Reliability

The Intraclass Correlation Coefficient (ICC) [28] and weighted kappas determined the reliability for the volume measurement and white matter lesion rating respectively.

ICCs for the left and right hippocampus were 0.94 and 0.90. An expert (FEL) examined all scans for white matter lesions. The intrarater study showed good to excellent agreement, weighted kappas for grading the periventricular and subcortical white matter lesions ranged between 0.87-0.92.

Statistical analyses

Data were examined for outliers, extreme values and the normality of the distribution. Total brain volume was normalized for head size by dividing by the intracranial volume. Hippocampal volume was normalized for brain size by dividing by total brain volume. The relationship between hippocampal volume and age of onset of depression was tested with a one-way Analysis of Variance (ANOVA) with post-hoc tests. Adjustments were made for age, total brain volume and Mini-Mental Status Examination score. Intracranial volume served as a covariate in the analysis of total brain volume. Secondly, subcortical white matter lesions were added to the model to assess whether the volumes across groups changed. Demographical and clinical continuous and non-continuous data were analyzed using independent samples t-Test and the Fisher exact test. Chi-Square analyses and the Fischer exact test were used to assess group differences in the prevalence of white matter lesions.

RESULTS

Patients with late-onset depression had significantly fewer years of education and lower Mini-Mental Status Examination scores compared to healthy controls (see Table 1). Mini-Mental Status Examination scores did not differ between the two patient subgroups. Montgomery- Åsberg Depression Rating Scale scores at the time of MRI

Table 1 Demographic and clinical data of normal controls (NC, n=22), early-onset depression (EOD, n=13) and late-onset depression (LOD, n=15) subjects.

	EOD	LOD	NC	EOD vs LOD[A]	EOD vs NC	LOD vs NC
Age (years), mean (sd)	70.38 (8.3)	72.67 (6.7)	71.05 (7.5)	p=0.41	p=0.81	p=0.50
Years of education, mean (sd)	10.54 (4.1)	8.00 (2.3)	10.68 (3.1)	p=0.05	p=0.92	p=0.02
MADRS score, mean (sd)	9.77 (7.0)	33.93 (7.4)	4.77 (4.3)	p<0.01	p=0.03	p<0.01
MMSE score, mean (sd)	27.69 (1.8)	26.33 (3.2)	28.14 (1.8)	p=0.18	p=0.48	p=0.03
Age at onset (years), mean (sd)	33.62 (8.8)	69.93 (6.4)		p<0.01		
Cerebrovascular risk factors						
Smoking , n (%)	4 (31%)	4 (29%)	1 (5%)	p=0.22	p=0.04	p=0.07
Diabetes, n (%)	1 (8%)	1 (8%)	0	p=0.52	p=0.37	p=0.41
Hypertension, n (%)	5 (39%)	4 (29%)	5 (23%)	p=0.25	p=0.18	p=0.29

MADRS, Montgomery-Asberg Depression Rating Scale; MMSE, Mini-Mental State Examination, C, controls, EOD, patients with early-onset depression, LOD, patients with late-onset depression, [A]Differences in continuous variables and non-continuous variables were tested with independent-samples t-Test and the Fisher Exact Probability Test, respectively.

acquisition differed significantly between the two patient subgroups and between the patient subgroups and the healthy controls (see Table 1). Smoking was more prevalent among the patients subgroups compared to controls, hypertension and diabetes did not differ between the three subgroups (see Table 1).

Hippocampal volume was smaller in patients with early-onset depression compared to controls (5.6 ml vs 6.1 ml, df=44, p=0.04, see Table 2) after controlling age, total brain volume and Mini-Mental Status Examination score.

In the same analysis patients with late-onset depression did not differ in hippocampal volume from patients with early-onset depression (5.8 ml vs 5.5 ml, df=44, p=0.15) and controls (5.8 ml versus 6.0 ml, df=44, p=0.70). Adding subcortical white matter lesions to the model did not change the results.

Table 2 Raw total brain and hippocampal volumes and number of white matter lesions of normal control (n=22), early-onset depression (n=13) and late-onset depression (n=15) subjects.

	EOD	LOD	NC	EOD vs LOD	EOD vs NC	LOD vs NC
Total brain volume (ml), mean (sd) [A]	1058.62 (14.3)	1031.95 (13.4)	1081.47 (11.1)	p=0.17	p=0.13	p<0.01
Total hippocampal volume (ml), mean (sd) [B]	5.51 (0.2)	5.92 (0.2)	6.0 (0.1)	p=0.16	p=0.04	p=0.65
White matter lesions						
Periventricular prevalence						
Frontal, n (%)	4 (31%)	6 (40%)	5 (23%)	p=0.27	p=0.27	p=0.19
Lateral, n (%)	4 (31%)	5 (33%)	6 (27%)	p=0.31	p=0.29	p=0.26
Occipital, n (%)	0	3 (20%)	3 (14%)	p=0.14	p=0.24	p=0.30
Subcortical prevalence						
Small, n (%)	7 (54%)	10 (67%)	9 (41%)	p=0.76	p=0.89	p=0.35
Larger, n (%)	1 (8%)	7 (47%)	1 (5%)	p=0.03	p=0.48	p<0.01

C, controls, EOD, patients with early-onset depression, LOD, patients with late-onset depression. [A]The difference in total brain volume was tested with Analysis of Variance (ANOVA), adjusting for age, intracranial volume and Mini-Mental State Examination. [B]The difference between groups in hippocampal volume was tested with ANOVA, adjusting for age, total brain volume and Mini-Mental State Examination. Adding larger subcortical white matter lesions as a covariate did not change the results. Differences between groups in white matter lesion prevalence were tested with Chi Square analyses and the Fisher Exact Probability Test.

For larger subcortical white matter lesions, the prevalence was significantly higher for patients with late-onset depression compared to early-onset depression and controls (χ^2=11.98, df=2, p=0.002). The frequency of small subcortical white matter lesions did not differ between the three subgroups (see Table 2). The prevalence of frontal, lateral

and occipital periventricular white matter lesions was not different between the three subgroups (see Table 2).

Total brain volume was smaller in patients with late-onset depression compared to controls (1037.1 ml versus 1071.7 ml, F=3.05, df=44, p=0.02) after controlling for age, intracranial volume and Mini-Mental Status Examination score. There were no significant differences in total brain volume in the other comparisons (see Table 2). Adding subcortical white matter lesions to the model did not change the results.

Excluding the four patients who received lithium did not change the results.

DISCUSSION

The main findings of our study are a reduced hippocampal volume in older patients with recurrent early-onset depression and a higher prevalence of larger subcortical white matter lesions in patients with late-onset depression compared to controls. Hippocampal volume of LOD patients did not differ from normal controls

Early-onset depression was associated with a smaller hippocampal volume. This is in line with previous reports in adult and older patients with chronic recurrent depression. [1,3-5] In the current study, all but one of the older patients with EOD had more than three episodes while none of patients with LOD had more than two episodes. Moreover, in seven patients with LOD the current episode was the first. Recent reports found decreased total hippocampal volume in patients with LOD, but not in patients with EOD, compared to healthy controls. [10,11] However, one study included younger EOD patients (mean age 50 years) compared to the current study (mean age 70 years) and duration of illness was estimated by subtracting age of onset from current age. In the other study, older patients

with EOD had a substantially lower mean number of depressive episodes compared to our sample (5.1 vs 16.7). Therefore it may be that the EOD patients in these studies had a less severe history of depressive illness and consequently less damage to the hippocampus.

The patients with LOD in our study had a smaller total brain volume. Smaller cerebral gray matter volume, particularly in the prefrontal cortex has been associated with late-onset depression. [29-31] It is not clear whether this finding is related to the subcortical lesions, although one study showed such an association. [32]

On the basis of previous research that described a relation between white matter lesions and hippocampal atrophy among patients with Alzheimer's disease we would have anticipated a lower hippocampal volume in LOD patients since they had more subcortical white matter lesions. [12-20] However this was not the case. It might be that our patients with LOD did not have ischemic cerebrovascular pathology to the same degree as patients with dementia. Alternatively, the subcortical white matter lesions may not represent generalized ischemic damage in patients with LOD. Rather, it has been suggested that region-specific subcortical white matter lesions may be necessary to cause hippocampal atrophy for example by disrupting hippocampal-cortical connections leading to Wallerian degeneration. [17,18,33]

Our findings of different structural brain abnormalities in patients with EOD and LOD strengthen previous findings of different neuropathological mechanisms leading to late-life depression. [34] For EOD, stress-related neurotoxic factors associated with repeated episodes of depression may result in a small hippocampal volume. [35] Unfortunately, we did not have data on cortisol levels to further investigate the possible stress-related

neurotoxicity on the hippocampus. In LOD, cerebrovascular risk factors or disease may be related to the depression, probably with large subcortical white matter lesions as an intermediate. [36] Whether age of onset affects these neuropathological mechanisms needs further investigation using for example a large sample with homogeneous age of illness onset groups such as patients with first-episode LOD and patients with recurrent LOD.

This study was limited in several aspects. First, the number of patients in our sample was small. Therefore, limited statistical power may have prevented us from finding differences in hippocampal volume between patients with EOD and LOD. Second, the use of medication may have influenced our results. Although we controlled for the use of lithium, we cannot rule out the effect of cumulative years of medication.

Longitudinal studies, combining clinical, MRI, neuroendocrinological and neuropsychological data are needed to further elucidate the potential separate neural pathways that may lead to late-life depression.

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