Late-life Depression: Structural Brain Abnormalities, Treatment and Risk Factors

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Late-life Depression: Structural Brain Abnormalities, Treatment and Risk Factors

Ouderdoms-depressie: Structurele Hersenafwijkingen, Behandeling en Risicofactoren

(met een samenvatting in het Nederlands)

Proefschrift

ter verkrijging van de graad van doctor aan de Universiteit Utrecht
op gezag van de rector magnificus, prof. dr. W.H. Gispen,
ingevolge het besluit van het college voor promoties in het openbaar
te verdedigen op dinsdag 5 september 2006 des ochtends om 10.30 uur.

door

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geboren op 5 maart 1976, te Grubbenvorst

Contents

Chapter 1

Late-Life Depression: Introduction and research questions

Late-life depression

Depression in late-life, as well as depression in younger adults, is a severe psychiatric illness. Core depressive symptoms and signs in younger and older patients are sadness, low mood, pessimism about the future, self-criticism and self-blame, retardation or agitation, slow thinking, and difficulty concentrating. Core vegetative signs include loss of appetite and sleep disturbances. Whether late-life depression and depression in younger adults differ in clinical symptoms, neuropathology and aetiology is still a matter of debate. Nevertheless, population-based epidemiological studies report different risk factors for older depressed subjects compared to depression in younger adults. These risk factors encompass specific live events as well as changes in cognitive, physical and social functioning. Older people in western countries have less professional obligations, their children live separate lives, and their friends become sparser. In addition, older people are more likely to lose their partner and, in particular, acquire chronic physical illnesses. Poor physical health may be the principal risk factor for late-life depression.[1] The prevalence of depression requiring clinical attention in community dwelling older people is 13.5%, which underlines the importance of depression in terms of individual suffering and public health, especially with regard to the rapid ageing of the population in western countries.[2] Furthermore, the physical health problems and cognitive impairment experienced by patients with late-life depression and their need for support weigh heavily on caregivers and lead to an increased service utilization.[3] Therefore the recognition, treatment and prevention of late-life depression are becoming a major global health issue.

The role of age of onset of depression in late-life depression

The presence of depressive symptoms in late-life disorders such as dementia has stimulated research on the role of age of first depression onset in the aetiology and phenomenology of late-life depression. There is substantial evidence that indicates clinical, epidemiological, and biological differences between depressive disorders that are recurring illnesses starting during adolescence or middle age, early-onset depression (EOD) and depression that emerge for the first time late in life, late-onset depression (LOD).

To use age of onset as a dichotomous variable is to some extent arbitrary and different studies have used varying cut-offs from 45 to 65 years.[4] Studies have suggested that

when comparing patients with EOD and LOD, patients with LOD are less likely to have psychiatric co-morbidity and a family history of mood disorder suggesting an increased genetic influence in EOD. Some studies indicate more medical co-morbidity, loss of interest and apathy, and a poorer prognosis in patients with LOD but other reports do not support this.[4,5] It is well-known that increased levels of cortisol are present during episodes of depression in a considerable number of patients. An influential hypothesis regarding the aetiology of late-life EOD and LOD states that EOD patients are, by definition, more exposed to the possibly neurotoxic damaging effects of cortisol compared to LOD patients.[6] This may lead to EOD-specific neuroanatomic and functional impairment.[7]

Since the 1920ties, a strong association between vascular disease and the development of late-life depression has been observed, sparking theories regarding the neurobiology of late-life depression.[8,9] Particularly in patients with LOD, increased vascular risk factors and vascular disease has been observed.[10] The vascular damage in these patients may however be subtle as studies assessing vascular factors for stroke risk have not always found an association between LOD and vascular disease.[11] The potential association between vascular mechanisms, brain changes and the development of late-life depression sparked a relatively early interest in neuroimaging techniques because these methods made it possible to investigate subtle vascular damage in the brain.

Neuroimaging in late-life depression

In the late 1970s, a modern imaging technique called Computed Tomography (CT) made it possible to investigate structural brain abnormalities non-invasively. In 1980, Jacoby and Levy published the first CT study of mood disorder in the elderly. They compared older patients with depression and healthy age-matched controls and also reported larger ventricles in older patients with depression.[12]

More recently, the advent of Magnetic Resonance Imaging (MRI) brought several advantages compared to CT, allowing more accurate localization and high-resolution measurement of brain structures, not involving radiation, and providing unprecedented grey-white matter resolution.[13] Further developments in MRI processing improved quantitative volumetric analysis of cortical and subcortical regions at higher levels of resolution.[14]

Structural MRI-studies in late-life depression

MRI studies in adult and older patients with depression can generally be divided into two types of studies: studies investigating volumes of brain structures and studies examining white matter lesions.

Volumetric studies

It is well known that brain volume decreases with normal ageing.[15,16] Nevertheless, some volumetric MRI studies reported smaller volumes in specific cortical and subcortical brain structures of older depressed patients compared to age-matched healthy controls. Volumetric MRI research in late-life depression has primarily focused on structures that are part of the neuroanatomic circuit called the limbic-cortical-striatal-pallidal-thalamic tract. This neuroanatomic circuit is thought to be involved in mood regulation.[7,17] Prime cerebral structures of this circuit are the hippocampus, amygdala, putamen, caudate nucleus, and the orbitofrontal cortex. Particularly the hippocampus is of interest as it plays an important role in regulating the potential neurotoxic effects of cortisol during repeated depressive episodes.[6,19] Unfortunately, the hippocampus itself is particularly vulnerable for these damaging effects which may limit its functioning as a regulator.[6] MRI studies reporting a smaller hippocampus volume in EOD compared to LOD and normal controls and a positive association between smaller hippocampal volume and the number of depressive episodes would provide indirect support for the hypothesis that a small hippocampal volume facilitates onset or continuation of depression.[20,21] In addition, the smaller hippocampus volume may have functional consequences in late-life EOD patients. [22]

White matter lesion studies

Lesion studies have primarily focused on white matter lesions. These are regions in the cerebral white matter that appear bright on T2-weighted imaging. White matter lesions are strongly correlated with ageing.[23] The exact aetiology of these lesions remains unknown. Microscopic research has indicated a number of different histopathological changes in lesion areas such as decreased myelin content, loss of ependymal cell layer and reactive gliosis, smaller and fewer axons, enlarged perivascular spaces, demyelination and artheriolosclerosis.[24]

White matter lesions may vary in location and number. Therefore a number of rating scales were developed to quantify the lesions in a reliable way.[25] The majority of

scales distinguish between periventricular, the lesions that ring the ventricles, and subcortical white matter lesions. This distinction probably has clinical significance.

Research consistently demonstrates that white matter lesions are more common in elderly depressed subjects compared to controls.[26-30] In addition, white matter lesions seem particularly more prevalent in patients with a late-onset of depression (LOD, onset after 60 years of age) when compared to older people with a early-onset of depression (EOD).[31-35] However, white matter lesions are far from specific for depression. They are associated with normal aging, Alzheimer's dementia and multiple sclerosis.[36,37] An increased prevalence of white matter lesion also correlates strongly with cerebrovascular risk factors such as hypertension, diabetes, smoking, low cerebral blood flow velocity, carotid artery disease and prior episodes of cerebral ischemia.[37-40] However, they may also occur in subjects without these vascular risk factors.

Larger subcortical white matter lesions, not periventricular lesions, may be of particular importance for the development of late-life depression.[41] Recent research has emphasized that not only quantity but also anatomical location of subcortical lesions, particularly in the frontal lobe white matter circuitry, might also be of significance in the relation between subcortical white matter lesions and late-life depression.[42]

It is unclear whether white matter lesions and clinical depressive symptoms are related. One study reported anhedonia to be more frequent in patients with more severe white matter lesions but replication studies are lacking.[42] Cognitive functions such as recall and executive functioning were more impaired in older depressed patients with increased prevalence of subcortical white matter lesions compared to those with less subcortical white matter lesions.[33] Furthermore, the presence of white matter lesions seems to limit activities of daily living in older depressed patients.[43]

Post-mortem research of white matter lesions of older patients with late-life depression is sparse. One study compared 20 brains of elderly persons with a history of major depression and 20 controls. All subcortical white matter lesions in the depression group were ischemic in origin which was significantly different from the control group.[44] The nature and the cause of the ischemic processes in older depressed patients remain unclear but these findings do strengthen the reported relationship between white matter lesions and cerebrovascular disease in late-life depression.

Structural brain abnormalities and the aetiology of late-life depression

Based on the reports of the strong association between increased white matter damage, vascular comorbidity and depression in elderly patients, the concept of vascular depression was proposed.[42,45] This hypothesis argues that vascular problems cause white matter lesions which disrupt mood regulation circuits ultimately leading to depression. However, the evidence for this hypothesis is not conclusive. As mentioned before, white matter lesions occur in non-vascular conditions such as hydrocephalus, multiple sclerosis and normal aging. Furthermore, the relationship between depression and vascular risk is bidirectional. There is an overwhelming weight of evidence that depression independently contributes to the cause and progression of vascular disease.[39] Also, Alexopoulos et al (1997) used an age at onset cut-off of 65 years to distinguish people with vascular depression whereas Krishnan et al (1997) did not use age at onset as an inclusion criteria when investigating vascular depression.[42,45] This difference illustrates the ongoing debate about whether age at illness onset is an important factor in relation to aetiology, cognition and clinical symptoms of late-life depression. Differences in aetiology between patients with EOD and LOD may be more apparent than differences in clinical symptomatology and cognition.

Rationale of the studies

In this thesis we describe several studies concerning brain volume abnormalities and risk factors in late-life depression. The rationale for the studies in **Chapters 2** and **3** are essentially based on the following premises. First, neuroimaging studies have shown an increased number of subcortical white matter lesions and reduced cerebral blood flow in patients with LOD compared to patients with EOD and controls.[33,46] This is seen as neuroimaging support for an ischemic origin of LOD, the vascular depression hypothesis.[45] Second, in late-life EOD, may have led to volumetric changes in the brain, particularly the hippocampus, as consequence of repeated episodes of depression.[7] Thus, late-life EOD and LOD might be associated with different structural brain abnormalities reflecting differences in aetiology.

Yet there have been few studies investigating both hippocampal volume and white matter lesions in late-life EOD and LOD patients. Moreover, some studies did match EOD and LOD patients for age which confounds the potential effect of disease onset.

Therefore, whether smaller hippocampal volume is specific for late-life recurrent EOD when compared to LOD has not been well tested. Furthermore, it is also not clear whether the subcortical white matter lesions are related to the reported atrophy in certain cerebral grey matter structures. In **Chapters 2** and **3** we compare hippocampal volume in age-matched patients with EOD, LOD and normal controls in order to assess whether the hippocampal volume decrease is specific for EOD and whether subcortical white matter lesions confound this specificity.

Previous studies have suggested an association between brain abnormalities and treatment. White matter lesions are the primary neuroimaging measures used as potential predictors of treatment outcome. There is evidence for an association between increased presence of subcortical white matter lesions and poor long-term (more than 1 year) treatment outcome.[47-51] However, few studies have investigated the association between volumes of depression-associated brain structures, including white matter lesions, and short-term treatment response. Moreover, previous reports were not controlled treatment trials and did only measure white matter lesions, not brain volumes. Therefore, it remains unclear whether structural abnormalities are associated with response to short-term antidepressant monotherapeutic treatment. In **Chapter 4** we therefore compare structural brain volumes of responders and non-responders to a short-term 12 weeks controlled anti-depressive monotherapeutic trial.

Late-life depression is highly underdiagnosed in The Netherlands. In addition, increased medical comorbidity may facilitate referral to specialized care. Therefore, a bias towards increased medical comorbidity may exist in clinically diagnosed late-life depressed patients compared to depressed elderly without somatic disorders. This could be an important confounder for results of clinical studies comparing EOD and LOD patients. These studies report for example a higher rate of life events and increased vascular disease in EOD and LOD patients respectively. This may thus be due to the referral bias and not related to differences in aetiology.[52] A population-based study comparing elderly EOD and LOD patients and assessing the generalizibility of the reported EOD-LOD findings from clinical samples is described in **chapter 5.**

Aims and hypotheses of this study:

1. To study the importance of age of first depression onset in late-life depression with regard to the structural abnormalities in the brain and the underlying neurobiological mechanisms of late-life depression. Late-life depression is associated with structural brain abnormalities. EOD and LOD are associated with different structural brain abnormalities. The studies described in chapters 2 and 3 address these hypotheses;

2. To study the role of structural brain abnormalities in treatment response in late-life depression because structural brain abnormalities may affect short-term treatment response. This hypothesis is addressed in chapter 4;

3. To study the generalizability of the EOD-LOD distinction found in clinical samples to the elderly depressed in the general population. In late-life depression a referral bias exists and as a result, differences between EOD and LOD in the population are less clear. This hypothesis is addressed in chapter 5.

Finally, in chapter six the results of this thesis are summarized and the merits and limitations of the studies are discussed.

REFERENCES

1   Prince, M. J., Harwood, R. H., Thomas, A. and Mann, A. H. (1998). Psychol Med 28(2), 337-350.

2   Beekman, A. T., Copeland, J. R. and Prince, M. J. (1999). Br J Psychiatry 174, 307-311.

3   Katon, W. J., Lin, E., Russo, J. and Unutzer, J. (2003). Arch Gen Psychiatry 60(9), 897-903.

4   Lyness, J. M., Pearson, J. L., Lebowitz, B. D., Kupfer, D. J. (1994). Am J Geriatr Psychiatry 2, 4-8.

5   Brodaty, H., Luscombe, G., Parker, G., Wilhelm, K., Hickie, I., Austin, M. P. and Mitchell, P. (2001). J Affect Disord 66(2-3), 225-236.

6   Sapolsky, R. M. (2000). Arch Gen Psychiatry 57(10), 925-935.

7   Sheline,Y. I. (2003). Biol. Psychiatry 54: 338-352.

8   Gilarowski-Moskau D. (1926). Allg Z Psychiat Grenzgebiete 84: 169-182.

9   Post, F. (1962). London: Oxford University Press.

10   Baldwin, R. C. and Tomenson, B. (1995). Br J Psychiatry 167(5), 649-652.

11   Lyness, J. M., King, D. A., Conwell, Y., Cox, C., Caine, E. D. (2000). Am J Psychiatry 157: 1499-1501.

12   Jacoby, R. J. and Levy, R. (1980). Br J Psychiatry 136, 270-275.

13   Steiner, R. E. and Bydder, G. M. (1984). Diagn Imaging Clin Med 53(1), 13-21.

14   Krishnan, K. R. (1993). J Geriatr Psychiatry Neurol 6(1), 39-58.

15   Jernigan, T. L., Archibald, S. L., Berhow, M. T., Sowell, E. R., Foster, D. S. and Hesselink, J. R. (1991). Biol Psychiatry 29(1), 55-67.

16   DeCarli, C., Massaro, J., Harvey, D., Hald, J., Tullberg, M., Au, R., Beiser, A., D'Agostino, R. and Wolf, P. A. (2005). Neurobiol Aging 26(4), 491-510.

17   Swerdlow, N. R. and Koob, G. F. (1987). Behav Brain Sci 10, 197-245.

19   Carroll, B. J. (1984). Adv Biochem Psychopharmacol 39, 179-188.

20   Janssen, J., Hulshoff Pol, H. E., Lampe, I. K., Schnack, H. G., de Leeuw, F. E., Kahn, R. S. and Heeren, T. J. (2004). Biological Psychiatry 56(11), 825-831.

21   Sheline,YI, Sanghavi,M, Mintun,MA, Gado,MH (1999). J.Neurosci. 19: 5034-5043.

22   MacQueen,GM, Campbell,S, McEwen,BS, Macdonald,K, Amano,S, Joffe,RT et al (2003. Proc.Natl.Acad.Sci.U.S.A 100: 1387-1392.

23   Fazekas, F., Niederkorn, K., Schmidt, R., Offenbacher, H., Horner, S., Bertha, G. and Lechner, H. (1988). Stroke 19(10), 1285-1288.

24   Pantoni, L. and Garcia, J. H. (1995). Stroke 26(7), 1293-1301.

25   Scheltens, P., Erkinjunti, T., Leys, D., Wahlund, L. O., Inzitari, D., del Ser, T., Pasquier, F., Barkhof, F., Mantyla, R., Bowler, J., Wallin, A., Ghika, J., Fazekas, F. and Pantoni, L. (1998). Eur Neurol 39(2), 80-89.

26   Dolan, R. J., Poynton, A. M., Bridges, P. K. and Trimble, M. R. (1990). Br J Psychiatry 157, 107-110.

27   Coffey, C. E., Wilkinson, W. E., Weiner, R. D., Parashos, I. A., Djang, W. T., Webb, M. C., Figiel, G. S. and Spritzer, C. E. (1993). Arch Gen Psychiatry 50(1), 7-16.

28   Greenwald, B. S., Kramer-Ginsberg, E., Krishnan, R. R., Ashtari, M., Aupperle, P. M. and Patel, M. (1996). Am J Psychiatry 153(9), 1212-1215.

29   Steffens, D. C., Helms, M. J., Krishnan, K. R. and Burke, G. L. (1999). Stroke 30(10), 2159-2166.

30   Kumar, A., Bilker, W., Jin, Z. and Udupa, J. (2000). Neuropsychopharmacology

22(3), 264-274.

31 Figiel, G. S., Krishnan, K. R., Doraiswamy, P. M., Rao, V. P., Nemeroff, C. B. and Boyko, O. B. (1991). Neurobiol Aging 12(3), 245-247.

32 Hickie, I., Scott, E., Mitchell, P., Wilhelm, K., Austin, M. P. and Bennett, B. (1995). Biol Psychiatry 37(3), 151-160.

33 Salloway, S., Malloy, P., Kohn, R., Gillard, E., Duffy, J., Rogg, J., Tung, G., Richardson, E., Thomas, C. and Westlake, R. (1996). Neurology 46(6), 1567-1574.

34 de Groot, J. C., de Leeuw, F. E., Oudkerk, M., Hofman, A., Jolles, J. and Breteler, M. M. (2000). Arch Gen Psychiatry 57(11), 1071-1076.

35 Tupler, L. A., Krishnan, K. R., McDonald, W. M., Dombeck, C. B., D'Souza, S. and Steffens, D. C. (2002). J Psychosom Res 53(2), 665-676.

36 Bennett, D. A., Gilley, D. W., Wilson, R. S., Huckman, M. S. and Fox, J. H. (1992). J Neurol 239(4), 186-190.

37 Fazekas, F., Barkhof, F. and Filippi, M. (1998). J Neurol Neurosurg Psychiatry 64 Suppl 1, S2-5.

38 de Leeuw, F. E., de Groot, J. C., Oudkerk, M., Witteman, J. C., Hofman, A., van Gijn, J. and Breteler, M. M. (2002). Brain 125(Pt 4), 765-772.

39 Longstreth, W. T., Jr., Manolio, T. A., Arnold, A., Burke, G. L., Bryan, N., Jungreis, C. A., Enright, P. L., O'Leary, D. and Fried, L. (1996). Stroke 27(8), 1274-1282.

40 Sato, R., Bryan, R. N. and Fried, L. P. (1999). Am J Epidemiol 150(9), 919-929.

41 Krishnan, K. R., Taylor, W. D., McQuoid, D. R., MacFall, J. R., Payne, M. E., Provenzale, J. M. and Steffens, D. C. (2004). Biol Psychiatry 55(4), 390-397.

41 MacFall, J. R., Payne, M. E., Provenzale, J. E. and Krishnan, K. R. (2001). Biol Psychiatry 49(9), 803-806.

42 Krishnan, K. R., Hays, J. C. and Blazer, D. G. (1997). Am J Psychiatry 154(4), 497-501.

43 Steffens, D. C., Bosworth, H. B., Provenzale, J. M. and MacFall, J. R. (2002). Depress Anxiety 15(1), 23-28.

44 Thomas, A. J., O'Brien, J. T., Davis, S., Ballard, C., Barber, R., Kalaria, R. N. and Perry, R. H. (2002). Arch Gen Psychiatry 59(9), 785-792.

45 Alexopoulos, G. S., Meyers, B. S., Young, R. C., Kakuma, T., Silbersweig, D. and Charlson, M. (1997). Am J Psychiatry 154(4), 562-565.

46 Lesser, I. M., Boone, K. B., Mehringer, C. M., Wohl, M. A., Miller, B. L. and Berman, N. G. (1996). Am J Psychiatry 153(10), 1280-1287.

47 Hickie, I., Scott, E., Wilhelm, K. and Brodaty, H. (1997). Biol Psychiatry 42(5), 367-374.

48 O'Brien, J., Ames, D., Chiu, E., Schweitzer, I., Desmond, P. and Tress, B. (1998). Bmj 317(7164), 982-984.

49 Simpson, S., Baldwin, R. C., Jackson, A. and Burns, A. S. (1998). Psychol Med 28(5), 1015-1026.

50 Yanai, I., Fujikawa, T., Horiguchi, J., Yamawaki, S. and Touhouda, Y. (1998). J Affect Disord 47(1-3), 25-30.

51 Taylor, W. D., Steffens, D. C., MacFall, J. R., McQuoid, D. R., Payne, M. E., Provenzale, J. M. and Krishnan, K. R. (2003). Arch Gen Psychiatry 60(11), 1090-1096.

52 Janssen, J., Beekman, A. T. F., Comijs, H., Deeg, D. J., Heeren, T. J. (2006). Int J Geriatr Psych 21, 86-93.

Chapter 2

Hippocampal Changes and White Matter Lesions in Early-Onset Depression

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Abstract

Background: Hippocampal volume reduction and increased prevalence of subcortical white matter lesions have been reported in late-life depression. We aimed to examine whether total number of subcortical white matter lesions were associated with reduced hippocampal volume in aged female subjects with early-onset depression (<45 years) and healthy comparison subjects.

Methods: The study included 28 middle-aged and elderly subjects with major depression and 41 age-matched control subjects. Hippocampal, parahippocampal gyrus, and orbitofrontal cortex volumes were determined using manual tracing methods. White matter lesions were rated from T2-weighted MRI scans using a semi-quantitative classification scale.

Results: After controlling for total brain volume and age, patients had reduced hippocampal volume due to right hippocampal volume decrease (2.84 mL vs. 3.12 mL, $F=16.6$, $p<.001$). Parahippocampal and orbitofrontal volumes did not differ significantly between groups. Multiple linear regression analysis indicated that reduced hippocampal volume did not significantly correlate with total number of subcortical white matter lesions ($t=.673$, $p=.518$).

Conclusions: Right hippocampal volume was reduced in aged female early-onset subjects with depression. Total number of subcortical white matter lesions was not associated with the decrease in right hippocampal volume. Our data suggests hippocampal involvement, independent of subcortical white matter lesions, in the neuropathology of early-onset depression.

INTRODUCTION

Mood disorders are thought to involve abnormalities in limbic and frontal brain regions.[1,2] Structural magnetic resonance imaging (MRI) studies have reported decreased volumes of the hippocampus, the amygdala, and the orbitofrontal cortex in middle-aged and elderly subjects with early-onset depression (EOD).[3] In addition, there is neuropathological evidence that the number of glia cells is reduced in limbic (Bowley et al 2002) and frontal areas.[4-7]

Increased prevalence of subcortical white matter lesions is a consistent finding in MRI studies of depressed subjects with first onset after the age 60, that is, late-onset depression; however, increased frequency of subcortical white matter lesions has also been reported in elderly EOD subjects when compared with healthy comparison subjects.[8-13] Some studies have even reported increased numbers of subcortical white matter lesions in younger depressed subjects although these findings have not been consistent.[14-16]

It is unclear whether hippocampal volume decrease and subcortical white matter lesions are related to each other. Subcortical white matter lesions might cause disruptions in white matter tracts between limbic and prefrontal areas leading to functional and perhaps to structural impairment of the hippocampus, and as such may contribute to the onset of depressive symptoms.[17,18]

To date, only one study has investigated the association between white matter lesions and hippocampal atrophy.[17] This study reported a positive association between number of white matter lesions and hippocampal atrophy in a group of patients with probable Alzheimer's disease. In depression, decreased orbitofrontal cortex volume has been associated with increased gray matter lesion severity, but not white matter lesion severity, in elderly depressed subjects with mixed age of disease onset.[19]

In this study, we investigated whether hippocampal and orbitofrontal cortex volumes are associated with prevalence of subcortical white matter lesions in a group of middle-aged and elderly female EOD subjects and healthy comparison subjects. The aims of the study were to investigate whether hippocampal, parahippocampal, and orbitofrontal cortex volumes were decreased in aged EOD subjects compared with healthy comparison subjects and whether these volumes were associated with the frequency of subcortical white matter lesions.

METHODS

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. Patients (n=28) were recruited from the outpatient clinic of the University Medical Center Utrecht and from several outpatient clinics of Altrecht, a large mental health care center in the region of Utrecht as described earlier.[20] Included were female patients, 45 years and older, with a lifetime diagnosis of a DSM-IV major depressive disorder, and an age at onset of the first depressive episode before 45 years. Diagnoses were established by a trained physician (IKL) with the Mini-International Neuropsychiatric Interview.[21] If necessary, an experienced geriatric psychiatrist (TJH) was consulted. Furthermore, participants were screened for their medical history through a self-report health-questionnaire and inspection of their medical records by a trained physician (IKL). The Mini-Mental State Exam (MMSE) was used to measure global cognitive functioning.[22] We used a cut-off score of 24. Based on the gathered information we excluded participants with a history of central nervous system disease, dementia, and substance dependence

within the last year, terminal somatic illness, and contraindications for MRI-acquisition. Participants with hypertension, diabetes, thyroid disease, or who smoked were not excluded to ensure a normal epidemiological representation of the population.

Mean duration of illness was 93.5 months (SD = 17.5 months); we did not have information on duration of illness for five patients. Twenty-three patients in this study were also included in a previous study.[20] Healthy female controls (n = 41), between 45 and 85 years were recruited within the community from general practitioners' practices situated in the city of Utrecht and from advertisements in regional newsletters. Comparison subjects were matched to the patients on age, handedness and level of education. Furthermore, comparison subjects were given the same self-report health-questionnaire as the patients enabling matching on health status. Exclusion criteria were similar to the patient group, with the addition of excluding those with any current or past Axis I psychiatric diagnosis as established by the MINI-Plus interview. The Montgomery-Åsberg Depression Rating Scale (MADRS) was assessed at the time of the scan to measure the severity of any present depressive symptoms in both groups.[23] The MADRS score range is 0-60; a score of 20 or higher indicates a moderate depression with a probable need for treatment.[24] At the time of the MRI scan 22 patients (79%) were receiving psychotropic medication: antidepressants (*n*=11), lithium (*n*=4), benzodiazepines only (*n*=1), or a combination of antidepressants with neuroleptics (*n*=3), with lithium (*n*=2), or with both (*n*=1). Two independent clinical neuroradiologists examined brain MRIs; no gross abnormalities were reported in any participant.

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. T1-weighted, 3-dimensional, fast field echo scans with 160 to 180 1.2-mm contiguous coronal slices (echo time [TE], 4.6 msec; repetition time [TR], 30 msec; flip angle, 30°; field of view [FOV], 256 mm; and in-plane voxel sizes, 1 x 1 mm^2) and T2-weighted, dual echo turbo spin echo scans (DTSE) with 120 1.6-mm contiguous coronal slices (TE1, 14 msec; TE2, 80 msec; TR, 6350 msec; flip angle, 90°; FOV, 256 mm; and in-plane voxel sizes, 1 x 1 mm^2) of the whole head were used for quantitative measurements. In addition, T2-weighted, dual echo turbo spin echo scans with 17 axial 5-mm slices and a 1.2-mm gap (TE1, 9 msec; TE2, 100 msec; flip angle, 90°; FOV, 250 mm; and in-plane voxel sizes, 0.98 x 0.98 mm^2) were used for clinical neurodiagnostic evaluation and all 17 axial 5-mm slices (1.2 mm gap) of both scans were inspected for white matter lesion rating.

Before quantitative assessments and white matter lesion rating, 10 MRIs were randomly chosen and cloned for intrarater and interrater reliability determined by the intraclass correlation coefficient (ICC) for volumetric assessments and weighted kappas for white matter lesion rating. All MRIs were coded to ensure masking for subject identification and diagnosis. The MRI datasets were transformed (no scaling) to fit Talairach coordinates (Talairach and Tournoux 1988) with software developed in house.[25] 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.[26] Intracranial, total brain, gray and white matter volumes of the cerebrum (total

brain excluding cerebellum and stem) were measured automatically by using histogram analysis algorithms and a series of mathematical morphology operators to connect all voxels of interest.[27] Intracranial volume was segmented on the DTSE scans, with the foramen magnum being used as inferior boundary. Total brain volumes were segmented on the 3D-FFE (T1-weighted) scans and contained gray and white matter tissue only. All images were checked after the measurements and corrected manually if necessary.

Quantitative measurements of the hippocampus, parahippocampal gyrus, and orbitofrontal cortex were done with the software package DISPLAY developed at the Montreal Neurological Institute. This program allows simultaneous viewing in coronal, sagittal and axial sections.[28] Neuroanatomic borders of the hippocampus and parahippocampal gyrus have been previously described.[29,30] 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. Parahippocampal gyrus segmentation began in the coronal slice in which the optic tract is situated above the amygdala. The posterior commissure was its posterior border.[31] The orbitofrontal cortex was manually segmented within the total brain mask in the coronal plane using a geometrical method.[32]

To summarize this method briefly, the posterior border was determined by the tip of the genu of corpus callosum located in the sagittal plane. The anterior border was the first slice where brain tissue could be identified. The superior limit was divided in two parts; in the subgenual regions, the superior boundary was represented by the inferior border of the anterior cingulate corresponding to a midpoint at the interhemispheric fissure about five slices below the intercommissural line. More anteriorly, the superior limit was represented by a midpoint placed on the intercommissural line. For the

lateral borders, horizontal and vertical crosshairs were placed as tangent lines at the inferior and lateral surfaces of the frontal lobes in all slices. The intersection of these two lines generated two lateral points that were connected to the superior limit point, composing the lateral boundaries of the segment. Anterior and inferior borders were crossed, as segmentations in these areas were larger then necessary. This manual segmentation was multiplied with the binary mask of the total brain resulting in an orbitofrontal cortex segmentation without the superfluous segmentation. The orbitofrontal cortex was also subdivided into medial orbital gray matter (gyrus rectus) and lateral orbital gray matter by tracing a line through the olfactory sulcus. The number and size of subcortical white matter lesions were rated semi quantitatively. For each slice, they were categorized according to their largest diameter in small (<3 mm), medium (3-10 mm), or large lesions (>10 mm). Small lesions could by definition (< 3 mm) be observed on only a single slice. Multiple slices were inspected in rating medium and large sized slices. If it was clear that a lesion was also visible on adjacent slices then it was considered to be part of one large lesion and consequently counted only one time. Periventricular white matter lesions were rated per region (adjacent to the frontal horn, the lateral ventricles and the occipital horn) on a scale ranging from 0 (no lesions) to 3 (large confluent lesions). The total number of subcortical lesions of all categories was used in the analysis investigating the association between white matter lesions and brain volumes. This rating scale has been previously used.[8,33] Furthermore, highly comparable findings between this rating scale and volumetric assessment of white matter lesions have been reported.[34]

Reliability

A single operator (JJ) performed the volume measurements of the hippocampus and the parahippocampal gyrus. The reliability of the volume measurements was

determined by the ICC.[35] ICCs for the left and right hippocampus were 0.95 and 0.91, and for the parahippocampal gyrus 0.92 and 0.81. Two operators performed the volume measurements of the orbitofrontal cortex. ICCs of the left, right, medial, and lateral orbitofrontal cortex ranged between 0.74-0.99. 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 WML ranged between 0.90 and 0.95.

Statistical Analysis

Data were examined for outliers, extreme values, and the normality of the distribution. The total number of subcortical white matter lesions was the only variable that had to be transformed. This variable was normalized using a square root transformation. For demographic variables and white matter lesion ratings, chi-square analyses were used to test for differences in frequency except for the total number of subcortical white matter lesions, which were assessed by an analysis of covariance (ANCOVA), with age as covariate. For volumetric data, repeated measurement ANCOVAs were done to assess the main and interaction effects of the within-subjects factor of hemisphere (left, right) and the between-subjects factor of diagnosis (patient, healthy control subject), with age and total brain volume as covariates. Pearson partial correlation coefficients, controlling for age and total brain volume, were calculated to examine associations between volumes of interest and clinical variables. The relation between total number of subcortical white matter lesions and decreased volumes of interest was assessed using multiple linear regression. The square root of the total number of subcortical lesions entered the analysis as predictor variable, and total brain volume

and age as covariates. Intracranial volume served as covariate for analysis of total brain volume.

RESULTS

Depressed subjects did not significantly differ from healthy comparison subjects in age, height, weight, handedness and level of education (Table 1). Depressed subjects had greater white matter lesion severity compared with healthy comparison subjects but this difference was not significant (see Table 1 and legend).

Hippocampus, Parahippocampal Gyrus, and Orbitofrontal Cortex

A significant main effect on hippocampal volume was found for diagnosis (F = 8.6, *df* = 1,65, p<.005) (see Table 1). Post hoc tests revealed a significant volume decrease in the right hippocampus of patients compared to controls (F = 16.6, *df* = 1,65, p<.001) whereas the left hippocampus was not significantly decreased (F = 2.2, *df* = 1,65, p = .144; Figure 1). No significant main effects of diagnosis were found on parahippocampal volume (F = 0.4, *df* = 1,65, p = .518), orbitofrontal gray matter volume (F = 1.2, *df* = 1,52, p = .224), orbitofrontal white matter (F = .05, *df* = 1,52, p = .825), medial orbitofrontal gray matter (F = 2.6, *df* = 1,52, p = .130), and lateral orbital gray matter (F = .005, *df* = 1,52, p = .942; also shown in Table 1).

There was no significant Pearson partial correlation between volumes of the hippocampus, parahippocampal gyrus, and orbitofrontal cortex and the MMSE score, MADRS score, and duration of depression.

Hippocampal Volumes and White Matter Lesions

Results from multiple linear regression analysis indicated that total hippocampal volumes and right hippocampal volume were not significantly associated with total number of subcortical lesions using the semi-quantitative rating scale (see Table 2).

Table 1: Demographic, Clinical and Neuroimaging data of Female subjects with Early-Onset Depressive Disorder and Healthy Comparison Subjects

	Patients (N=28)	Controls (N=41)	p
Age, Years, Mean (SD)	64.04 (10.90)	62.37 (11.38)	.55
Height[*A], Centimeters, Mean (SD)	168.43 (7.63)	168.73 (6.32)	.36
Weight[B], Kilograms, Mean (SD)	73.38 (11.89)	71.02 (11.62)	.44
Handedness[C], Right/Left/Ambidexter	22/1/0	36/1/4	.28
Level of education, yr , Mean (SD)	10.89 (4.05)	11.20 (2.89)	.12
MADRS score, Mean (SD)	18.32 (13.02))	3.90 (3.88)	.01
MMSE score, Mean (SD)	27.39 (2.46)	28.58 (1.52)	.02
Age of onset, Years, Mean (SD)	33.04 (9.48)		
Cum. Duration of Illness [D], Months, Mean (SD)	93.50 (17.50)		
Health status			
Smoking [E], n (%)	8 (30.77)	7 (17.07)	.24
Diabetes, n (%)	4 (14.29)	0 (0)	.02
Hypertension, n (%)	8 (28.57)	9 (21.95)	.58
Thyroid disease, n (%)	5 (17.86)	5 (12.20)	.73
White Matter Hyperintensity Rating			
Periventricular[F]			
Frontal, n (%)	6 (21.43)	7 (17.07)	.65
Lateral, n (%)	6 (21.43)	6 (14.63)	.47
Occipital, n (%)	1 (3.57)	3 (7.32)	.64
Subcortical[G]			
Small, n (%)	13 (46.43)	15 (36.59)	.41
Medium, n (%)	2 (7.14)	2 (4.88)	.46
Large, n (%)	0 (0)	1 (2.44)	1.00
Subcortical White Matter Lesions[H], Mean (SD)	6.93 (7.89)	14.15 (11.38)	.06
Hippocampal Volume			
Total, mL, Mean (SD)	5.94 (0.70)	6.32 (0.93)	.01
Left, mL, Mean (SD)	3.10 (0.37)	3.20 (0.52)	.12
Right, mL, Mean (SD)	2.84 (0.39)	3.12 (0.45)	.01
Parahippocampal Volume			
Total, mL, Mean (SD)	3.82 (0.68)	3.87 (0.67)	.52
Left, mL, Mean (SD)	1.92 (0.38)	1.98 (0.35)	.26
Right, mL, Mean (SD)	1.90 (0.36)	1.88 (0.39)	.97
Orbitofrontal Cortex Gray Matter Volume			
Total, mL, Mean (SD)	12.63 (4.56)	13.10 (3.33)	.22
Left, mL, Mean (SD)	6.21 (2.27)	6.42 (1.59)	.63
Right, mL, Mean (SD)	6.41 (2.36)	6.68 (1.80)	.69
Lateral, mL, Mean (SD)	4.60 (1.08)	4.54 (1.32)	.94
Medial, mL, Mean (SD)	4.64 (1.26)	5.00 (1.21)	.13
Orbitofrontal Cortex White Matter Volume			
Total, mL, Mean (SD)	7.61 (2.72)	8.42 (1.45)	.83
Left, mL, Mean (SD)	3.76 (1.40)	4.21 (.68)	.45
Right, mL, Mean (SD)	3.86 (1.37)	4.21 (.90)	.76
Total Brain Volume			
Total, mL, Mean (SD)	980.71 (87.91)	965.01 (107.02)	.56
Cranium			
Total, mL, Mean (SD)	1372.83 (89.91)	1330.70 (105.36)	.20

MADRS, Montgomery Åsberg Depression Rating Scale, MMSE, Mini-Mental State Examination. [a]Missing patient data for 7[b], 5[c], 4[d], 5[e], 2[f] subjects. [g]Periventricular white matter lesions are non-discrete in nature. A total score was calculated by adding up the scores at the three different locations. [h]Subcortical white matter lesions were categorized according to their largest diameter in small (<3 mm), medium (3-10 mm), or large lesions (>10 mm). These figures represent the total number of participants that had subcortical white matter lesions for each category. [i]Numbers represent raw data for patients (n = 13) and controls (n = 15) with white matter lesions. Statistical analysis indicated that total number of subcortical white matter lesions was not normally distributed. Therefore, this variable was transformed. Statistical analysis was done using the square root of the total number of subcortical white matter lesions.

Defining white matter lesion pathology as the total score of periventricular lesions (see Table 1 footnote) did not alter the outcome of any of the regression analyses.

Diabetes, Hypertension and Medication

Analyses were re-examined after patients and healthy comparison subjects with diabetes or hypertension or patients receiving lithium had been excluded. No significant differences in results were found.
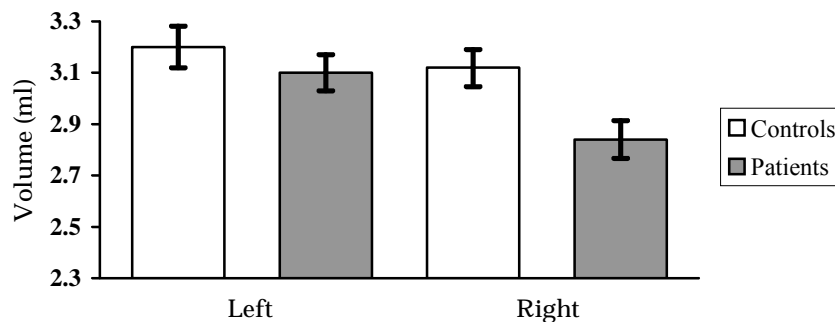

Figure 1. Left and right hippocampal volume (mean, SE) in aged female subjects with early-onset depression and healthy control subjects.

DISCUSSION

This study investigated structural brain abnormalities of 28 middle-aged and elderly female subjects with early-onset depression and 41 age-matched healthy comparison subjects. The main findings of this study were that right hippocampal volume was significantly decreased in EOD subjects whereas hippocampal volume was not associated with severity of white matter lesions. Additionally, orbitofrontal cortex volume and parahippocampal volume did not differ significantly between depressed subjects and healthy comparison subjects.

Our result of predominantly right hippocampal volume decrease is consistent with previous studies revealing reductions in right hippocampal volume as well as right

Table 2. Multiple Linear Regression Models for Total Number of Subcortical White Matter Lesions by Diagnosis

| | | | | | | White matter lesion severity[a] | | | | |
| | | | Patients | | | | | | Control | | |
	b^{b}	(SE)	t	p	(95% CI)		b^{b}	(SE)	t	p	(95% CI)
THC	.102	(.137)	.744	.476	(-.208, .411)		.0534	(.159)	.335	.744	(-.298, .404)
RHC	.0473	(.069)	.683	.512	(-.109, .204)		.0045	(.078)	.058	.955	(-.167, .175)

CI, confidence interval; , RHC, right hippocampal volume; SE, standard error; THC, total hippocampal volume.
[a]Total number of subcortical white matter lesions was defined as the square root of the total number of subcortical lesions of all categories per subject.
[b]Change in mL for every unit change in the independent variable (total number of subcortical white matter lesions) on the basis of regression by age and total brain volume.

hippocampal gray matter density in elderly depressed subjects with mixed age of onset; however, left-sided volume reductions as well as bilateral loss of hippocampal volume have also been described in aged female EOD subjects.[36-39] Neuropathologic mechanisms that could lead to hippocampal atrophy in depression are glucocorticoid-induced neurotoxicity with repeated episodes of depression, direct glia cell loss or glia cell loss leading to changes in levels of glutamate and brain derived neurotrophic factor resulting in increased vulnerability of the hippocampus to neurotoxic damage.[5,39,40,41] A causal relationship between repeated depressive episodes and hippocampal volume decrease is supported by studies describing inverse correlations between hippocampal volume and gray matter volume with duration of illness in EOD subjects; however, we did not find a significant association between decreased hippocampal volume and duration of depression.[20,38,39,42] Our results might be explained in light of a recent cross-sectional study that reported a nonlinear relationship between hippocampal volume decrease and duration of illness in EOD subjects. Reduction of hippocampal volume was greatest when illness duration was short (first two years) and remained stable after that period.[42] This finding suggests that inclusion of patients with a longer-standing depressive illness, as was the case in our sample, might obscure an association between hippocampal volume and illness duration. An alternative explanation for our finding is that smaller hippocampal volume at birth leads to increased vulnerability or increased risk for developing depression.

To date, there have been no reports on parahippocampal gyrus volume in aged EOD subjects. Increased parahippocampal atrophy ratings have been described in patients with Alzheimer's disease but not in bipolar patients when compared to depressed elders and

healthy comparison subjects, respectively.[43,44] These findings are congruent with studies in which parahippocampal volume reductions have been associated with Alzheimer's disease.[45,46] The fact that we did not find decreased parahippocampal gyrus volume reduction could thus be seen in the context of the more subtle neuropathologic mechanisms underlying early-onset depression.

Volumetric reductions of prefrontal cortex and orbitofrontal cortex have recently been reported in middle-aged and elderly EOD subjects.[47-50] We were not able to replicate previous findings of decreased OFC volume in aged EOD subjects. An explanation for the discrepancy between the findings might be the differences in the patient samples. Our patient group consisted of middle-aged and elderly depressed subjects, whereas other studies have only examined middle-aged depressed subjects.[48,50] Kumar et al (2000) reported a high rate on a measure of overall medical comorbidity in the patients compared with control subjects.[47] We did not measure medical comorbidity in the same manner; however, our data suggests smaller differences in medical co-morbidity between patients and control subjects compared with the differences in medical co-morbidity reported by Kumar et al (2000). Therefore it seems unlikely that the results of the current study can be explained by differences in medical comorbidity. Another reason could be the variability in brain structure delineation as large differences in volume of the orbitofrontal cortex have been reported between studies examining healthy subjects.[50] However, in our sample medial orbitofrontal gray matter volume was clearly smaller in subjects with depression (4.64 mL versus 5.00 mL, $p = .13$) indicating that a greater patient sample might have led to a significant difference between the two groups.

This study did not reveal an association between hippocampal volume and the total number of subcortical white matter lesions. This is consistent with studies reporting a decrease in volume of the orbitofrontal cortex and hippocampus in late-life depressed subjects compared to healthy controls but no association between these decreased volumes and white matter lesions.[19,51] Increased severity of white matter lesions has been associated with ageing and cerebrovascular disease in the elderly population and with late-onset depression in late-life depressed subjects particularly in frontal and subcortical areas.[8-10,33,52,54,55] White matter lesions might disrupt anatomic connections between parts of the prefrontal cortex and the limbic system leading to functional and ultimately, structural impairment of hippocampus and orbitofrontal cortex, which may result in depression; however, our sample consisted of aged EOD subjects in whom severity of white matter lesion pathology tends to be less prominent.[10,17-19] Indeed, both depressed subjects and healthy comparison subjects did not reveal severe white matter lesion pathology as reflected by the low ratings on the lesion classification scale. From these findings one could conclude that in this sample of aged EOD subjects smaller hippocampal volumes rather then white matter lesions represent structural neuropathology associated with depression. Furthermore, our results point to a dissociation between reduced hippocampal volume and total number of subcortical white matter lesions, which might be explained by separate underlying neuropathologic mechanisms. Two independent neuropathologic pathways to late-life depression have been proposed: first, smaller prefrontal and limbic volumes may interact with complex neurobiological events, leading to major depression in the elderly; second, increased subcortical white matter lesion severity, indicative of cerebrovascular pathology, may

dominantly contribute to the development of major depression in elders.[47,56-59] Our results suggest that in aged EOD subjects, the first pathway might be dominant, with smaller hippocampal volume as an important contributor. The second pathway is more dominant in subjects with late age of onset because these tend to present with increased white matter lesion severity and vascular risk factors.[8-10] This hypothesis should be seen as preliminary. Future studies combining white matter lesion pathology and hippocampal volumes in subjects with early- and late-onset depression are necessary to determine whether and when white matter lesions are associated with reduced hippocampal volume. This study is limited in several aspects, which should be taken into consideration when interpreting its results. First, the number of patients in which measurements were completed was limited. Therefore, limited statistical power may have prevented us from finding differences in parahippocampus gyrus volume. Second, the use of medication. Although we accounted for lithium use in our analyses, the effect of cumulative years of medication treatment cannot be ruled out. Third, we used a visual rating scale for rating of white matter lesions, which might be a lesser correlate of underlying pathology compared to volumetric assessment of lesions. Additionally, we did not have information on location of subcortical lesions preventing us from investigating the association between decreased hippocampal volume and neuroanatomically relevant positioned subcortical lesions. Fourth, the olfactory sulcus was used to divide the orbitofrontal cortex in a medial and lateral part, which may not reflect actual borders. However there are no generally accepted anatomic landmarks used as a reference for subdividing the orbitofrontal cortex.[32]

We examined female middle-aged and elderly subjects with early-onset depression and healthy comparison subjects and found right hippocampal volume to be decreased in depressed subjects. Additionally, reduced hippocampal volume was not related to severity of white matter lesions. Both follow-up and basic studies using large samples are needed to determine whether disruptions in frontal-limbic white matter tracts can affect hippocampal volume.

REFERENCES

1   Cummings,JL (1993): The neuroanatomy of depression. J.Clin.Psychiatry 54 Suppl: 14-20.

2   Drevets,WC (2000): Neuroimaging studies of mood disorders. Biol.Psychiatry 48: 813-829.

3   Sheline,YI (2003): Neuroimaging studies of mood disorder effects on the brain. Biol.Psychiatry 54: 338-352

4   Bowley,M, Drevets,W, Ongur,D, Price,J (2002): Low glial numbers in the amygdala in major depressive disorder. Biol.Psychiatry 52: 404.

5   Harrison,PJ (2002): The neuropathology of primary mood disorder. Brain 125: 1428-1449.

6   Ongur,D, Drevets,WC, Price,JL (1998): Glial reduction in the subgenual prefrontal cortex in mood disorders. Proc.Natl.Acad.Sci.U.S.A 95: 13290-13295.

7   Rajkowska,G, Miguel-Hidalgo,JJ, Wei,J, Dilley,G, Pittman,SD, Meltzer,HY et al (1999): Morphometric evidence for neuronal and glial prefrontal cell pathology in major depression. Biol.Psychiatry 45: 1085-1098.

8   de Groot,JC, de Leeuw,FE, Oudkerk,M, Hofman,A, Jolles,J, Breteler,MM (2000): Cerebral white matter lesions and depressive symptoms in elderly adults. Arch.Gen.Psychiatry 57: 1071-1076.

9   Figiel,GS, Krishnan,KR, Doraiswamy,PM, Rao,VP, Nemeroff,CB, Boyko,OB (1991): Subcortical hyperintensities on brain magnetic resonance imaging: a comparison between late age onset and early onset elderly depressed subjects. Neurobiol.Aging 12: 245-247.

10   Salloway,S, Malloy,P, Kohn,R, Gillard,E, Duffy,J, Rogg,J et al (1996): MRI and neuropsychological differences in early- and late-life-onset geriatric depression. Neurology 46: 1567-1574.

11   Greenwald,BS, Kramer-Ginsberg,E, Krishnan,RR, Ashtari,M, Aupperle,PM, Patel,M (1996): MRI signal hyperintensities in geriatric depression. Am.J.Psychiatry 153: 1212-1215.

12   Kumar,A, Bilker,W, Jin,Z, Udupa,J, Gottlieb,G (1999): Age of onset of depression and quantitative neuroanatomic measures: absence of specific correlates. Psychiatry Res. 91: 101-110.

13   Rabins,PV, Pearlson,GD, Aylward,E, Kumar,AJ, Dowell,K (1991): Cortical magnetic resonance imaging changes in elderly inpatients with major depression [see comments]. Am.J.Psychiatry 148: 617-620.

14   Coffey,CE, Wilkinson,WE, Weiner,RD, Parashos,IA, Djang,WT, Webb,MC et al (1993): Quantitative cerebral anatomy in depression. A controlled magnetic resonance imaging study. Arch.Gen.Psychiatry 50: 7-16.

15   Hickie,I, Scott,E, Mitchell,P, Wilhelm,K, Austin,MP, Bennett,B (1995): Subcortical hyperintensities on magnetic resonance imaging: clinical correlates and prognostic significance in patients with severe depression. Biol.Psychiatry 37: 151-160.

16   Dupont,RM, Jernigan,TL, Heindel,W, Butters,N, Shafer,K, Wilson,T et al (1995): Magnetic resonance imaging and mood disorders. Localization of white matter and other subcortical abnormalities. Arch.Gen.Psychiatry 52: 747-755.

17   de Leeuw,FE, Barkhof,F, Scheltens,P (2004): White matter lesions and hippocampal atrophy in Alzheimer's disease. Neurology 62: 310-312.

18   Soares,JC, Mann,JJ (1997): The anatomy of mood disorders--review of structural neuroimaging studies [see comments]. Biol.Psychiatry 41: 86-106.

19   Lee,SH, Payne,ME, Steffens,DC, McQuoid,DR, Lai,TJ, Provenzale,JM et al (2003): Subcortical lesion severity and orbitofrontal cortex volume in geriatric depression. Biol.Psychiatry 54: 529-533.

20   Lampe,IK, Hulshoff Pol,HE, Janssen,J, Schnack,HG, Kahn,RS, Heeren,TJ (2003): Association of depression duration with reduction of global cerebral gray matter volume in female patients with recurrent major depressive disorder. Am.J.Psychiatry 160: 2052-2054.

21   Sheehan,DV, Lecrubier,Y, Sheehan,KH, Amorim,P, Janavs,J, Weiller,E et al (1998): The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. J.Clin.Psychiatry 59 Suppl 20: 22-33.

22   Folstein,MF, Folstein,SE, McHugh,PR (1975): "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J.Psychiatr.Res. 12: 189-198.

23   Montgomery,SA, Asberg,M (1979): A new depression scale designed to be sensitive to change. Br.J.Psychiatry 134: 382-389.

24   Snaith,RP, Harrop,FM, Newby,DA, Teale,C (1986): Grade scores of the Montgomery-Asberg Depression and the Clinical Anxiety Scales. Br.J.Psychiatry 148: 599-601.

25   Talairach, J. and Tournoux, P. (1988). Co-planar stereotaxic atlas of the human brain. Thieme: New York.

26   Sled,JG, Zijdenbos,AP, Evans,AC (1998): A nonparametric method for automatic correction of intensity nonuniformity in MRI data. IEEE Trans.Med.Imaging 17: 87-97.

27   Schnack,HG, Hulshoff Pol,HE, Baare,WF, Staal,WG, Viergever,MA, Kahn,RS (2001): Automated separation of gray and white matter from MR images of the human brain. Neuroimage. 13: 230-237.

28   Pruessner,JC, Li,LM, Serles,W, Pruessner,M, Collins,DL, Kabani,N et al (2000): Volumetry of hippocampus and amygdala with high-resolution MRI and three-dimensional analysis software: minimizing the discrepancies between laboratories. Cereb.Cortex 10: 433-442.

29   Baare,WF, van Oel,CJ, Hulshoff Pol,HE, Schnack,HG, Durston,S, Sitskoorn,MM et al (2001): Volumes of brain structures in twins discordant for schizophrenia. Arch.Gen.Psychiatry 58: 33-40.

30   Cahn,W, Pol,HE, Bongers,M, Schnack,HG, Mandl,RC, Van Haren,NE et al (2002): Brain morphology in antipsychotic-naive schizophrenia: a study of multiple brain structures. Br.J.Psychiatry Suppl 43: s66-s72.

31   Watson,C, Andermann,F, Gloor,P, Jones-Gotman,M, Peters,T, Evans,A et al (1992): Anatomic basis of amygdaloid and hippocampal volume measurement by magnetic resonance imaging. Neurology 42: 1743-1750.

32   Lacerda,AL, Hardan,AY, Yorbik,O, Keshavan,MS (2003): Measurement of the orbitofrontal cortex: a validation study of a new method. Neuroimage. 19: 665-673.

33   de Leeuw,FE, de Groot,JC, Oudkerk,M, Witteman,JC, Hofman,A, van Gijn,J et al (2002): Hypertension and cerebral white matter lesions in a prospective cohort study. Brain 125: 765-772.

34   Prins,ND, van Straaten,EC, van Dijk,EJ, Simoni,M, van Schijndel,RA, Vrooman,HA et al (2004): Measuring progression of cerebral white matter lesions on MRI: visual rating and volumetrics. Neurology 62: 1533-1539.

35   Bartko,JJ, Carpenter,WT, Jr. (1976): On the methods and theory of reliability. J.Nerv.Ment.Dis. 163: 307-317.

36   Steffens,DC, Byrum,CE, McQuoid,DR, Greenberg,DL, Payne,ME, Blitchington,TF et al (2000): Hippocampal volume in geriatric depression. Biol.Psychiatry 48: 301-309.

37   Bell-McGinty,S, Butters,MA, Meltzer,CC, Greer,PJ, Reynolds,CF, III, Becker,JT (2002): Brain morphometric abnormalities in geriatric depression: long-term neurobiological effects of illness duration. Am.J.Psychiatry 159: 1424-1427.

38   Sheline,YI, Wang,PW, Gado,MH, Csernansky,JG, Vannier,MW (1996): Hippocampal atrophy in recurrent major depression. Proc.Natl.Acad.Sci.U.S.A 93: 3908-3913.

39   Sheline,YI, Sanghavi,M, Mintun,MA, Gado,MH (1999): Depression duration but not age predicts hippocampal volume loss in medically healthy women with recurrent major depression. J.Neurosci. 19: 5034-5043.

40   Sapolsky,RM (2000): Glucocorticoids and hippocampal atrophy in neuropsychiatric disorders. Arch.Gen.Psychiatry 57: 925-935.

41   Szatkowski,M, Attwell,D (1994): Triggering and execution of neuronal death in brain ischaemia: two phases of glutamate release by different mechanisms. Trends Neurosci. 17: 359-365.

42   43   O'Brien,JT, Desmond,P, Ames,D, Schweitzer,I, Chiu,E, Tress,B (1997): Temporal lobe magnetic resonance imaging can differentiate Alzheimer's disease from normal ageing, depression, vascular dementia and other causes of cognitive impairment. Psychol.Med. 27: 1267-1275.

44   Pearlson,GD, Barta,PE, Powers,RE, Menon,RR, Richards,SS, Aylward,EH et al (1997): Ziskind-Somerfeld Research Award 1996. Medial and superior temporal gyral volumes and cerebral asymmetry in schizophrenia versus bipolar disorder. Biol.Psychiatry 41: 1-14.

45   Chetelat,G, Baron,JC (2003): Early diagnosis of Alzheimer's disease: contribution of structural neuroimaging. Neuroimage. 18: 525-541.

46   Du,AT, Schuff,N, Zhu,XP, Jagust,WJ, Miller,BL, Reed,BR et al (2003): Atrophy rates of entorhinal cortex in AD and normal aging. Neurology 60: 481-486.

47   Kumar,A, Bilker,W, Jin,Z, Udupa,J (2000): Atrophy and high intensity lesions: complementary neurobiological mechanisms in late-life major depression. Neuropsychopharmacology 22: 264-274.

48   Bremner,JD, Vythilingam,M, Vermetten,E, Nazeer,A, Adil,J, Khan,S et al (2002): Reduced volume of orbitofrontal cortex in major depression. Biol.Psychiatry 51: 273-279.

49   Ballmaier,M, Sowell,ER, Thompson,PM, Kumar,A, Narr,KL, Lavretsky,H et al (2004): Mapping brain size and cortical gray matter changes in elderly depression. Biol.Psychiatry 55: 382-389.

50   Lacerda,AL, Keshavan,MS, Hardan,AY, Yorbik,O, Brambilla,P, Sassi,RB et al (2004): Anatomic evaluation of the orbitofrontal cortex in major depressive disorder. Biol.Psychiatry 55: 353-358.

51   Lloyd,AJ, Ferrier,IN, Barber,R, Gholkar,A, Young,AH, O'Brien,JT (2004): Hippocampal volume change in depression: late- and early-onset illness compared. Br.J.Psychiatry 184: 488-495.

52   Schmidt,R, Schmidt,H, Kapeller,P, Enzinger,C, Ropele,S, Saurugg,R et al (2002): The natural course of MRI white matter hyperintensities. J.Neurol.Sci. 203-204: 253-257.

53   O'Brien,J, Desmond,P, Ames,D, Schweitzer,I, Harrigan,S, Tress,B (1996): A magnetic resonance imaging study of white matter lesions in depression and Alzheimer's disease. Br.J.Psychiatry 168: 477-485.

54   Taylor,WD, MacFall,JR, Steffens,DC, Payne,ME, Provenzale,JM, Krishnan,KR (2003): Localization of age-associated white matter hyperintensities in late-life depression. Prog.Neuropsychopharmacol.Biol.Psychiatry 27: 539-544.

55   Thomas,AJ, Perry,R, Kalaria,RN, Oakley,A, McMeekin,W, O'Brien,JT (2003): Neuropathological evidence for ischemia in the white matter of the dorsolateral prefrontal cortex in late-life depression. Int.J.Geriatr.Psychiatry 18: 7-13.

56   Lopez,JF, Chalmers,DT, Little,KY, Watson,SJ (1998): A.E. Bennett Research Award. Regulation of serotonin1A, glucocorticoid, and mineralocorticoid receptor in rat and human hippocampus: implications for the neurobiology of depression. Biol.Psychiatry 43: 547-573.

57   Thomas,AJ, O'Brien,JT, Davis,S, Ballard,C, Barber,R, Kalaria,RN et al (2002): Ischemic basis for deep white matter hyperintensities in major depression: a neuropathological study. Arch.Gen.Psychiatry 59: 785-792.

58   Alexopoulos,GS, Meyers,BS, Young,RC, Campbell,S, Silbersweig,D, Charlson,M (1997): 'Vascular depression' hypothesis. Arch.Gen.Psychiatry 54: 915-922.

59   Krishnan,KR, Hays,JC, Blazer,DG (1997): MRI-defined vascular depression. Am.J.Psychiatry 154: 497-501.

Chapter 3

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

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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 $\geq$ 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 ($\geq$ 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]

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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

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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.

REFERENCES

1   Sheline,YI, Sanghavi,M, Mintun,MA, Gado,MH (1999): Depression duration but not age predicts hippocampal volume loss in medically healthy women with recurrent major depression. J.Neurosci. 19: 5034-5043.

2   Steffens,DC, Byrum,CE, McQuoid,DR, Greenberg,DL, Payne,ME, Blitchington,TF et al (2000): Hippocampal volume in geriatric depression. Biol.Psychiatry 48: 301-309.

3   Bell-McGinty,S, Butters,MA, Meltzer,CC, Greer,PJ, Reynolds,CF, III, Becker,JT (2002): Brain morphometric abnormalities in geriatric depression: long-term neurobiological effects of illness duration. Am.J.Psychiatry 159: 1424-1427.

4   Janssen,J, Hulshoff Pol,HE, Lampe,IK, Schnack,HG, de Leeuw,FE, Kahn,RS et al (2004): Hippocampal changes and white matter lesions in early-onset depression. Biol.Psychiatry 56: 825-831.

5   O'Brien,JT, Lloyd,A, McKeith,I, Gholkar,A, Ferrier,N (2004): A longitudinal study of hippocampal volume, cortisol levels, and cognition in older depressed subjects. Am.J.Psychiatry 161: 2081-2090.

6   Axelson,DA, Doraiswamy,PM, McDonald,WM, Boyko,OB, Tupler,LA, Patterson,LJ et al (1993): Hypercortisolemia and hippocampal changes in depression. Psychiatry Res. 47: 163-173.

7   Sheline,YI, Wang,PW, Gado,MH, Csernansky,JG, Vannier,MW (1996): Hippocampal atrophy in recurrent major depression. Proc.Natl.Acad.Sci.U.S.A 93: 3908-3913.

8   Lampe IK, Hulshoff Pol HE, Janssen J, Schnack HG, Kahn RS, Heeren TJ (2003): Association of depression duration with reduction of global cerebral gray matter volume in female patients with recurrent major depressive disorder. Am J Psychiatry 160:2052-2054.

9   MacQueen,GM, Campbell,S, McEwen,BS, Macdonald,K, Amano,S, Joffe,RT et al (2003): Course of illness, hippocampal function, and hippocampal volume in major depression. Proc.Natl.Acad.Sci.U.S.A 100: 1387-1392.

10   Lloyd,AJ, Ferrier,IN, Barber,R, Gholkar,A, Young,AH, O'Brien,JT (2004): Hippocampal volume change in depression: late- and early-onset illness compared. Br.J.Psychiatry 184: 488-495.

11   Hickie,I, Naismith,S, Ward,PB, Turner,K, Scott,E, Mitchell,P et al (2005): Reduced hippocampal volumes and memory loss in patients with early- and late-onset depression. Br.J.Psychiatry 186: 197-202.

12   Figiel,GS, Krishnan,KR, Doraiswamy,PM, Rao,VP, Nemeroff,CB, Boyko,OB (1991): Subcortical hyperintensities on brain magnetic resonance imaging: a comparison between late age onset and early onset elderly depressed subjects. Neurobiol.Aging 12: 245-247.

13   Salloway,S, Malloy,P, Kohn,R, Gillard,E, Duffy,J, Rogg,J et al (1996): MRI and neuropsychological differences in early- and late-life-onset geriatric depression. Neurology 46: 1567-1574.

14   Steffens,DC, Helms,MJ, Krishnan,KR, Burke,GL (1999): Cerebrovascular disease and depression symptoms in the cardiovascular health study. Stroke 30: 2159-2166.

15   de Groot,JC, de Leeuw,FE, Oudkerk,M, Hofman,A, Jolles,J, Breteler,MM (2000): Cerebral white matter lesions and depressive symptoms in elderly adults. Arch.Gen.Psychiatry 57: 1071-1076.

16   Tupler,L, Krishnan,K, McDonald,W, Dombeck,C, D'Souza,S, Steffens,D (2002): Anatomic location and laterality of MRI signal hyperintensities in late- life depression. J.Psychosom.Res. 53: 665.

17   Kril JJ, Patel S, Harding AJ, Halliday GM (2002): Patients with vascular dementia due to microvascular pathology have significant hippocampal neuronal loss. J Neurol Neurosurg Psychiatry 72:747-751.

18   de Leeuw FE, Barkhof F, Scheltens P (2004): White matter lesions and hippocampal atrophy in Alzheimer's disease. Neurology 62:310-312.

19   den Heijer T, Launer LJ, Prins ND, van Dijk EJ, Vermeer SE, Hofman A, et al (2005): Association between blood pressure, white matter lesions, and atrophy of the medial temporal lobe. Neurology 64:263-267.

20   van der Flier WM, Middelkoop HA, Weverling-Rijnsburger AW, Admiraal-Behloul F, Spilt A, Bollen EL, et al (2004): Interaction of medial temporal lobe atrophy and white matter hyperintensities in AD. Neurology 62:1862-1864.

21   Folstein,MF, Folstein,SE, McHugh,PR (1975): "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J.Psychiatr.Res. 12: 189-198.

22   Montgomery,SA, Asberg,M (1979): A new depression scale designed to be sensitive to change. Br.J.Psychiatry 134: 382-389.

23   Talairach, J., Tournoux, P. (1988). Co-planar stereotaxic atlas of the human brain. Thieme: NewYork.

24   Sled,JG, Zijdenbos,AP, Evans,AC (1998): A nonparametric method for automatic correction of intensity nonuniformity in MRI data. IEEE Trans.Med.Imaging 17: 87-97.

25   Schnack,HG, Hulshoff Pol,HE, Baare,WF, Staal,WG, Viergever,MA, Kahn,RS (2001): Automated separation of gray and white matter from MR images of the human brain. Neuroimage. 13: 230-237.

26   Watson,C, Andermann,F, Gloor,P, Jones-Gotman,M, Peters,T, Evans,A et al (1992): Anatomic basis of amygdaloid and hippocampal volume measurement by magnetic resonance imaging. Neurology 42: 1743-1750.

27   Prins,ND, van Straaten,EC, van Dijk,EJ, Simoni,M, van Schijndel,RA, Vrooman,HA et al (2004): Measuring progression of cerebral white matter lesions on MRI: visual rating and volumetrics. Neurology 62: 1533-1539.

28   Bartko,JJ, Carpenter,WT, Jr. (1976): On the methods and theory of reliability. J.Nerv.Ment.Dis. 163: 307-317.

29   Lai T, Payne ME, Byrum CE, Steffens DC, Krishnan KR (2000): Reduction of orbital frontal cortex volume in geriatric depression. Biol Psychiatry 48:971-975.

30   Almeida OP, Burton EJ, Ferrier N, McKeith IG, O'Brien JT (2003): Depression with late onset is associated with right frontal lobe atrophy. Psychol Med 33:675-681.

31   Ballmaier M, Kumar A, Thompson PM, Narr KL, Lavretsky H, Estanol L, et al (2004): Localizing gray matter deficits in late-onset depression using computational cortical pattern matching methods. Am J Psychiatry 161:2091-2099.

32   Lee SH, Payne ME, Steffens DC, McQuoid DR, Lai TJ, Provenzale JM, Krishnan KR (2003): Subcortical lesion severity and orbitofrontal cortex volume in geriatric depression. Biol Psychiatry 54:529-533.

33   Waldemar, G, Christiansen, P, Larsson, HB, Hogh, P, Laursen, H, Lassen, NA, Paulson OB (1994): White matter magnetic resonance hyperintensities in dementia of the Alzheimer type: morphological and regional cerebral blood flow correlates. J Neurol Neurosurg Psychiatry, 57: 1458-65.

34   Kumar,A, Mintz,J, Bilker,W, Gottlieb,G (2002): Autonomous neurobiological pathways to late-life major depressive disorder. Clinical and pathophysiological implications. Neuropsychopharmacology 26: 229-236.

35   Sapolsky,RM (2000): Glucocorticoids and hippocampal atrophy in neuropsychiatric disorders. Arch.Gen.Psychiatry 57: 925-935.

36   Krishnan,KR, Taylor,WD, McQuoid,DR, MacFall,JR, Payne,ME, Provenzale,JM et al (2004): Clinical characteristics of magnetic resonance imaging-defined subcortical ischemic depression. Biol.Psychiatry 55: 390-397.

Chapter 4

Cerebral volume measurements and subcortical white matter lesions and short-term treatment response in late life depression.

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Abstract

Background: Late-life depression is associated with volumetric reductions of gray matter and increased prevalence of subcortical white matter lesions. Previous studies have shown a poorer treatment outcome in those with more severe structural brain abnormalities. In this study, quantitative and semi-quantitative magnetic resonance imaging (MRI) measures were studied in relation to response to a 12-week controlled antidepressant monotherapy trial.

Methods: MRI (1.5T) brain scans of 42 elderly inpatients with major depression, of which 23 were non-responder to a controlled 12-week antidepressant monotherapy trial, were acquired. In addition, clinical outcome was assessed after a one year period. Measures were volumes of global cerebral and subcortical structures. White matter lesions were measured volumetrically and semi-quantitatively.

Results: After controlling for age, intracranial volume and sex, no differences were found between non-responders and responders after 12 weeks and after one year in volumes of cerebral gray and white matter, orbitofrontal cortex, hippocampus and white matter lesions.

Conclusions: Structural brain measures associated with late-life depression may not be related to short-term treatment response.

INTRODUCTION

Structural Magnetic Resonance Imaging (MRI) studies report that depression is associated with volumetric decreases in the frontal and orbitofrontal cortex and hippocampus in adult and older subjects.[1-7] In addition, many found an increased prevalence of white matter lesions in late-life depressed subjects compared to controls.[8-11] In late-life depression, the relation of decreased cerebral volume and increased white matter lesion prevalence with treatment response has been investigated. In studies that looked at long-term outcome ($\geq$ 2 years), reduced hippocampal gray matter density and increased white matter lesion load at baseline were associated with a chronic course of illness.[12-17] Others have shown that progression of lesions over time, rather than static baseline lesion severity, is an important predictor for long-term outcome.[18]

Evidence for an association of poor short-term antidepressant treatment response with decreased cerebral volumes and increased subcortical white matter lesion prevalence is inconclusive.[19-24] For example, in older severely depressed inpatients with a long history of treatment resistance an association between increased subcortical white matter lesion severity, especially in the frontal white, basal ganglia, and the pontine reticular formation, and poorer acute treatment response was reported.[19-21] However, a recent study among in- and outpatients suggest no such relation.[24] Most of the studies investigating the relationship between structural brain measures and short-term antidepressant treatment response have used an uncontrolled naturalistic treatment protocol or they have focused exclusively on white matter lesion load as a potential predictor for short-term treatment response. We therefore wanted to investigate the difference in baseline global cerebral and subcortical brain measures, including white matter lesions, associated with late-life

depression between responders and non-responders who participated in a controlled 12-week antidepressant monotherapy trial.

METHODS

Participants

This study was designed as an adjunct to a double-blind, randomized 12 week parallel-group trial of venlafaxine and nortryptiline in elderly depressed inpatients. All subjects were inpatients from the depression unit at the Altrecht old age psychiatry department in Zeist, The Netherlands. Inclusion criteria required that patients were 60 years of age or older, all patients had to meet the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria for major depression (single episode or recurrent) as assessed by an old age psychiatrist and confirmed by the International Diagnostic Check List and a total score of at least 20 on the Montgomery Åsberg Depression Rating Scale (MADRS).[25,26] Patients in the treatment trial were excluded if the current episode had been treated unsuccessfully with venlafaxine or nortriptyline, if there was a medical contra-indication to the study medication, if they met DSM-IV diagnostic criteria for dementia or had a Mini Mental Status Examination score (MMSE) < 15, or if they met DSM-IV diagnostic criteria for alcohol or drug abuse within the last year.[27] At baseline complete psychiatric and medical histories were taken, and a thorough physical examination was performed prior to study entry. Physical illnesses were recorded according to Burvill.[28]

This trial was conducted in accordance with the Declaration of Helsinki (1964), as amended in South Africa (1996) and Scotland (2000) and has been approved by the ethics

committee of the University Medical Center Utrecht. Written informed consent was obtained from all patients or their legal representatives before study entry.

Efficacy measures

Efficacy was evaluated with the MADRS. Remission was defined as a final score of 10 or less on the MADRS. Good response was a reduction of at least 50% of score on the MADRS. Partial response was defined as a 25-49% reduction in score on MADRS. Poor response was defined as less then 25% reduction in score on MADRS or drop-out due to insufficient response. Non-response was defined as partial- or poor response; response was defined as good response or remission.

Functional limitations were measured by the Barthel index of Activities of Daily Living (ADL) with a score of 0-20 and functional status was assessed at baseline using the 100-point Global Assessment of Functioning (GAF) scale, on which a score of 100 represent best possible functioning (American Psychiatric Association 1994).[29] Vital signs (hart frequency and blood pressure) were measured weekly. Orthostatic hypotension was defined as a fall of $\geq$ 20 mg Hg in systolic blood pressure or $\geq$ 10 mg Hg in diastolic blood pressure, within 3 minutes of standing. All baseline and endpoint assessments were made by an old age psychiatrist (RMK).

Description short-term trial sample

Of the 50 subjects who received an MRI scan, eight did not finish the 12-week antidepressant trial due serious adverse events according to the patient (n=2), refusal of the patient for other reasons (n=2), protocol violation (n=1), and withdrawal for medical reasons (n=3). These patients were excluded from the study. Of the remaining 42 patients, five patients did not finish the trial due to insufficient response (all had at least

seven weeks of treatment) and these subjects were analyzed as non-responders in the completers group. This left a final sample of 23 non-responders (55%) and 19 responders. There were no significant psychiatric, cognitive, physical and treatment response differences between patients having a scan and those not (analyses not shown).

Description of follow-up sample

Patients that finished the short-term treatment trial were asked for assessment of their clinical outcome after a one year period. To investigate whether clinical response, independent of treatment type, was related to the neuroimaging variables we classified patients into poor outcome and good outcome using the baseline and one year follow-up MADRS score. Classification-criteria were identical to the division in non-response and response. At the one year mark, eight patients were lost due to missing MADRS data. Of the remaining 34 patients, 24 (71%) were responders.

MRI Acquisition

Scans were acquired as soon as possible after initiation of treatment. In a number of cases, patients consented to the MRI acquisition only after the treatment trial had ended. Magnetic resonance images were acquired using a scanner (Philips Gyroscan; Philips Medical Systems, Best, the Netherlands) operating at 1.5 T in all subjects. T1-weighted, 3-dimensional, fast field echo scans with 160 to 180 1.2-mm contiguous coronal slices (echo time [TE], 4.6 milliseconds; repetition time [TR], 30 milliseconds; flip angle, 30°; field of view [FOV], 256 mm; and in-plane voxel sizes, 1 x 1 mm^2) and T2-weighted, dual echo turbo spin echo scans with 90 2.1-mm contiguous coronal slices (TE1, 14 milliseconds; TE2, 90 milliseconds; TR, 4530 milliseconds; flip angle, 90°; FOV, 256 mm; and in-plane voxel sizes, 1 x 1 mm^2) of the whole head were used for quantitative

measurements. In addition, FLAIR-weighted scans with 19 axial 5-mm slices and a 1.2-mm gap (TE1, 100 milliseconds, TE2, 90 milliseconds, flip angle, 90°, FOV 256 mm, and in-plane voxel sizes, 0.89 x 0.89 mm^2) and T2-weighted, dual echo turbo spin echo scans with 19 axial 5-mm slices and a 1.2-mm gap (TE1, 30 milliseconds; TE2, 90 milliseconds; TR, 2377 milliseconds, flip angle, 90°; FOV, 256 mm; and in-plane voxel sizes, 0.89 x 0.89 mm^2) were used for clinical neurodiagnostic evaluation and all 19 axial 5-mm slices (1.2 mm gap) of both scans were used for manual segmentation of white matter lesions and inspected for white matter lesion ratings.

Before quantitative assessments and white matter lesion rating, 10 MRI scans were randomly chosen and cloned for intrarater and reliability determined by the intraclass correlation coefficient (ICC) for volumetric assessments and weighted kappas for white matter lesion rating.[30] All MRI scans were coded to ensure masking for subject identification and diagnosis. The MRI data sets were transformed (no scaling) to the Talairach frame with software developed in house.[31] 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. In addition, scans were corrected for inhomogeneities in the magnetic field.[32] Intracranial, total brain, gray and white matter volumes of the cerebrum (total brain excluding cerebellum and stem), and ventricular volume were measured automatically by using histogram analysis algorithms and a series of mathematical morphology operators to connect all voxels of interest.[33,34] Intracranial volume was segmented on the DTSE scans, with the foramen magnum being used as inferior boundary. Total brain volumes were segmented on the 3D-FFE (T1-weighted)

scans and contained gray and white matter tissue only. All images were checked after the measurements and corrected manually if necessary.

Quantitative measurements of the hippocampus, parahippocampal gyrus, orbitofrontal cortex, and white matter lesions were 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 and parahippocampal gyrus have been previously described.[6] 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. Parahippocampal gyrus segmentation began in the coronal slice in which the optic tract is situated above the amygdala. The posterior commissure was its posterior border.[35] The orbitofrontal cortex was manually segmented within the total brain mask in the coronal plane using a geometrical method.[6] To summarize this method briefly, the posterior border was determined by the tip of the genu of corpus callosum located in the sagittal plane. The anterior border was the first slice where brain tissue could be identified. The superior limit was divided in two parts. In the subgenual regions, the superior boundary was represented by the inferior border of the anterior cingulate corresponding to a midpoint at the interhemispheric fissure about five slices below the intercommissural line. More anteriorly, the superior limit was represented by a midpoint placed on the intercommissural line. For the lateral borders, horizontal and vertical crosshairs were placed as tangent lines at the inferior and lateral surfaces of the frontal lobes in all slices. The intersection of these two lines generated two lateral points that were connected to the superior limit point, composing the lateral boundaries of the segment. Anterior and

inferior borders were crossed, as segmentations in these areas were larger then necessary. This manual segmentation was multiplied with the binary mask of the total brain resulting in an orbitofrontal cortex segmentation without the superfluous segmentation. White matter lesions were manually segmented on the FLAIR scan by the first author under supervision of an expert (FEL) who identified and marked the lesions using both dual echo and FLAIR scans. Finally, the expert inspected the segmentations for accuracy. In addition, the expert rated the number and size of subcortical white matter lesions using a semi-quantitative scale.[36]

Reliability

A single operator (JJ) performed the volume measurements of the hippocampus, parahippocampal gyrus and orbitofrontal cortex. ICCs for the left and right hippocampus were 0.98 and 0.97, for the parahippocampal gyrus 0.73 and 0.78, for the orbitofrontal cortex 0.98, for the periventricular lesions 0.94, and for the subcortical lesions 0.98. For semi-quantitative white matter lesion rating the intrarater study showed good to excellent agreement, weighted kappas for grading the periventricular and subcortical WML ranged between 0.90 and 0.95.

Statistical analysis

Data were examined for outliers, extreme values and the normality of the distribution. Non-normally distributed data were transformed using natural logarithms and re-examined for fit to the normal distribution. To assess the relationship between short-term treatment response, one year outcome and brain volumes we used analysis of covariance (ANCOVA) with brain volumes as the dependent variables and response or outcome as the independent variable. Adjustments were made for age, sex and intracranial volume.

Total brain volume was used as a covariate instead of intracranial volume in the analysis of covariance of orbitofrontal cortex, hippocampal and parahippocampal gyrus volumes. For continuous and non-continuous variables (demographic, clinical and prevalence of white matter lesions), independent-samples t-Test and Chi-Square analyses were used to test for differences.

RESULTS

Short-term treatment trial

Non-responders versus responders

Non-responders were older, and had a trend for more family psychiatric history (see Table 1). Responders and non-responders did not differ significantly in sex, level of education, vascular (smoking, hypertension and diabetes) comorbidity, and number of previous depressive episodes.

Non-responders versus responders: baseline neuroimaging

After controlling for cranial volume and age, total brain volume did not differ between non-responders and responders (F=1.48, df=1,37, p=0.23, see Table 1). In addition, other neuroimaging variables, both raw data and logarithmically transformed data, did not differ between non-responders and responders as well (see Table 1). Leaving out age as a covariate did not change the results.

One year follow-up

Poor outcome versus good outcome: baseline neuroimaging

No differences in baseline neuroimaging variables between patients with poor outcome and good outcome after a one year follow-up were found (Table 2).

Response versus outcome

Response to the short-term treatment trial was not associated with good outcome, 11 responders (46%) and 13 non-responders (54%) had good outcome (χ^2=0.05, degrees of freedom (df)=1, p=0.82).

DISCUSSION

We compared structural brain abnormalities between older non-responders and responders in a controlled short-term antidepressant monotherapy trial and after a one year follow-up period. Non-responders and responders did not differ on any of the quantitative and semi-quantitative structural brain measures.

Our findings in inpatients are in line with a previous short-term controlled trial that measured white matter lesions in older depressed outpatients and also found no association with acute treatment response.[24] In addition, naturalistic treatment studies in older in-and outpatients did not report a relationship between total white matter lesion load and a poorer response to short-term antidepressant monotherapy as well.[20,21,37,38] Moreover, the current finding of no differences in neuroimaging variables between patients that had poor outcome or good outcome after one year compared to baseline strengthen the evidence that no clear association exists between short-term treatment response and structural brain volume changes. In older severely depressed inpatients with a long history of treatment resistance an association between increased total white matter lesion load and poor acute antidepressant response was found.[19] Simpson et al reported a relationship between regionally specific subcortical lesion load (frontal white, basal ganglia, and pontine reticular formation) and poorer response to short-term antidepressant

Table 1: Demographical, clinical and neuroimaging data of responders and non-responders to a 12-week antidepressant monotherapy trial and outcome after 1 year.

	Response 12 weeks			Outcome 52 weeks		
	Non-Responders (N=23)	Responders (N=19)	*p*	Poor outcome (N=10)	Good outcome (N=24)	*p*
Age, years, mean (SD)	72.35 (7.48)	67.95 (4.71)	0.03	68.20 (3.52)	70.08 (6.41)	0.39
Sex, female (%)	15 (65)	13 (68)	0.83	5 (50%)	17 (71%)	0.25
Weight, kilograms, mean (SD)[a]	62.47 (13.00)	68.00 (12.77)	0.24	69.80 (12.75)	65.93 (12.29)	0.46
Level of education, years , mean (SD)	10.04 (3.00)	9.11 (2.40)	0.28	9.10 (3.57)	9.75 (2.36)	0.54
Married, n (%)	13 (57)	10 (53)	0.80	7 (70%)	13 (54%)	0.39
Widow, n (%)	7 (30)	5 (26)	0.77	2 (20%)	7 (29%)	0.58
MADRS score baseline , mean (SD)	33.39 (6.61)	31.58 (6.87)	0.39	30.30 (4.97)	32.13 (6.81)	0.45
MADRS score final, mean (SD)	26.48 (7.97)	8.00 (5.27)	<0.001	21.90 (7.45)	2.96 (2.80)	<0.0
MMSE score baseline, mean (SD)	26.17 (3.14)	27.47 (1.76)	0.12	27.50 (1.84)	26.75 (2.21)	0
						0.35
Age of onset, years, mean (SD)[b]	61.00 (13.39)	57.00 (12.07)	0.33	58.70 (15.10)	57.86 (9.6)	0.85
Number of previous episodes, mean (SD)[c]	1.20 (1.28)	1.58 (1.92)	0.47	0.80 (0.92)	1.23 (0.97)	0.25
Family history of depression, n (%)	17 (74)	8 (42)	0.06	7 (70%)	13 (54%)	0.39
Health status at baseline[d]						
Smoking , n (%)	7 (39%)	7 (39%)	1.00	4 (40%)	7 (37%)	0.87
Diabetes, n (%)	3 (17)	5 (28)	0.42	2 (20%)	5 (26%)	0.71
Hypertension, n (%)	7 (39)	9 (50)	0.50	5 (50%)	8 (42%)	0.68
Burvill acute baseline, mean (SD)[e]	0.11 (0.46)	0 (0)	0.33	0 (0)	0.8 (0.41)	0.53
Burvill chronic baseline, mean (SD)	1.05 (1.08)	1.57 (1.65)	0.25	1.00 (0.94)	1.29 (1.55)	0.58
Barthel ADL baseline, mean (SD)	19.63 (0.96)	18.65 (2.84)	0.16	19.80 (0.63)	18.63 (2.84)	0.21
DSM IV GAF score baseline, mean (SD)	38.91 (12.43)	37.89 (11.22)	0.78	42.00 (11.60)	34.79 (11.65)	0.11
Time between start of trial and scan (weeks), mean (SD)	21.37 (11.72)	21.11 (14.49)	0.95			

MADRS, Montgomery Åsberg Depression Rating Scale; MMSE, Mini-Mental State Examination; ADL, Assessment of Daily Living; GAF, Global Assessment of Functioning; MRI, Magnetic Resonance Imaging; Missing data for [a]10, [b]3, [c]3, [d]6 subjects; [e]Other Burvill summary scores were similar.

Table 2: Baseline neuroimaging data of responders and non-responders to a 12-week antidepressant monotherapy trial and outcome after 1 year.

	Response 12 weeks			Outcome 52 weeks		
	Non-Responders (N=23)	Responders (N=19)	*p*	Poor outcome (N=10)	Good outcome (N=24)	*p*
Baseline MRI						
Cranium, ml, mean (SD)[f]	1400.53 (132.98)	1377.73 (121.43)	0.66	1470.65 (150.35)	1373.22 (113.21)	0.98
Total Brain Volume, ml, mean (SD)	1084.76 129.39)	1072.09 (91.10)	0.23	1165. 69 (130.92)	1058.37 (92.33)	0.18
Cerebral Gray Matter Volume, ml, mean (SD)	502.21 (63.95)	491.01 (49.99)	0.09	553.10 (97.17)	494.27 (45.65)	0.26
Cerebral White Matter Volume, ml, mean (SD)	432.01 (45.41)	444.51 (49.53)	0.68	467.02 (58.68)	437.20 (44.78)	0.80
Lateral Ventricle Volume, ml, mean (SD)	36.89 (16.81)	28.88 (15.46)	0.55	36.58 (19.50)	31.21 (17.09)	0.35
Third Ventricle Volume, ml, mean (SD)	2.03 (0.83)	1.97 (0.85)	0.46	2.06 (0.68)	1.91 (0.97)	0.72
Cerebellum Volume, ml, mean (SD)	128.18 (13.89)	126.84 (12.51)	0.42	134.33 (12.90)	124.98 (12.25)	0.45
Orbitofrontal Cortex Volume, ml, mean (SD)	23.27 (6.79)	20.72 (4.35)	0.30	25.25 (7.36)	22.21 (5.31)	0.67
Orbitofrontal Gray Volume, ml, mean (SD)	14.09 (3.90)	12.59 (2.68)	0.11	15.85 (5.35)	13.71 (3.00)	0.99
Hippocampus Volume, ml, mean (SD)	6.18 (0.79)	6.06 (0.95)	0.42	6.20 (0.98)	6.14 (0.74)	0.17
Parahippocampus Volume, ml, mean (SD)	3.43 (0.69)	3.65 (0.79)	0.43	3.73 (0.99)	3.52 (0.65)	0.94
Periventricular lesion volume, ml, mean (SD)	3.66 (2.87)	5.07 (5.81)	0.49	3.51 (4.09)	4.75 (4.96)	0.47
Subcortical lesion volume, ml, mean (SD)	1.24 (1.12)	2.03 (1.77)	0.14	1.65 (1.57)	1.59 (1.36)	0.63
White matter lesion Prevalence[g]						
Periventricular						
Frontal, n (%)	16 (70)	12 (63)	0.66	7 (70%)	15 (63%)	0.68
Lateral, n (%)	16 (70)	12 (63)	0.66	6 (60%)	16 (67%)	0.71
Occipital, n (%)	3 (13)	5 (26)	0.28	1 (10%)	7 (29%)	0.23
Subcortical						
Small, n (%)	21 (91)	16 (84)	0.48	8 (80%)	22 (92%)	0.34
Medium, n (%)	6 (26)	9 (47)	0.15	2 (20%)	8 (33%)	0.44
Large, n (%)	1 (4)	4 (21)	0.10	1 (10%)	3 (13%)	0.84

Volumes are raw volumes, *p*-value represents significance after controlling for cranial volume, age and sex; [g]Number of people with periventricular and subcortical white matter lesions. Periventricular lesions were rated per region (adjacent to the frontal horn, the lateral ventricles and the occipital horn), subcortical lesions were categorized according to their largest diameter in small (<3 mm), medium (3-10 mm), or large lesions (>10 mm).

treatment in older depressed patients.[21] These latter findings suggests that lesion location rather than total lesion load might be related to short-term antidepressant treatment response. However, these findings need to be replicated in future studies.

In our study, global cerebral volumes and volumes of the orbitofrontal cortex and hippocampus were not associated with treatment response. This is congruent with the negative results from previous short-term and long-term treatment studies in adult and elderly subjects.[23,39,40] Patients with the smallest hippocampal volume had a poor short-term treatment response in one study but there was no difference in hippocampal volume when responders and non-responders were compared.[41] One study, using computed tomography instead of MRI, reported an association between global cerebral atrophy and poorer treatment response.[22]

In the current sample, we did not find a correlation of increased white matter lesion prevalence and decreased cerebral volumes with poorer response to short-term antidepressant treatment in late-life depressed inpatients and with poor outcome after a one year follow-up period. The majority of previous MRI studies investigating short-term treatment response (< one year) in older depressed patients have yielded similar results. Our findings should be interpreted with care due to a relatively small sample size and the delay of the scan acquisition after the start of treatment in a number of patients. Nevertheless, all scans were made preceding the one year mark with a mean period of 32 weeks between the date of the scan and the one year follow-up observation. This makes it unlikely that prompt post-trial brain changes, such as the development of white matter lesions, (< 12-52 weeks) have influenced our results. The previous and current findings do not give substantial evidence for an alteration of the short-term treatment strategy in the presence of structural cerebral abnormalities. In addition, the benefit of one MRI measurement in short-term treatment trials in late-

life depression is expected to be minimal. Future larger controlled trials that include longitudinal MRI data in specific groups of older depressed patients (for example those with a first-episode of late-onset depression) are needed in order to explore the possibilities for clinical contribution of brain changes over time.

DECLARATION OF INTEREST

None.

REFERENCES

1   Coffey, C. E., Wilkinson, W. E., Weiner, R. D., Parashos, I. A., Djang, W. T., Webb, M. C., Figiel, G. S. and Spritzer, C. E. (1993). Archives of General Psychiatry 50(1), 7-16.
2   Lai, T., Payne, M. E., Byrum, C. E., Steffens, D. C. and Krishnan, K. R. (2000). Biological Psychiatry 48(10), 971-975.
3   Sheline, Y. I., Sanghavi, M., Mintun, M. A. and Gado, M. H. (1999). Journal of Neuroscience 19(12), 5034-5043.
4   Steffens, D. C., Byrum, C. E., McQuoid, D. R., Greenberg, D. L., Payne, M. E., Blitchington, T. F., MacFall, J. R. and Krishnan, K. R. (2000). Biological Psychiatry 48(4), 301-309.
5   MacQueen, G. M., Campbell, S., McEwen, B. S., Macdonald, K., Amano, S., Joffe, R. T., Nahmias, C. and Young, L. T. (2003). Proceedings of the National Academy of Scencei U S A 100(3), 1387-1392.
6   Janssen, J., Hulshoff Pol, H. E., Lampe, I. K., Schnack, H. G., de Leeuw, F. E., Kahn, R. S. and Heeren, T. J. (2004). Biological Psychiatry 56(11), 825-831.
7   O'Brien, J. T., Lloyd, A., McKeith, I., Gholkar, A. and Ferrier, N. (2004). American Journal of Psychiatry 161(11), 2081-2090.
8   Krishnan, K. R., Goli, V., Ellinwood, E. H., France, R. D., Blazer, D. G. and Nemeroff, C. B. (1988). Biological Psychiatry 23(5), 519-522.
9   O'Brien, J., Desmond, P., Ames, D., Schweitzer, I., Harrigan, S. and Tress, B. (1996). British Journal of Psychiatry 168(4), 477-485.
10   Steffens, D. C., Helms, M. J., Krishnan, K. R. and Burke, G. L. (1999). Stroke 30(10), 2159-2166.
11   Kumar, A., Bilker, W., Jin, Z. and Udupa, J. (2000). Neuropsychopharmacology 22(3), 264-274.
12   Hickie, I., Scott, E., Wilhelm, K. and Brodaty, H. (1997). Biological Psychiatry 42(5), 367-374.
13   O'Brien, J., Ames, D., Chiu, E., Schweitzer, I., Desmond, P. and Tress, B. (1998). British Medical Journal 317(7164), 982-984.
14   Shah, P. J., Ebmeier, K. P., Glabus, M. F. and Goodwin, G. M. (1998). British Journal of Psychiatry 172, 527-532.
15   Lavretsky, H., Lesser, I. M., Wohl, M., Miller, B. L. and Mehringer, C. M. (1999). American Journal of Geriatric Psychiatry 7(4), 309-316.
16   Baldwin, R. C., Walker, S., Simpson, S. W., Jackson, A. and Burns, A. (2000). International Journal of Geriatric Psychiatry 15(12), 1097-1104.
17   Chen, P. S., McQuoid, D. R., Payne, M. E. and Steffens, D. C. (2006). International Psychogeriatrics, 1-12.
18   Taylor, W. D., Steffens, D. C., MacFall, J. R., McQuoid, D. R., Payne, M. E., Provenzale, J. M. and Krishnan, K. R. (2003). Archives of General Psychiatry 60(11), 1090-1096.
19   Hickie, I., Scott, E., Mitchell, P., Wilhelm, K., Austin, M. P. and Bennett, B. (1995). Biological Psychiatry 37(3), 151-160.
20   Simpson, S. W., Jackson, A., Baldwin, R. C. and Burns, A. (1997). International Psychogeriatrics 9(3), 257-275.
21   Simpson, S., Baldwin, R. C., Jackson, A. and Burns, A. S. (1998). Psychological Medicine 28(5), 1015-1026.
22   Young, R. C., Kalayam, B., Nambudiri, D. E., Kakuma, T. and Alexopoulos, G. S. (1999). American Journal of Geriatric Psychiatry 7(2), 147-150.

23 Simpson, S. W., Baldwin, R. C., Burns, A. and Jackson, A. (2001). International Journal of Geriatric Psychiatry 16(5), 469-476.

24 Salloway, S., Boyle, P. A., Correia, S., Malloy, P. F., Cahn-Weiner, D. A., Schneider, L., Krishnan, K. R. and Nakra, R. (2002). American Journal of Geriatric Psychiatry 10(1), 107-111.

25 Hiller, W., Zaudig, M. and Mombour, W. (1990). Archives of General Psychiatry 47(8), 782-784.

26 Montgomery, S. A. and Asberg, M. (1979). British Journal of Psychiatry 134, 382-389.

27 Folstein, M. F., Folstein, S. E. and McHugh, P. R. (1975). Journal of Psychiatric Research 12(3), 189-198.

28 Burvill, P. W., Mowry, B., Hall,W. D. (1990). International Journal of Geriatric Psychiatry 5(3), 161-170.

29 de Haan, R., Limburg, M., Schuling, J., Broeshart, J., Jonkers, L. and van Zuylen, P. (1993). Nederlands Tijdschrift voor Geneeskunde 137(18), 917-921.

30 Bartko, J. J. and Carpenter, W. T., Jr. (1976). Journalof Nervous and Mental Disorders 163(5), 307-317.

31 Talairach, J., Tournoux, P. (1988). Co-planar stereotaxic atlas of the human brain. Thieme: NewYork.

32 Sled, J. G., Zijdenbos, A. P. and Evans, A. C. (1998). IEEE Transactions in Medical Imaging 17(1), 87-97.

33 Schnack, H. G., Hulshoff, H. E., Baare, W. F., Viergever, M. A. and Kahn, R. S. (2001a). Neuroimage 14(1 Pt 1), 95-104.

34 Schnack, H. G., Hulshoff Pol, H. E., Baare, W. F., Staal, W. G., Viergever, M. A. and Kahn, R. S. (2001b). Neuroimage 13(1), 230-237.

35 Watson, C., Andermann, F., Gloor, P., Jones-Gotman, M., Peters, T., Evans, A., Olivier, A., Melanson, D. and Leroux, G. (1992). Neurology 42(9), 1743-1750.

36 de Groot, J. C., de Leeuw, F. E., Oudkerk, M., Hofman, A., Jolles, J. and Breteler, M. M. (2000). Archives of General Psychiatry 57(11), 1071-1076.

37 Krishnan, K. R., Hays, J. C., George, L. K. and Blazer, D. G. (1998). Depression and Anxiety 8(4), 142-146.

38 Baldwin, R., Jeffries, S., Jackson, A., Sutcliffe, C., Thacker, N., Scott, M. and Burns, A. (2004). Psychological Medicine 34(1), 125-136.

39 Frodl, T., Meisenzahl, E. M., Zill, P., Baghai, T., Rujescu, D., Leinsinger, G., Bottlender, R., Schule, C., Zwanzger, P., Engel, R. R., Rupprecht, R., Bondy, B., Reiser, M. and Moller, H. J. (2004). Archives of General Psychiatry 61(2), 177-183.

40 Vythilingam, M., Vermetten, E., Anderson, G. M., Luckenbaugh, D., Anderson, E. R., Snow, J., Staib, L. H., Charney, D. S. and Bremner, J. D. (2004). Biological Psychiatry 56(2), 101-112.

41 Hsieh, M. H., McQuoid, D. R., Levy, R. M., Payne, M. E., MacFall, J. R. and Steffens, D. C. (2002). International Journal of Geriatric Psychiatry 17(6), 519-525.

Chapter 5

Late-life depression: the differences between early and late-onset illness in a community-based sample

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Abstract

Background: Several studies have described etiological and clinical differences between elderly depressed patients with early-onset of their illness compared to late-onset. While most studies have been carried out in clinical samples it is unclear whether the findings can be generalized to the elderly population as a whole. The aim of this study was to compare early-onset (EOD) and late-onset (LOD) depressive illness in a community-based sample.

Methods: Large (n=3107) representative sample of older persons (55-85 years) in the Netherlands. Two-stage screen procedure to identify elderly with MDD. The Center for Epidemiologic Studies Depression scale (CES-D) was used as a screen and the Diagnostic Interview Schedule (DIS) to diagnose MDD. Data on 90 older persons with early-onset depression and 39 with late-onset depression were available.

Results: Those with LOD were older, and more often widowed. Family psychiatric history, vascular pathology, and stressful early and late-life events did not differ between groups. EOD subjects had more often double depression and more anxiety.

Conclusions: In a community-based sample we did not detect clear differences in aetiology and phenomenology between EOD and LOD. This discrepancy with reports from clinical samples could be due to selection bias in clinical studies. Consequently, all patients with late-life depression deserve a diagnostic work-up of both psychosocial and somatic risk factors and treatment interventions should be focused accordingly.

INTRODUCTION

Major depression is one of the most prevalent and under diagnosed psychiatric disorders in the elderly population and significantly decreases quality of life.[1-3] The first onset of a depressive episode can be early in life as well as first occur in old age. Clinical studies comparing in- and outpatients, have reported differences in aetiology and symptoms between early-onset depression (EOD) and late-onset depression (LOD) in late-life.[4-7] A higher rate of family history of major depression in patients with EOD compared to patients with LOD has suggested increased genetic susceptibility to mood disorders to be associated with earlier age at onset, whereas later age at onset of depression has been associated with increased subcortical vascular pathology.[4,7-11] Additionally, subcortical vascular pathology has been associated with poor treatment outcome suggesting that pharmacological treatment aimed at preventing and reducing cerebrovascular disease might be more suited for LOD subjects.[12-14]

Findings from phenomenological comparisons between patients with EOD and LOD have been inconsistent as some studies show differences in experience of guilt, anxiety, apathy or loss of interest, and executive functioning while others have not replicated this.[5,7,15-18]

Only a minority of the depressed older people in the community is referred to psychiatric care, potentially biasing results from clinical studies.[19] Moreover, patients with EOD usually have been in psychiatric care for a longer time while comorbid features of the depression like apathy, cognitive impairment or a transient ischemic attack might enhance referral of patients with LOD. Therefore it is not clear whether the reported differences between EOD and LOD patients from clinical studies can be generalized to the depressed older people in the community. Using the data of the

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Longitudinal Aging Study Amsterdam (LASA) this study aims to investigate whether differences in etiological risk indicators and phenomenology exist between older EOD and LOD subjects in a community-based sample.

METHODS

Sampling and procedures

The Longitudinal Aging Study Amsterdam (LASA) is an *ongoing* 13-year interdisciplinary study on predictors and consequences of changes in autonomy and well being in the aging population. Full details on sampling and response have been described elsewhere.[20] At baseline (1992/1993), a large (n=3107), random sample of older (55-85) inhabitants, drawn from 11 community registers in three regions of the Netherlands, was interviewed. In order to be able to study age and sex differences, the sample was stratified for age and sex. Due to item non-response on the screen for depression, 51 subjects were lost, leaving 3056 participants at baseline. Depression was diagnosed using a two-stage screening design. All the screen positives and a similarly sized random sample of the screen negatives were approached for diagnostic interviews. The follow up of the baseline study sample consisted of infrequent (3 yearly) interviews, which were identical to the baseline procedure. For the present study, data from baseline and from 2 additional assessments, after 3 years and after 6 years, was used. Eligibility for inclusion in the sample was defined as a diagnosis of major depression at one of the three diagnostic interviews (maximum recency of diagnosis 1 year) and known age at first-onset of depression. A number of subjects in our sample had more then one assessment for first onset of depressive symptoms during participation in the LASA study. Of these subjects, two subjects reported different categories of age at onset between assessments. These subjects were

removed from the sample, reducing the final study sample to 129 subjects, 60 from baseline, and 29 from the second measurement, and 40 from the third measurement.

As previously described, the older old and those with chronic physical illness and cognitive impairment were more likely to drop out at all stages of the study.[20] However, due to the stratified sampling design, these factors remained well represented in the study sample. All interviews were conducted in the homes of respondents by specially trained and intensively supervised interviewers. Informed consent was obtained prior to the study, in accordance with legal requirements in The Netherlands.

Measures

Depression. To *screen* for depression, the Center for Epidemiologic Studies Depression scale (CES-D) was used.[21] The CES-D is a twenty-item scale, developed to measure depressive symptoms in the community. It has been widely used in older community samples and has good psychometric properties in this age group.[22,23] The Dutch translation had similar psychometric properties in three previously studied samples of older persons in the Netherlands. Due to the emphasis on affective symptoms, the overlap with symptoms of physical illness is limited.[24,25] The CES-D generates a total score, ranging from 0 to 60. In order to identify respondents with clinically relevant levels of depression, the generally used cut-off score ≥16 was used. Using this score, the criterion validity of the CES-D for MDD was excellent (sensitivity 100%, specificity 88%).

For *diagnosis*, the Diagnostic Interview Schedule was used (DIS).[26] Possible diagnoses for entry in the study sample were MDD and Double depression. Double depression was defined as the subject fulfilling DSM III criteria for both MDD and Dysthymic Disorder. The DIS interview was designed for epidemiological research

and has been widely used among the elderly. Interviewers were fully trained by certified staff, using the official Dutch translation of the DIS.[27] Information about age at onset of depressive symptoms was obtained from the DIS. A cut-off of 60 years was used to distinguish between early- and late-onset depression. This cut-off was arbitrarily chosen, but has been frequently used in studies of late-life depression.[5,7] The *symptom profile* was derived from the specific depressive symptoms measured in the DIS while anxiety was measured as a *psychiatric comorbidity* measure. *Anxiety* was measured with the Dutch translation of the Hospital Anxiety and Depression Scale-Anxiety subscale (HADS-A).[28] It is composed of 7 Likert type items, in which the respondent is asked to indicate whether over the past 4 weeks he/she has experienced feelings such as restlessness, tenseness, or panic on a scale from 0 (seldom or never) to 3 (always or almost always). The scale has a theoretical range from 0 to 21. We used a cut-off of >7 to identity those with high levels of anxiety.[29]

Risk indicators

Demographic variables include age, sex, level of education, marital status, widowhood, and the size of contact network. Education was measured on an eight-point ordinal scale ranging from uncompleted primary school to completed university. For this study, education was dichotomized as follows: low education (uncompleted or completed primary school) and middle to high education (some secondary education up to and including university). Measures of social support were constructed from a questionnaire, which included detailed questions on both the size and the quality of contacts with members of the social network.[30] In this paper we report on the size of the contact network. *Family history* of affective disorders was assessed with a questionnaire constructed for the present study. *Health related*

variables were cognitive impairment, and physical health. *Physical health* was measured by self-report and crosschecked with data supplied by General Practitioners.[31] Measures include the number of chronic diseases and functional limitations. Chronic diseases included cardiac disease, peripheral arteriosclerosis of the abdominal aorta or the arteries of the lower limb, stroke, diabetes mellitus, lung disease (asthma or chronic obstructive pulmonary disease), malignant neoplasm's, arthritis and any other major chronic diseases. Vascular risk or vascular pathology included cardiac disease, peripheral arteriosclerosis of the abdominal aorta or the arteries of the lower limb, stroke, diabetes mellitus, and hypertension. The questionnaire on functional limitations included the following activities: climbing up and down a staircase of 15 steps without stopping, cutting one's own toenails, and using one's own or public transport. Response categories were 'yes without difficulty', 'yes with difficulty', 'only with help', and 'no, I cannot'. The presence of a functional limitation was defined as a response other then 'yes without difficulty'. *Cognitive impairment* was measured using the Mini-Mental State Examination, using a cut-off of 24 to indicate cognitive decline.[32] *Life events* include catastrophic events experienced in early childhood (five items regarding parental loss, serious personal illness, neglect, and physical and sexual abuse early in life), extreme experiences during the Second World War which have had a lasting effect (one item), and interpersonal losses, separations and conflicts experienced during the past year (seven items). Partner loss during the past year was one of the latter seven items. Because of its importance, this event is also reported on separately. For the present study, the presence of chronic diseases, vascular risk or vascular pathology, functional limitations, and early and late-life events was dichotomized as follows: none (0) and

one or more present (1). All scales used in the present study were previously validated in comparable samples in The Netherlands, or in LASA pilot studies. [33]

Data-analysis

Data were analyzed in two steps. First, logistic regression was used to calculate odds ratios for the bivariate associations between all categorical variables, except depressive symptoms, with age at onset of depression, thereby using 'early-onset depression' as the reference category. The specific depressive symptoms of EOD and LOD were compared using Fischer exact statistics. Age, size of network, CES-D score, and age at onset were compared using ANOVA and *F*-statistics. Secondly, to adjust for potential confounding, odds ratios for the associations between the independent variables (cognition, health, life events, and depressive symptoms) with age at onset of depression were reported after adjustment for sociodemographic variables that were significantly associated with onset of depression in the first step. Throughout, conventional levels of statistical significance were used ($p < 0.05$).

RESULTS

As summarized in Table 1, the following sociodemographic and health related factors were significantly associated with LOD: being older, being widowed, and having impaired cognition. A trend level was reached for having a low education. The following variables were significantly associated with EOD: a diagnosis of double depression, comorbid anxiety, and WWII experiences as a traumatic life event. As summarized in Table 2, the only depressive symptom significantly associated with LOD was weight loss (Odds Ratio (OR) = 2.76; 95% confidence interval (CI) 1.26-6.00). The following depressive symptoms were associated with EOD: feeling

worthless (OR = 0.43; CI 0.20–0.93), and ever thinking of suicide (OR=0.31; CI 0.12–0.83). In the next step, the associations between significant risk indicators and depressive symptoms with onset of depression were adjusted for confounding demographic variables (Table 3). As expected, for most variables the associations weakened. Having a double depression, ever thinking of suicide, weight loss, and the long-term effects of suffering catastrophic events during WWII remained significant associated with EOD.

DISCUSSION

This study aimed to investigate in a community-based sample whether differences in etiological risk indicators and phenomenology exist between elderly subjects with early-onset depression and late-onset depression. We found age, being widowed, cognitive impairment, and traumatic WWII experiences to be associated with age at depression onset. Depression variables associated with age at depression onset were a diagnosis of double depression, anxiety, weight loss, worthlessness, and ever thinking about suicide. After controlling for confounding, traumatic WWII experiences, having a double depression, weight loss, and ever thinking about suicide remained significant.

This study had several limitations, which should be kept in mind when considering the results. First of all, at all stages of the study the older and frailer subjects were at a greater risk of dropping out. Selective loss of the most frail limits somewhat the generalizability of findings. However, due to the stratified sampling frame, health related risk factors were well represented in the study sample. Data on age at depression onset and previous history of MDD was gathered retrospectively and may have been biased due to selective recall in depressed older persons. This implies that

Table 1: Characteristics and odds ratios of the study sample consisting of subjects with early-onset depression (*n*=90) and late-onset depression (*n*=39). For all independent categorical variables, '0' indicates the reference category.

Characteristic	Early-onset n(%)	Late-onset	OR[1] (95% CI)
Age, mean (sd)	71.1 (8.4)	75.3 (6.7)	F=7.40 p<0.00
Sex			
female (0)	72 (80)	27 (69)	
male	18 (20)	12 (31)	1.78 (0.76-4.18)
Level of education			
low (0)	37 (41)	23 (59)	
middle/high	53 (59)	16 (41)	0.49 (0.23-1.04)
Marital status			
not married (0)	32 (36)	19 (49)	
married	58 (64)	20 (51)	0.58 (0.27-1.24)
Widowhood			
not widow (0)	55 (61)	14 (36)	
widowed	35 (39)	25 (64)	2.81 (1.29-6.12)
Network size, mean (sd)	13.1 (8.6)	13.6 (9.1)	F=0.00 p<0.93

Characteristic	Early-onset n(%)	Late-onset	OR (95% CI)
CES-D, mean (sd)	23.29 (9.4)	25.00 (10.7)	F=0.83 p=0.37
Double depression			
no (0)	39 (43)	28 (72)	
yes	51 (57)	11 (28)	0.30 (0.13-0.68)
Family history			
no (0)	40 (58)	19 (76)	
yes	29 (42)	6 (24)	0.44 (0.16-1.23)
Anxiety			
low (0)	33 (38)	22 (58)	
high	53 (62)	16 (42)	0.45 (0.21-0.99)
Cognitive functioning			
MMSE ≥24 (0)	86 (96)	32 (82)	
MMSE <24	4 (4)	7 (18)	4.70 (1.29-17.15)
Chronic physical illness			
no (0)	18 (20)	11 (29)	
one or more	72 (80)	27 (71)	0.56 (0.24-1.32)
Vascular pathology/risk			
no (0)	37 (41)	14 (37)	
one or more	53 (59)	24 (63)	1.11 (0.51-2.41)
Functional limitations			
no (0)	34 (39)	11 (28)	
one or more	54 (61)	28 (72)	1.70 (0.75-3.83)
Early-life events			
no (0)	54 (67)	25 (76)	
one or more	27 (33)	8 (24)	0.64 (0.26-1.61)
Late-life events			
no (0)	16 (23)	7 (23)	
one or more	53 (77)	23 (77)	0.99 (0.36-2.74)
WWII			
no (0)	53 (65)	31 (94)	
yes	28 (35)	2 (6)	0.12 (0.03-0.58)
Partner loss			
no (0)	78 (91)	32 (82)	
yes	8 (9)	7 (18)	2.13 (0.71-6.37)

[1]OR, Odds Ratio for the bivariate associations between categorical variables with age at onset of depression, thereby using 'early-onset depression' as the reference category. *n*, number of patients; CI, Confidence Interval; CES-D, Center for Epidemiologic Studies Depression scale; MMSE, Mini-Mental State Examination.

some of our LOD subjects may have been in reality EOD subjects. This misclassification might have weakened the interpretation of our results. However, a great number of subjects in our sample had more than one assessment for first onset of depressive symptoms (through the DIS) during their participation in the overall LASA study. Of these subjects only two changed category between assessments. Thus, the agreement between assessments can be considered good.

Table 2: Distribution of specific depressive symptoms and age of onset: comparing subjects with early-onset (*n*=90) depression and late-onset depression (*n*=39).

Symptoms	Early-onset	Late-onset	χ^2	p
Lack of appetite	42%	54%	1.6	0.25
Weight loss	37%	62%	6.83	0.01
Appetite increased	26%	10%	3.85	0.06
Lack of sleep	89%	92%	0.35	0.75
Sleep too much	9%	8%	0.05	0.99
Lack of energy	60%	59%	0.01	0.99
Psychomotor inhibition	19%	26%	0.75	0.48
Agitation	32%	41%	0.93	0.42
Lack of libido	20%	18%	0.07	0.99
Worthlessness	64%	44%	4.86	0.03
Lack of concentration	72%	56%	3.10	0.10
Slowing of thought	39%	46%	0.59	0.44
Thinking of death	66%	72%	0.48	0.54
Death wishes	38%	33%	0.23	0.69
Thinking of suicide	37%	15%	5.84	0.02
Suicide attempt	11%	5%	1.15	0.35
Age at onset, years, mean (sd)	33 (15)	70 (7)	*F*=117.2	<0.000

Note. The specific depressive symptoms of EOD and LOD were compared using Fischer exact statistics.

Clinical studies comparing EOD and LOD subjects have emphasized genetic vulnerability to play a more important etiological role in the onset of depression at a younger age while subcortical cerebral deterioration associated with increased

vascular risk or disease has been reported to be more implicated in the onset of depression at a later age.[7-10]

Table 3: Associations between significant risk indicators of the dependent variable and depressive symptoms with onset of depression adjusted for potential confounding demographic variables. Early-onset depression is the reference category. OR represents the odds of belonging to the late-onset depression group as compared to the reference category of the independent variable

Characteristic (reference)	OR(95% CI adjusted)
Depression:Double depression	
no (0)[1]	0.26 (0.11–0.63)[*]
yes	
Anxiety:	
low (0)	0.53 (0.23–1.20)
high	
Symptoms: Weight loss	
no (0)	2.48 (1.11–5.54)[*]
yes	
Appetite increased	
no (0)	0.35 (0.11–1.12)
yes	
Worthlessness	
no (0)	0.53 (0.23-1.20)
yes	
Thinking of suicide	
no (0)	0.32 (0.12–0.86)[*]
yes	
Health:	
MMSE ≥ 24 (0)	2.91 (0.73–11.60)
MMSE < 24	
WWII	
no (0)	0.10 (0.02-0.49)[*]
yes	

[*] $p<0.05$; [1](0)=reference category.
Note. Potential confounding variables were age, education and being widowed. CI = Confidence Interval; MMSE = Mini-Mental State Examination; WWII = World War II.

In our study we did not find clear evidence to support this. There were no differences in family psychiatric history or general somatic or vascular morbidity between the EOD and LOD subjects. Our results are in accordance with a community-based study in which a positive family psychiatric history was not more common among EOD subjects.[34] Additionally, a recent neuroimaging study found no association between older age of onset and increased subcortical cerebrovascular pathology.[35] Cognitive impairment was greater in LOD, which some studies have associated with increased

neurodegeneration.[9,34] However, the difference was no longer significant after we controlled for confounding. Considering life events, early and late-life events did not differ between the groups, only a traumatic experience during WWII was more prevalent in EOD subjects. Our findings contrast with a recent clinical report of increased late-life events in EOD subjects compared to LOD subjects.[36] These authors have suggested psychosocial factors to play a greater role in EOD while other etiological factors are more important in LOD.[36]

We did not find a difference in level of disability between EOD and LOD whereas previous studies have associated disability with later age at depression onset although the association reported in these studies was no longer significant after controlling for confounding.[37,38] Being widowed was but recent loss of partner was not more prevalent among subjects with LOD. This difference disappeared when we partialled out the effect of age (result not shown). With regard to the psychiatric co-morbidity and symptom profile, we report a higher prevalence of double depression and anxiety as well as an increased prevalence of worthlessness, and thinking about suicide in subjects with EOD. Loss of weight was more prevalent in LOD. These results are in line with studies investigating dysthymia and double depression in older patients while the differences in clinical depressive symptoms between EOD and LOD subjects are in part consistent with previous findings of increased depressive ideation in EOD.[5,16,39,40] Although other studies have not replicated this finding.[7,18]

Previous clinical studies have suggested separate etiological pathways to EOD and LOD.[7,12,36,41] However, in our population-based sample we found very few differences. Referral bias might explain the difference in findings. In general, depression in the elderly is under diagnosed and also referral to mental health care seems to be lower than in younger age groups.[1,42,43] The selection mechanisms are not

known but one could speculate that apart from severity of the disorder, conspicuous or unfamiliar features of the depression may lower the threshold for referral. However, they may not be the same mechanisms in EOD and LOD. For example in EOD cases, previous referral or knowledge about mental health care through affected family members may encourage referral. In LOD, features like apathy or the presence of vascular brain pathology may contribute to referral, while the patient who is depressed after having lost her spouse is either not recognized or not referred because of the idea that "one can understand why she is depressed".

Considering the possible selection mechanisms and the small proportion of older depressed people that is seen in clinical care, it is unlikely that this group reflects the total population of those with late-life depression in the community.

Our results suggest that in late-life EOD and LOD both stressful life events and vascular impairment play a role in the etiology. Therefore all patients with late-life depression, independent of age at depression onset, deserve a complete diagnostic work-up of both psychosocial and vascular risk factors. Treatment interventions should be focused accordingly.

REFERENCES

1   Blazer DG. 2003. Depression in late life: review and commentary. J.Gerontol.A
     Biol.Sci.Med.Sci. 58(3): 249-265.
2   Wells KB, Stewart A, Hays RD, Burnam MA, Rogers W, Daniels M, Berry S,
     Greenfield S, Ware J. 1989. The functioning and well-being of depressed
     patients. Results from the Medical Outcomes Study. JAMA 262(7): 914-919.
3   Gurland B. 1992. The impact of depression on quality of life of the elderly.
     Clin.Geriatr.Med. 8(2): 377-386.
4   Baldwin RC, Tomenson B. 1995. Depression in later life. A comparison of
     symptoms and risk factors in early and late onset cases. Br.J.Psychiatry 167(5):
     649-652.
5   Krishnan KR, Hays JC, Tupler LA, George LK, Blazer DG. 1995. Clinical and
     phenomenological comparisons of late-onset and early-onset depression.
     Am.J.Psychiatry 152(5): 785-788.
6   Lyness JM, Conwell Y, King DA, Cox C, Caine ED. 1995. Age of onset and
     medical illness in older depressed inpatients. Int.Psychogeriatr. 7(1): 63-73.
7   Brodaty H, Luscombe G, Parker G, Wilhelm K, Hickie I, Austin MP, Mitchell
     P. 2001. Early and late onset depression in old age: different aetiologies, same
     phenomenology. J.Affect.Disord. 66(2-3): 225-236.
8   Figiel GS, Krishnan KR, Doraiswamy PM, Rao VP, Nemeroff CB, Boyko OB.
     1991. Subcortical hyperintensities on brain magnetic resonance imaging: a
     comparison between late age onset and early onset elderly depressed subjects.
     Neurobiol.Aging 12(3): 245-247.
9   Salloway S, Malloy P, Kohn R, Gillard E, Duffy J, Rogg J, Tung G, Richardson
     E, Thomas C, Westlake R. 1996. MRI and neuropsychological differences in
     early- and late-life-onset geriatric depression. Neurology 46(6): 1567-1574.
10   Alexopoulos GS, Meyers BS, Young RC, Campbell S, Silbersweig D, Charlson
     M. 1997. 'Vascular depression' hypothesis. Arch.Gen.Psychiatry 54(10): 915-
     922.
11   Krishnan KR, Hays JC, Blazer DG. 1997. MRI-defined vascular depression.
     Am.J.Psychiatry 154(4): 497-501.
12   Hickie I, Scott E, Mitchell P, Wilhelm K, Austin MP, Bennett B. 1995.
     Subcortical hyperintensities on magnetic resonance imaging: clinical correlates
     and prognostic significance in patients with severe depression. Biol.Psychiatry
     37(3): 151-160.
13   Simpson S, Baldwin RC, Jackson A, Burns AS. 1998. Is subcortical disease
     associated with a poor response to antidepressants? Neurological,
     neuropsychological and neuroradiological findings in late-life depression.
     Psychol.Med. 28(5): 1015-1026.
14   Hickie, I, Scott, E, Naismith, S, Ward, PB, Turner, K, Parker, G, Mitchell, P,
     Wilhelm, K. 2001. Late-onset depression: genetic, vascular and clinical
     contributions. Psychol Med. 31(8):1403-12.
15   Brown RP, Sweeney J, Loutsch E, Kocsis J, Frances A. 1984. Involutional
     melancholia revisited. Am.J.Psychiatry 141(1): 24-28.
16   Conwell Y, Nelson JC, Kim KM, Mazure CM. 1989. Depression in late life: age
     of onset as marker of a subtype. J.Affect.Disord. 17(2): 189-195.
17   Lesser IM, Boone KB, Mehringer CM, Wohl MA, Miller BL, Berman NG.
     1996. Cognition and white matter hyperintensities in older depressed patients.
     Am.J.Psychiatry 153(10): 1280-1287.

18 Greenwald BS, Kramer-Ginsberg E. 1988. Age at onset in geriatric depression: relationship to clinical variables. J.Affect.Disord. 15(1): 61-68.

19 Sonnenberg CM, Beekman AT, Deeg DJ, van Tilburg T. 2003. Drug treatment in the Dutch community. Int. J. Geriatr. Psychiatry. 18(2): 99-104.

20 Beekman AT, Deeg DJ, van Tilburg T, Smit JH, Hooijer C, Van Tilburg W. 1995. Major and minor depression in later life: a study of prevalence and risk factors. J.Affect.Disord. 36 (1-2): 65-75.

21 Radloff LS. 1977. The CES-D scale: a self-report depression scale for research in the general population. Appl.Psychol.Meas. 1: 385-401.

22 Himmelfarb S, Murrell SA. 1983. Reliability and validity of five mental health scales in older persons. J.Gerontol. 38(3): 333-339.

23 Radloff LS, Teri L. 1986. Use of the CES-D with older adults. Clin.Gerontol. 5: 119-136.

24 Berkman LF, Berkman CS, Kasl S, Freeman DH, Jr., Leo L, Ostfeld AM, Cornoni-Huntley J, Brody JA. 1986. Depressive symptoms in relation to physical health and functioning in the elderly. Am.J.Epidemiol. 124(3): 372-388.

25 Foelker GA, Jr., Shewchuk RM. 1992. Somatic complaints and the CES-D. J.Am.Geriatr.Soc. 40(3): 259-262.

26 Robins LN, Helzer JE, Croughan J, Ratcliff KS. 1981. National Institute of Mental Health Diagnostic Interview Schedule. Its history, characteristics, and validity. Arch.Gen.Psychiatry 38(4): 381-389.

27 Dingemans P, van Engeland H, Dijkhuis JH, Bleeker J. 1985. De "diagnostic interview schedule" (DIS). Tijdschr.Psychiatrie. 27: 341-359.

28 Zigmond AS, Snaith RP. 1983. The hospital anxiety and depression scale. Acta Psychiatr.Scand. 67(6): 361-370.

29 De Beurs E, Beekman A, Geerlings S, Deeg D, Van Dyck R, Van Tilburg W. 2001. On becoming depressed or anxious in late life: similar vulnerability factors but different effects of stressful life events. Br.J.Psychiatry 179 (11): 426-431.

30 van Tilburg T. 1998. Losing and gaining in old age: changes in personal network size and social support in a four-year longitudinal study. J.Gerontol.B Psychol.Sci.Soc.Sci. 53(6): S313-S323.

31 Kriegsman DM, Penninx BW, van Eijk JT, Boeke AJ, Deeg DJ. 1996. Self-reports and general practitioner information on the presence of chronic diseases in community dwelling elderly. A study on the accuracy of patients' self-reports and on determinants of inaccuracy. J.Clin.Epidemiol. 49(12): 1407-1417.

32 Folstein MF, Folstein SE, McHugh PR. 1975. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J.Psychiatr.Res. 12(3): 189-198

33 Deeg DJH, Knipscheer CPM, van Tilburg W. 1993. Autonomy and well-being in the aging population: concepts and design of the Longitudinal Aging Study Amsterdam, NIG-trend – studies No 7. Netherlands Institute for Gerontology: Bunnik, The Netherlands.

34 van Ojen R, Hooijer C, Bezemer D, Jonker C, Lindeboom J, Van Tilburg W. 1995. Late-life depressive disorder in the community. II. The relationship between psychiatric history, MMSE and family history. Br.J.Psychiatry 166(3): 316-319.

35   Krishnan KR, Taylor WD, McQuoid DR, MacFall JR, Payne ME, Provenzale JM, Steffens DC. 2004. Clinical characteristics of magnetic resonance imaging-defined subcortical ischemic depression. Biol.Psychiatry 55(4): 390-397.

36   Grace J, O'Brien JT. 2003. Association of life events and psychosocial factors with early but not late onset depression in the elderly: implications for possible differences in aetiology. Int.J.Geriatr.Psychiatry 18(6): 473-478.

37   Alexopoulos GS, Vrontou C, Kakuma T, Meyers BS, Young RC, Klausner E, Clarkin J. 1996. Disability in geriatric depression. Am.J.Psychiatry 153(7): 877-885.

38   Steffens DC, Hays JC, Krishnan KR. 1999. Disability in geriatric depression. Am.J.Geriatr.Psychiatry 7(1): 34-40.

39   Beekman AT, Deeg DJ, Smit JH, Comijs HC, Braam AW, de Beurs E, Van Tilburg W. 2004. Dysthymia in later life: a study in the community. J.Affect.Disord. 81(3): 191-199.

40   Devanand DP, Adorno E, Cheng J, Burt T, Pelton GH, Roose SP, Sackeim HA. 2004. Late onset dysthymic disorder and major depression differ from early onset dysthymic disorder and major depression in elderly outpatients. J.Affect.Disord. 78(3): 259-267.

41   Krishnan KR, McDonald WM, Doraiswamy PM, Tupler LA, Husain M, Boyko OB, Figiel GS, Ellinwood EH, Jr. 1993. Neuroanatomical substrates of depression in the elderly. Eur.Arch.Psychiatry Clin.Neurosci. 243(1): 41-46.

42   Crawford MJ, Prince M, Menezes P, Mann AH. 1998. The recognition and treatment of depression in older people in primary care. Int.J.Geriatr.Psychiatry 13 (3): 172-176.

43   Depla MF. 1996. Filters in mental health care for the elderly. A literature study of the prevalence of psychiatric problems and the utilization of care by the elderly. Tijdschr.Gerontol.Geriatr. 27: 206-214.

Chapter 6

The importance of structural abnormalities in Late-Life Depression: Discussion

Discussion

In the previous chapters the association between structural brain abnormalities, age of first depression onset and treatment response in late-life depression was assessed. By doing this, we intended to further elucidate possible different neuropathological mechanisms underpinning late-life depression. In addition, the generalizibility of the early-onset depression (EOD) versus late-onset depression (LOD) distinction from clinical samples to the general population was addressed.

Regarding the hypotheses if late-life depression is associated with structural brain abnormalities and whether EOD and LOD are associated with different structural brain abnormalities, we compared patients and normal controls in one study (**chapter two**) and late-life depressed EOD and LOD patients and normal controls in another study (**chapter three**). In both studies we measured hippocampal volume and white matter lesions to test whether they were differentially associated with age of onset. In both aged and older EOD subjects hippocampal volume was smaller compared to normal controls. Patients with LOD did not differ in hippocampal volume from the EOD group or the normal controls but they had an increased prevalence of larger subcortical white matter lesions. Finally, subcortical white matter lesions were not correlated to smaller hippocampal volume.

There are a number of explanations for the smaller hippocampal volume in early-onset recurrent depressed patients. The glucocorticoid-cascade hypothesis in major depression is based on the observation of prolonged glucocorticoid secretion during repeated episodes of depression. The hippocampus has a specific sensitivity to glucocorticoids and the prolonged high levels of glucocorticoids may have a neurotoxic effect.[1] Indeed, the hippocampal volume has been found to be inversely related to the number of depressive episodes.[2] Hippocampal volume loss might also

be due to a direct loss of glia cells possibly leading to decreased levels of brain-derived neurotrophic factor making the hippocampus more vulnerable to neurotoxic damage.[3] Another explanation may be that patients with major depression have a genetically predisposed small hippocampal volume in which case the small hippocampal volume would be a predictor rather than a consequence of the disease.[4] Recently, MRI studies examining patients with dementia have reported the frequent coexistence of subcortical white matter lesions and hippocampal atrophy.[11] In demented patients, there is neuropathologic evidence that large subcortical white matter lesions reflect ischemic brain damage due to small vessel disease which, in the absent of other pathology, might cause hippocampal atrophy.[12,13] In this context, we tested whether increased prevalence of larger subcortical white matter lesions were a confounder for hippocampal volume. They were not. Hippocampal volume remained smaller in EOD patients, also after controlling for subcortical white matter lesions. From these results we conclude that late-life depression is associated with structural brain abnormalities and that EOD and LOD are associated with different structural brain abnormalities. The differences between EOD and LOD may reflect differences in aetiology.

We and others therefore propose an aetiological model of late-life depression in which multiple possibly independent neuropathological pathways exist that can result in onset of depression late in life.[5,6] Age of first depression onset could be a significant factor in this model. In EOD patients, complex neurobiological events associated with severe chronic stress, such as elevated glucocorticoid levels, could lead to hippocampal atrophy which might increase vulnerability for depression. For LOD patients, another pathway may exist in which larger subcortical white matter lesions mediate between ongoing subtle cerebrovascular disease and the onset of depression.

Concerning the hypothesis that structural brain abnormalities may affect short-term treatment response, we describe a study in **chapter four** in which we tested whether structural brain differences existed between 19 older responders and 23 non-responders to a controlled short-term antidepressant monotherapeutic trial. Responders and non-responders did not differ on any of the baseline quantitative and semi-quantitative brain measures. In addition, after one year follow-up there was no difference in baseline brain measures between patients with poor outcome and good outcome. What does this mean? We focused on volumes of brain regions that have been repeatedly associated with depression such as cerebral grey matter, hippocampus, orbitofrontal cortex and subcortical white matter lesions. It was expected that subjects with smaller brain volumes and more subcortical white matter lesions would show poorer response to antidepressant treatment. We conclude that structural brain abnormalities and response to short-term treatment are not strongly correlated.

From a clinical perspective this implies that an alteration in the short-term treatment strategy in older depressed patients because of structural brain abnormalities should be taken with great precaution. However, there were some important limitations to our findings. Our sample size was relatively small which limited the power of our statistical analyses. In some patients, a delay existed between start of treatment and acquisition of scan. However, all follow-up data were assessed after scan acquisition. The fact that after one year, poor and good outcome patients did not differ in brain abnormalities strengthens our finding of no strong association between short-term response to treatment and brain abnormalities. Our study was cross-sectional, which limited interpretation of factors such as the effect of treatment on the brain and the rate of progression of the white matter lesions. Smaller frontal gray matter volume in

late-life depressed medication-naive patients compared to medication-exposed patients has been reported.[9] Antidepressant treatment may therefore protect against gray matter loss. In addition, brain volume change might be a better predictor of treatment response compared to static brain volume at baseline.[10] Longitudinal studies, including multiple MRI assessments are needed to further clarify these issues.

In reference to our hypothesis stating that the findings from clinical studies comparing elderly EOD and LOD patients cannot be generalized to the general population we describe a study in **chapter five** in which we compared aetiological risk indicators and clinical measures of 90 older EOD subjects and 39 LOD subjects. Subjects were diagnosed using standard epidemiological instruments. None of these patients were receiving specialized care at the time of sampling. After controlling for confounding, no clear pattern of neither aetiological nor clinical differences between the groups was found. Traumatic experiences in World War II, having a diagnosis of double depression, increased anxiety and weight loss, and suicidal thoughts were more prevalent in subjects with early-onset depression. From these findings we conclude that differences between elderly EOD and LOD patients reported from clinical samples cannot be unequivocally generalized to EOD and LOD subjects from the general population, who have not been diagnosed or treated in specialized psychiatric care.

A plausible reason for the differences between our findings and those from clinical studies might be referral bias. It is well known that depression is an underdiagnosed disease in the general population and referral to mental healthcare is lower in the elderly. It might be that special features of the depression facilitate referral to specialized care. For EOD this may mean that knowledge of affected family members may encourage referral while for LOD apathy or vascular problems could enhance

referral. On the other hand, patients who are depressed after having lost a spouse are not referred because their behaviour is ´conform the circumstances´. Subsequently, results from clinical studies using inpatients from academic settings may not be projected onto the community-dwelling depressed elderly. On an aetiological level this could mean that the multiple neurapathological mechanisms such as small hippocampal volume and increased prevalence of larger subcortical white matter lesions associated with EOD and LOD respectively, may be more applicable to inpatients, a group that probably not represents the total population of elderly with late-life depression.

MRI, neuropathology and functional impairment in late-life depression

Since the introduction of the MRI scanner in depression research our knowledge of the involvement of brain has increased considerably. Cross-sectional region-of-interest studies have provided evidence for the presence of brain volume abnormalities in medial temporal and frontal regions in the brains of patients with late-life depression.[14] However, quantitative brain measurement can only be indicative of tissue degeneration or, in a longitudinal design, abnormal brain development. Some support for the in vivo MRI findings has come from post-mortem research pointing to ischemia as the main cause for subcortical white matter lesions in late-life depressed patients but to date only one neuropathologic study investigated non-white matter lesion areas in late-life depressed patients.[15,16] They reported a lower density of pyramidal neurons in the orbitofrontal cortex of late-life depressed patients compared to age-matched controls which may be congruent with MRI studies describing decreased orbitofrontal cortex volume in late-life depressed patients.[17]

The results of our studies build on previous imaging findings by showing that the hippocampus is an important marker of recurrent late-life EOD while subcortical

white matter lesions are more important in LOD patients. Furthermore, subcortical white matter lesions do not seem to be associated with the smaller hippocampal volume in late-life depression. These findings strengthen the case for multiple independent neuropathological mechanisms leading to late-life depression. Of note, small hippocampal volume might be an important neuroanatomic marker of recurrent EOD but is probably not solely responsible for the onset of a depressive episode. Instead, small hippocampal volume and increased prevalence of subcortical white matter lesions may point to an increased vulnerability.

The structural brain abnormalities in EOD patients may have functional consequences. Older patients with early-onset depression had a smaller hippocampal volume and more memory problems compared to LOD patients.[18] This finding is supported by neuropsychological studies comparing late-life EOD and LOD patients reporting more severe memory problems in EOD patients.[19] A core cognitive deficit in late-life depressed patients seems a degradation of frontal lobe mediated cognitive processing speed.[20] One could hypothesize that for LOD patients this cognitive deficit is due to large subcortical white matter lesions disrupting frontal lobe connections.[19-21] However, this remains mere speculation. Some direct in vivo evidence for white matter tract disruptions in subcortical frontal lobe white matter lesions exists but future studies are needed to help clarify the mechanisms that lead to slower processing speed in late-life depressed patients, including the potential role of subcortical white matter lesions and age of depression onset in this process.[21]

While the glucorticoid-cascade theory provides some insight in the role of the hippocampus in EOD it remains unclear how the subcortical white matter lesions can contribute to or even cause LOD. The vascular depression theory posits that vascular mechanisms lead to cerebral ischemia in key circuitry underlying depressive

symptomatology. This thesis provides some evidence favouring this hypothesis; however, longitudinal studies are necessary to address the question of causation because it may be that depression is the cause rather than consequence of cerebrovascular disease. Depression is an established risk factor for cerebrovascular disease and there are several mechanisms in which depression could increase the risk for vascular disease.[22] Platelet and clotting changes reported in depression could lead to atherosclerosis; decreased heart variability in depressed patients with cerebrovascular disease might lead to hypotensive periods which are a risk factor for white matter lesions. Finally, unhealthy life styles, such as smoking, are associated with depression and worsen pre-existing vascular disease. Therefore, a bi-directional connection between cerebrovascular disease and depression seems to exist which may have clinical implications.[23]

Clinical Implications

In the context of the observed differences in neuroanatomic abnormalities between late-life EOD and LOD patients it is important to address whether age of depression onset is related to late-life depression treatment and whether neuroimaging can be a useful tool when deciding on the type of treatment. Most population-based studies that have compared depressive symptomatology of EOD and LOD report no clear differences, corroborated by the results of this thesis. Therefore, the clinical importance of age of onset in the general population is low. Clinical differences between EOD and LOD in late-life depressed inpatients undergoing medicine treatment are a bit more consistent but their short-term treatment prognosis does not seem to be dependent of structural brain abnormalities. Therefore, the value of an MRI scan as a clinical tool is limited.

MRI has proven to be useful in scientific research on late-life depression. The field of neuroimaging is quickly evolving, refinement of existing techniques and the development of new techniques can add to the increased specificity of the hypotheses regarding the neurobiological mechanisms underlying late-life depression.

Recommendations for future research

The majority of published MRI studies in late-life depression are cross-sectional. Therefore it is not known whether the structural abnormalities are progressive, e.g. associated with the course of disease, or static. Longitudinal MRI studies are needed to clarify this. Furthermore, many studies to date have used heterogeneous illness groups, including older EOD and LOD patients. The described studies and previous reports support the notion that assessing homogeneous patient groups, for example first-episode LOD patients may be beneficial. Also, MRI studies including neuroendocrinological measures are sparse. Future longitudinal neuroimaging studies will need to include measures of cortisol to test whether stress-related neurotoxicity can cause the structural abnormalities reported in depression. In addition, new imaging techniques such as diffusion tensor imaging open the opportunity for tracking neuronal fibers throughout the cerebral white matter. This will increase understanding of the status of the white mater integrity in the brain. The combination of structural and functional imaging techniques such as fMRI, PET and single-photon emission computed tomography are important to determine the functional significance of brain structure changes and allow a more precise localization of abnormalities in blood flow, blood metabolism and neurotransmitter receptors. Finally, post-mortem studies using large samples, carefully screened for comorbidity, are needed to examine the correlates of the volumetric and functional changes.

REFERENCES

1   Sapolsky,RM (2000): Glucocorticoids and hippocampal atrophy in neuropsychiatric disorders. Arch.Gen.Psychiatry 57: 925-935.

2   Bell-McGinty,S, Butters,MA, Meltzer,CC, Greer,PJ, Reynolds,CF, III, Becker,JT (2002): Brain morphometric abnormalities in geriatric depression: long-term neurobiological effects of illness duration. Am.J.Psychiatry 159: 1424-1427.

3   Sheline,YI (2003): Neuroimaging studies of mood disorder effects on the brain. Biol. Psychiatry 54: 338-352.

4   Frodl,T, Meisenzahl,EM, Zetsche,T, Hohne,T, Banac,S, Schorr,C, Jager,M, Leinsinger,G, Bottlender,R, Reiser,M, Moller,HJ 2004: Hippocampal and amygdala changes in patients with major depressive disorder and healthy controls during a 1-year follow-up. J. Clin. Psychiatry 65:492-499.

5   Kumar,A, Bilker,W, Jin,Z, Udupa,J (2000): Atrophy and high intensity lesions: complementary neurobiological mechanisms in late-life major depression. Neuropsychopharmacology 22: 264-274.

6   Kumar,A, Mintz,J, Bilker,W, Gottlieb,G (2002): Autonomous neurobiological pathways to late-life major depressive disorder. Clinical and pathophysiological implications. Neuropsychopharmacology 26: 229-236.

7   Lopez,JF, Chalmers,DT, Little,KY, Watson,SJ (1998): A.E. Bennett Research Award. Regulation of serotonin1A, glucocorticoid, and mineralocorticoid receptor in rat and human hippocampus: implications for the neurobiology of depression. Biol.Psychiatry 43: 547-573.

9   Lavretsky,H, Roybal,MA, Ballmaier,M, Toga,AW, Kumar,A (2005): Antidepressant exposure may protect against decrement in frontal gray matter volumes in geriatric depression. J. Clin. Psychiatry 66:964-967.

10   Taylor,WD, Steffens,DC, MacFall,JR, McQuoid,DR., Payne,ME, Provenzale, JM, Krishnan,KR (2003): White matter hyperintensity progression and late-life depression outcomes. Arch. of Gen. Psychiatry 60: 1090-1096.

11   van der Flier,WM, Middelkoop,HA, Weverling-Rijnsburger,AW, Admiraal-Behloul,F, Spilt,A, Bollen,EL (2004): Interaction of medial temporal lobe atrophy and white matter hyperintensities in AD. Neurology 62:1862-1864.

12   Kril,JJ, Patel,S, Harding, AJ, Halliday,GM (2002): Patients with vascular dementia due to microvascular pathology have significant hippocampal neuronal loss. J. Neurol. Neurosurg. Psychiatry 72:747-751.

13   de Leeuw,FE, Barkhof,F, Scheltens,P (2004): White matter lesions and hippocampal atrophy in Alzheimer's disease. Neurology 62: 310-312.

14   Ballmaier,M, Sowell,ER, Thompson,PM, Kumar,A, Narr,KL, Lavretsky,H (2004): Mapping brain size and cortical gray matter changes in elderly depression. Biol.Psychiatry 55: 382-389.

15   Thomas,AJ, O'Brien,JT, Davis,S, Ballard,C, Barber,R, Kalaria,RN (2002): Ischemic basis for deep white matter hyperintensities in major depression: a neuropathological study. Arch.Gen.Psychiatry 59: 785-792.

16   Rajkowska,G, Miguel-Hidalgo,JJ, Dubey,P, Stockmeier,CA, Krishnan, KR (2005): Prominent reduction in pyramidal neurons density in the orbitofrontal cortex of elderly depressed patients. Biol. Psychiatry 58: 297-306.

17   Lai,T, Payne,ME, Byrum,CE, Steffens,DC. Krishnan,KR (2000): Reduction of orbital frontal cortex volume in geriatric depression. Biol. Psychiatry 48: 971-975.

18   MacQueen,GM., Campbell,S, McEwen,BS, Macdonald,K, Amano,S, Joffe,RT, Nahmias,C, Young,LT (2003): Course of illness, hippocampal function, and hippocampal volume in major depression. Proc. Nat. Acad. of Sci U S A 100: 1387-1392.

19   Rapp,MA, Dahlman,K, Sano,M, Grossman,HT, Haroutunian,V, Gorman,JM (2005): Neuropsychological differences between late-onset and recurrent geriatric major depression. Am. J. Psychiatry, 162: 691.698.

20   Sheline,YI, Barch,DM, Garcia,K, Gersing,K, Pieper,C, Welsh-Bohmer,K, Steffens,DC, Doraiswamy,PM (2006): Cognitive Function in Late Life Depression: Relationships to Depression Severity, Cerebrovascular Risk Factors and Processing Speed. Biol. Psychiatry, in press.

21   Taylor,WD, Payne,ME, Krishnan,KR, Wagner,HR, Provenzale,JM, Steffens,DC, Macfall,JR (2001): Evidence of white matter tract disruption in MRI hyperintensities. Biol. Psychiatry, 50: 179-183.

22   Thomas, AJ, Kalaria, RN, O´Brien, JT. (2004). Depression and vascular disease: what is the relationship? J of Affect Disorders, 79: 81-95.

23   Hickie,I, Scott,E (1998): Late-onset depressive disorders: a preventable variant of cerebrovascular disease? Psych. Medicine, 28: 1007-1013.

Nederlandse Samenvatting

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Depressie is een veel voorkomend en ernstige psychiatrisch ziektebeeld. Depressie komt zowel bij ouderen als bij jong volwassenen voor. Ouderen en jongere mensen met een depressie hebben vaak één of meer van de volgende kenmerken: stemmings-problemen, voortdurend verdrietig, pessimistisch over de toekomst, moeite met concentreren en slaap- en eet-problemen. Of depressie bij ouderen, ouderdoms-depressie, en depressie bij jonge volwassenen verschillen qua kenmerken is onduidelijk. Bevolkingsonderzoeken in verschillende landen wijzen wel op bepaalde risicofactoren voor het krijgen van een depressie op jongere of oudere leeftijd. Ouderdom gaat vaak gepaard met cognitieve en fysieke achteruitgang en het verlies van partners en vrienden. Deze verschijnselen vergroten ook het risico op het krijgen van een ouderdoms-depressie.

Tot op heden is de oorzaak van ouderdoms-depressie onbekend. Een manier om meer te weten te komen over de oorzaak van depressie en de invloed van depressie op de hersenen is patienten te categoriseren aan de hand van de leeftijd waarop de ziekte zich voor het eerst openbaarde en het beloop van de ziekte hierna. Ouderdoms-depressie kan verdeeld worden in vroeg- en laat-ontstane depressie. Een vroeg-ontstane depressie wordt meestal gedefinieerd als een depressie die start op jonge of middelbare leeftijd terwijl een laat-ontstane depressie wordt gedefinieerd als de eerste episode zich na het 60^e levensjaar voordoet. Hoewel de grens tussen vroeg- en laat-ontstane ouderdoms-depressie in principe arbitrair is wijzen eerdere studies toch op consistente verschillen tussen de twee groepen. Patienten met een vroeg-ontstane depressie hebben bijvoorbeeld veel vaker familie-leden die ook depressief zijn dan patienten met een laat-ontstane depressie. Sommige onderzoekers wijzen op verschillen in klinische symptomen terwijl anderen daar twijfels over hebben. Een

belangrijke theorie stelt dat een vroeg-onstane depressie met een chronisch beloop gepaard gaat met een overmatige afscheiding van stress-gerelateerde stoffen. Deze stoffen brengen schade toe aan een belangrijke hersenstructuur, de hippocampus genaamd. De schade aan de hippocampus kan ervoor zorgen dat deze minder goed functioneert. Dit zou kunnen bijdragen aan het in stand houden van de depressie. Wat betreft laat-ontstane depressie, studies hebben gewezen op een hoge prevalentie van vasculaire risicofactoren en vasculaire aandoeningen zoals roken, diabetes en hypertensie. Deze factoren spelen wellicht een rol bij de ontwikkeling van de depressie op latere leeftijd.

Depressie is een hersenziekte. Dat wil zeggen, we kunnen veranderingen in de hersenen meten die te maken hebben met de depressie. Met behulp van Magnetische Resonantie Imaging (MRI) kunnen we de hersenen van ouderen met vroeg- en laat-ontstane depressie onderzoeken. Met MRI kunnen we het volume van hersenstructuren meten, zo kunnen we meten of de ziekte een invloed heeft op de hersenen. De hersenen bestaan uit grijze en witte stof. Grijze stof bestaat voornamelijk uit cellen, de witte stof bestaat uit de verbindingen tussen de cellen. MRI onderzoek bij ouderen met een depressie heeft zich zowel op hersenstructuren (grijze stof) als op de verbindingen die met de regulering van stemming te maken hebben. De hippocampus is één van die grijze stof structuren. Enkele MRI studies laten zien dat de hippocampus een kleiner volume heeft in ouderen met een depressie vergeleken met gezonde ouderen. Bovendien was de hippocampus het kleinst bij degene die het langst ziek waren. Mogelijk wijst dit op een invloed van depressie op de hippocampus. Een andere tak van het MRI onderzoek in ouderdoms-depressie heeft zich gefocused op de verbindingen (witte stof). Het blijkt dat ouder worden in veel gevallen gepaard gaat met een toename in zogenaamde witte stof laesies. Deze

zijn zichtbaar op MRI scans als witte hyperintensieve vlekjes. Uit onderzoek blijkt dat de hyperintensieve vlekjes schade aan de verbindingen tussen hersenstructuren representeren. De schade blijkt het gevolg te zijn van problemen met de circulatie van bloed in de hersenen. Vooral de laesies in de verbindingen die diep in de hersenen liggen (onder de hersenschors) lijken een belangrijke rol te spelen in ouderdoms-depressie en dan met name de laat-ontstane ouderdoms-depressie. Bovendien hebben patienten met veel van deze laesies ook vaker problemen met de bloed circulatie. Deze bevindingen vormen het fundament voor de vasculaire depressie hypothese. Deze hypothese stelt dat door problemen met de bloedcirculatie laesies ontstaan die de verbindingen tussen belangrijke hersendelen verbreken en zodoende bijdragen aan het ontstaan van een depressie.

Kortom, er zijn aanwijzingen voor verschillen tussen vroeg- en laat-ontstane ouderdoms-depressie. Echter, weinig studies onderzoek naar volume veranderingen in de cellen gecombineerd met onderzoek naar de laesies in de verbindingen. Deze 2 factoren kunnen met elkaar samenhangen. Als de verbindingen (witte stof) naar de cellen (hippocampus) beschadigt zijn, kan dit schade aan die cellen tot gevolg hebben. Er zijn echter nog maar enkele studies die dit onderzocht hebben. De centrale vraag die dit proefschrift tracht te beantwoorden is de volgende : is de verdeling in vroeg- en laat-ontstane depressie betekenisvol? We hopen door de duur van de depressie in ouderen als uitgangspunt te nemen meer te weten te komen over de invloed van depressie op de hersenen.

In hoofdstukken twee en drie is een antwoord gezocht op de volgende vraag: verschilt hersenvolume tussen vroeg- en laat-ontstane depressie? Het volume van de hippocampus en van de laesies werd gemeten. Patiënten met een laat-ontstane depressie hadden meer witte stof laesies terwijl patiënten met een vroeg-ontstane

depressie een kleinere hippocampus volume hadden. Mensen met een kleinere hippocampus hadden niet meer laesies. De patienten met een kleinere hippocampus waren sinds lang ziek. Zij hebben vele perioden van depressie achter de rug. Een kleinere hippocampus is hier wellicht het gevolg van. Echter, het is ook mogelijk dat deze personen bij geboorte al een kleinere hippocampus hadden. In beide gevallen is het zo dat een kleinere hippocampus ervoor zorgt dat deze mensen misschien kwetsbaarder zijn voor het krijgen van een periode van depressie. In de laat-ontstane depressie lijken de laesies een grotere rol te spelen dan verkleining van de hippocampus. Deze bevindingen wijzen in de richting van verschillende factoren die een rol spelen in de hersenen van enerzijds ouderen met een vroeg-ontstane depresie en anderzijds ouderen met een laat-ontstane depressie.

In hoofdstuk vier wordt een behandelstudie beschreven. We hebben een antwoord gezocht op de vraag of volumes van specifieke hersenstructuren de respons op antidepressieve behandeling kan voorspellen. De patiënten kregen vroeg in de behandeling een MRI scan. Een psychiater stelde vast hoe de patiënten reageerden op de behandeling. Tevens werden de patiënten een jaar na de behandeling opnieuw uitgenodigd om te bepalen of de behandeling een blijvend effect heeft gehad. Patiënten die uiteindelijk reageerden en degenen die niet reageerden verschilden op geen enkele MRI maat. Ook de patiënten die na een jaar depressief waren verschilden niet van patiënten die niet meer depressief waren. Dit betekent dat het volume van hersenstructuren geen rol lijkt te spelen in de respons op de antidepressieve behandeling.

Tot slot wordt in hoofdstuk 5 een populatie-studie beschreven. Deze studie betreft ouderen die niet opgenomen zijn maar na een interview wel ernstige depressieve klachten blijken te hebben. Het doel van de studie is om te kijken of resultaten van

klinische studies over ouderdoms-depressie gegeneraliseerd kunnen worden naar de algemene populatie. Heel veel depressieve ouderen zijn niet door een specialist gezien en zijn dus ook niet bij een gespecialiseerde zorginstelling in behandeling. Een reden hiervoor is bijvoorbeeld dat de depressieve klachten van een patiënt niet altijd als zodanig herkent worden. De klachten van de patient worden afgezet tegen de levens-fase waarin de patient zich bevindt (bijvoorbeeld rouw wat in werkelijkheid een depressie kan zijn). Is deze grote groep niet opgenomen depressieve ouderen wel vergelijkbaar met opgenomen ouderen? Dit onderzoek werd uitgevoerd in samenwerking met de Vrije Universiteit en in het bijzonder met de Longitudinal Aging Study Amsterdam (LASA). De ouderen werd gevraagd naar de aanvang van hun depressie. Op basis van deze data werden ze verdeeld in vroeg-ontstane en laat-ontstane depressies. Uit de resultaten bleken geen duidelijke verschillen tussen de groepen. Het lijkt dus dat gerapporteerde verschillen tussen ouderen met vroeg- en laat-ontstane depressie uit klinische studies niet gelden voor depressieve ouderen die niet gediagnosticeerd door of in behandeling bij een specialist zijn.

De centrale vraag was of de verdeling tussen vroeg- en laat-ontstane ouderdomsdepressie zinvol is. Dit proefschrift geeft aan van wel. De onderzoeken in dit proefschrift wijzen uit dat vroeg- en laat-ontstane depressie mogelijk een verschillende invloed op de hersenen hebben. De duur van de ziekte is blijkbaar een belangrijke factor voor de invloed die de ziekte op de hersenen heeft. De beschreven bevindingen in dit proefschrift kunnen daarom bijdragen aan verder onderzoek naar de etiologie en het beloop van ouderdomsdepressie.

Curriculum Vitae

Curriculum Vitae

Joost Janssen werd op 5 maart 1976 geboren te Lottum, Nederland. Hij behaalde in 1994 het eindexamen aan het College Den Hulster te Venlo. In 1999 haalde hij zijn doctoraalgetuigschrift in de Neuropsychologie aan de Radboud Universiteit Nijmegen.

Sinds oktober 1999 is Joost Janssen verbonden aan het Rudolf Magnus Instituut voor Neurowetenschappen, Afdeling Psychiatrie van het Universitair Medisch centrum Utrecht. In september 2001 begon hij aan promotieonderzoek in de neurowetenschappen. Sinds maart 2006 werkt hij als post-doctoraal onderzoeker in het Medical Imaging Laboratory in het University Hospital Gregorio Marañon te Madrid, Spanje.

List of publications

Janssen,J, Hulshoff Pol,HE, Schnack, HG, Lampe,IK, de Leeuw,FE, Kok, RM, Kahn,RS, Heeren,TJ. Cerebral volume measurements and subcortical white matter lesions and short-term treatment response in late life depression. *In revision*.

Janssen,J, Hulshoff Pol,HE, de Leeuw,FE, Schnack, HG, Lampe,IK, Kok, RM, Kahn,RS, Heeren,TJ. Hippocampal volume and subcortical white matter lesions in late-life depression: comparison of early- and late-onset depression. *In revision*.

Janssen,J, Beekman, ATF, Comijs, HC, Deeg, DJH, Heeren, TJ. Late-life depression: the differences between early and late-onset illness in a community-based sample. International Journal of Geriatric Psychiatry, 21, 2006, 86-93.

Janssen,J, Hulshoff Pol,HE, Lampe,IK, Schnack,HG, de Leeuw,FE, Kahn,RS, Heeren, TJ. Hippocampal changes and white matter lesions in early-onset depression. Biological Psychiatry, 2004, 56, 825-831.

De Bruin,EA, Hulshoff Pol,HE, Schnack,HG; Janssen,J, Bijl,S, Evans,AC, Kenemans,L, Kahn,RS, Verbaten, MN. Focal brain matter differences associated with lifetime alcohol intake and visual attention in male but not in female non-alcohol-dependent drinkers. Neuroimage, 26, 2005, 536-45.

Palmen,S, Hulshoff Pol,HE, Kemner,C, Schnack,HG, Janssen,J, Kahn,RS, van Engeland, H. Larger Brains in Medication Naive High-Functioning Subjects with Pervasive Developmental Disorder. Journal of Autism and Developmental Disorders, 34, 2004, 603-613.

Denys,D, Van Der Wee,N, Janssen,J, De Geus,F, Westenberg, HG. Low level of dopaminergic D(2) receptor binding in obsessive-compulsive disorder. Biological Psychiatry, 55, 2004, 1041-1045.

Lampe,IK, Hulshoff Pol,HE, Janssen,J, Schnack,HG, Kahn,RS, Heeren,TJ. Association of depression duration with reduction of global cerebral gray matter volume in female patients with recurrent major depressive disorder. American Journal of Psychiatry, 160, 2003, 2052-2054.

Dankwoord

Ik hou het kort.

Alle patienten die aan het tot stand komen van dit proefschrift meegewerkt hebben, heel erg bedankt.

Thea, hartelijk bedankt voor je uitstekende begeleiding. Ik heb veel van je geleerd, op het gebied van de ouderdomsdepressie maar ook wat betreft algemeen wetenschappelijk redeneren.

Hilleke, je bent een hele goede co-promotor voor mij geweest. Je kritische no-nonsense benadering staat me erg aan.

Thea, Hilleke, met veel plezier denk ik terug aan onze gesprekken.

Rene, bedankt voor het faciliteren van dit onderzoek. Hoewel ik niet in dienst van het UMCU was mocht ik toch gebruik maken van het imaging netwerk bij psychiatrie.

Speciale dank aan Rob, Hugo, Sjoerd en Frank-Erik. Zonder jullie hulp was dit proefschrift niet tot stand gekomen.

Ik bedank Altrecht voor hun investering in dit onderzoek.

Alle huidige en ex-kantoortuin I, II en III bewoners, stafcentrum bewoners, betablokje bewoners, kinderpsychiatrie kantoortuin bewoners, GROUP kantoortuin bewoners, neurochirurgie kantoortuin bewoner:

BEDANKT!!

Ana: thanks for your support!