RESEARCH PAPER

Structural brain changes associated with depressive symptoms in the elderly with Alzheimer's disease

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ABSTRACT

Objective To examine neuroanatomical changes associated with depressive symptoms in Alzheimer's disease (AD) and the relationship between brain structure and cerebrospinal fluid (CSF) AD biomarkers in depressed and non-depressed patients.

Methods Two independent cohorts were used in this study. The first cohort (KI) was collected from the Memory Clinic at Karolinska University Hospital and consisted of 41 AD patients. The second cohort was selected and downloaded from the Alzheimer's Disease Neuroimaging Initiative database (ADNI) and consisted of 148 patient. Patients underwent medical, neuropsychological assessment, laboratory analyses of CSF, including β amyloid 1–42 (Aβ 42), total τ (t-τ), phosphorylated τ 181 (p-τ) and brain MRI examination. In the KI cohort, depression was assessed using the Cornell Scale for Depression in Dementia, and in the ADNI cohort the Geriatric Depression Scale was applied. 3D T1-weighted MRI images were processed using automated steps for segmentation and surface reconstruction implemented in Freesurfer. General linear model analysis was used as a statistical approach.

Results Cortical thinning in AD patients with depressive symptoms compared with those without was observed in the left parietal and temporal brain regions in both cohorts. Negative correlation between cortical thickness and t-τ was greater in depressed compared with non-depressed AD patients in precuneus and parahippocampal cortex.

Conclusions Our findings suggest that depressive symptoms in AD patients are associated with cortical thinning in temporal and parietal regions. In addition, our findings suggest that τ protein pathology in these areas may contribute to the development of depressive symptoms in AD.

INTRODUCTION

Depression is very common in the elderly,[1] and the frequency of late life depression is increasing due to population aging. Depressive symptoms in late life are associated with increased rates of suicide and premature mortality[2] and more frequent use of healthcare with significantly higher healthcare costs.[3] Importantly, depression is found to be strongly connected with cognitive impairment.[4] Thus, it has been estimated that a 10% reduction in the prevalence of depression could lead to 326 000 less cases of dementia worldwide.[5] Subjects with depressive symptoms have higher risk of cognitive decline and dementia,[6] and approximately 40% of patients with Alzheimer's disease (AD) have depression, which can be one of the first symptoms of dementia.

Thus, depression may be a risk factor for developing dementia, a symptom, an early reaction to cognitive deficit, or depression may disturb cognitive function itself, which is clinically represented as 'pseudodementia'. Understanding the relationship between depressive symptoms and cognitive impairment and their underlying mechanisms is important in order to increase the efficiency of early diagnostics, differential diagnosis and the selection of optimal treatment strategy for these conditions.

Several hypotheses linking depression and cognitive impairment have been suggested. The glucocorticoid cascade hypothesis proposes that stress-induced increase in glucocorticoid levels leads to regression of dendritic arborisation, inhibition of neurogenesis and neurotoxic effects on the hippocampus.[7] The 'vascular' depression hypothesis suggests a link between white matter lesions, vascular risk factors and depression. Inflammatory changes may also play an important role, as increased levels of pro-inflammatory cytokines have been observed in both depression and dementia.[8] Changes in brain-derived neurotrophic factor (BDNF), serotonin transporter genotype and choline acetyltransferase genotype have also been reported for both conditions.[4]

Each of these hypotheses is not mutually exclusive. In contrast, the pathogenesis of depression in dementia is likely multifactorial with a dominance of one or more factors at different stages of the disease or in different individuals.

Evidence suggests an association between depression and AD pathology. For example, it has been found that depressed e4 carriers of apolipoprotein E gene had greater cognitive decline than those without the e4 allele.[9] It has been shown that amyloid plaques and neurofibrillary tangles accumulate in higher numbers in the hippocampus of depressed patients with AD than in those without depression.[10] A longitudinal study of non-demented elderly found that the e4 allele was associated with more rapid hippocampal volume loss in depressed subjects over 2 years compared with non-depressed subjects.[11] Neuropathological studies suggest that a previous history and comorbid depression are associated with more severe AD pathology.[10] Recent amyloid imaging studies have been consistent with these autopsy findings.[12 13] On the other hand, however, cerebrospinal fluid (CSF) studies have not supported this hypothesis.[14]

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Neuroimaging studies have made an important impact on our understanding of the brain changes underlying depression. In non-demented elderly subjects, depression has been shown to be associated with structural and functional brain abnormalities, in prefrontal and limbic regions,[15 16] supporting the hypothesis that frontal-subcortical and limbic circuitry plays a key role in depression. However, little is known about the neuroanatomical correlates of depression in AD patients.

The main aim of this study was to investigate structural changes of the brain cortex associated with depressive symptoms in elderly people with AD using structural MRI. We included data from the ADNI study and from the Karolinska Memory Clinic cohort.

METHODS

To assess the reliability of our findings, we replicated analysis using two independent cohorts. The first cohort (KI) was collected from the Memory Clinic at Karolinska University Hospital in Huddinge, Sweden, between 2010 and 2011.[17] We used the second cohort in order to verify whether the result obtained in our small KI cohort could be replicated in a larger independent sample. The second cohort (ADNI) was selected and downloaded from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (http://www.loni.ucla.edu/ADNI, PI Michael M Weiner).

Subjects

The KI cohort consists of 41 AD patients, and the ADNI cohort consists of 148 patients with AD in accordance with the inclusion and exclusion criteria listed below.

Inclusion criteria for both cohorts were (1) depression scale administered, (2) brain MRI examination and scan with sufficient quality and (3) diagnosis of AD. Patients with physical disease significantly affecting cognitive performance, life-threatening disease with expected reduced survival time and dementia due to diseases other than AD were excluded. In the ADNI cohort, NINCDS/ADRDA 1984 criteria for probable AD were used. In the KI cohort, patients were diagnosed according to DSMIV/ICD-10 criteria.

Assessment procedures

Subjects from both cohorts underwent clinical, neuropsychological, laboratory assessment and brain MRI examination. More detailed information about the ADNI cohort is available at http://www.adni-info.org. In the KI cohort, clinical assessment included patient and informant interview, cognitive screening with mini–mental state examination (MMSE), brain MRI examination, analyses of blood, urine and CSF routine laboratory analyses, including β amyloid 1–42 (Aβ 42), total τ (t-τ) and phosphorylated τ 181 (p-τ). The neuropsychological examination included Wechsler Adult Intelligence Scale Revised and III (WAIS–R and WAIS III), Trail Making Test A and B, Rey auditory verbal learning test and Rey-Osterrieth complex figure tasks. Electrocardiogram, electroencephalography and other supplementary tests were performed as clinically indicated. Diagnosis of AD was made after a consensus meeting with licensed specialists in geriatric medicine, psychiatry and neurology, neuropsychologists and speech-language pathologist taking into account all available information.

Assessment of depressive symptoms

In the ADNI study, the 15-item version of the Geriatric Depression Scale (GDS-15) was used.[18] The GDS consists of 15 questions and total scores range from 0 to 15, with higher scores denoting more depressive symptoms. Subjects with subsyndromal depression were defined with a score of 1–5 on the GDS and non-depressed subjects with a score of 0 as previously reported.[19] The 'memory' item, asking "if the subject feels he/she has more memory problems than most", was excluded due to its association with cognitive performance. The GDS was completed by a research nurse.

In the KI cohort, the Cornell scale for depression in dementia (CSDD) was used. The CSDD is a combined patient-based and informant-based scale, which showed appropriate psychometric properties in both demented and non-demented people.[20] This is a 19-item scale with scores ranging from 0 to 38. Each item can be scored between 0 (not present), 1 (mild or intermittent), 2 (often present) and a (unable to evaluate). The CSDD was completed by a licensed geriatrician or psychiatrist, or an experienced nurse after training. We defined depressive symptoms as six or more points on the CSDD, which has demonstrated adequate sensitivity and specificity to diagnose depression in elderly with dementia.[20]

CSF measurement

ADNI cohort

CSF was collected after an overnight fast using a 20- or 24-gauge spinal needle, frozen within 1 h of collection, and transported on dry ice to the ADNI Biomarker Core laboratory at the University of Pennsylvania Medical Center. The complete descriptions of the collection and transportation protocols are provided in the ADNI procedural manual at http://www.adni-info.org. CSF data were available for 79 subjects.

KI cohort

CSF was collected in a subgroup (n=39) in the morning after an overnight fast. Participants underwent lumbar puncture in the L3–4 or L4–5 interspace. CSF Ab42 was analysed using a sandwich ELISA, constructed to specifically measure b-amyloid 42. CSF t-τ and p-τ were determined using a sandwich ELISA. All CSF samples were analysed at the University Hospital of Karolinska Huddinge, Stockholm, Sweden.

Magnetic resonance imaging

In the ADNI cohort, all subjects had MRI at 1.5 T. The data were collected at multiple ADNI sites using a standardised MRI protocol (http://www.loni.ucla.edu/ADNI/Research/Cores/index.shtml), which was developed after a major effort evaluating and comparing 3D T1-weighted sequences for morphometric analyses. In this study, the MRI data came from 58 centres. Details of MRI acquisition and processing are described previously.[21] Briefly, for each subject two T1-weighted MRI scans were collected using a sagittal volumetric magnetisation-prepared rapid gradient echo (3D MP-RAGE) sequence with the following acquisition parameters: echo time of 4 ms, repetition time of 9 ms and resolution of 1.1×1.1×1.2 mm. The ADNI MRI quality control centre at the Mayo Clinic (Rochester, MN) selected the MP-RAGE image with higher quality based on standardised criteria.

In the KI cohort, high-resolution T1-weighted images were acquired with MPRAGE sequence on a 3-T TIM TRIO scanner (Siemens, Erlangen, Germany) at the Memory Clinic at Karolinska University Hospital in Huddinge (Sweden). These images were obtained using the following sequence parameters: 176 sagittal slices; time of repetition/time of echo=1900/2.57 ms; flip angle 9°; acquisition matrix=256×256, voxel size 1×1×1 mm^3.

Full brain and skull coverage was required for the MRI datasets and detailed quality control carried out on all MR images according to previously published quality control criteria.[22]

Image analysis

All the structural T1 images were analysed using Freesurfer (V.5.1), where regional cortical thicknesses and volumetric measures were estimated. The software is documented and available for download online (http://surfer.nmr.mgh.harvard.edu/). Cortical reconstruction and volumetric segmentation includes removal of non-brain tissue using a hybrid watershed/surface deformation procedure,[23] automated Talairach transformation, segmentation of the subcortical white matter and deep grey matter volumetric structures,[23] intensity normalisation, tessellation of the grey matter–white matter boundary, automated topology correction,[24] and surface deformation following intensity gradients to optimally place the grey/white and grey/CSF borders at the location where the greatest shift in intensity defines the transition to the other tissue class.[25] Cortical thickness was calculated as the shortest distance between the previous surfaces at each vertex across the cortical surface. Once the cortical models are complete, registration to a spherical atlas takes place, which uses individual cortical folding patterns to match cortical geometry across subjects.[26] This is followed by parcellation of the cerebral cortex into units based on gyral and sulcal structure.[27] The accuracy of the thickness measurements derived by this technique has been validated by histological[28] and manual measurements. To map each subject to a common space, the surface representing the grey matter–white matter border was registered to an average cortical surface atlas using a non-linear procedure that optimally aligned sulcal and gyral features across subjects.[29] For the vertex-by-vertex cluster analysis, the thickness maps for all subjects in both groups were converted to the common atlas space.[26 29] The data were smoothed by applying a 2D Gaussian-smoothing kernel of 10 mm. Freesurfer output for all subjects underwent visual quality control. Images from two depressed subjects required intervention. After manual correction, Freesurfer steps were repeated; however, some regions remain misclassified. These subjects were excluded from further analysis.

Statistical analysis

Clinical and demographic data were analysed using the Statistical Package for the Social Sciences (SPSS) software, V.20. To assess the normality, Kolmogorov–Smirnov test of normality was performed. For group comparisons of demographic and clinical variables, the χ^2 test was used to analyse categorical variables and t test or Mann–Whitney where appropriate for continuous variables.

Mass-univariate surface-based analysis was performed using linear modelling to examine the relationship between depressive symptoms and cortical thickness. We compared cortical thickness between AD patients with and without depressive symptoms, adjusting for age, gender, education and MMSE score. We used 148 subjects from ADNI cohort and 41 subjects from KI cohort for this analysis. The smoothing kernel (full width at half maximum (FWHM)) for the reported results was 10 mm. Correction for multiple comparisons was carried out using the Monte Carlo simulation method. Data were tested against an empirical null distribution of maximum cluster size by running 10 000 synthesised Gaussian noise simulations with an initial cluster-forming threshold of $p < 0.05$. Furthermore, an interaction term was included in the model to test whether the slope of the relationship between cortical thickness and CSF biomarkers of AD (Aβ 42, t-τ, p-τ) significantly differed between depressed and non-depressed group. If significant difference in slopes had been observed, CSF-thickness correlation was tested in each group separately. CSF data were available for 79 subjects from ADNI cohort and 39 subjects from KI cohort

RESULTS

Sample characteristics

Demographic and clinical characteristics of the cohorts are provided in table 1. AD patients with and without depressive symptoms did not differ significantly on age, gender, education and MMSE scores in the two cohorts, although in the KI cohort there were clinically relevant differences in gender and MMSE. Subjects from the KI cohort were significantly younger and tended to be less educated than subjects from the ADNI cohort.

Depression-associated structural brain changes

In the ADNI cohort, comparison of cortical thickness in AD patients with and without depressive symptoms revealed significant depression-associated thinning in the left temporal and inferior parietal regions, including supramarginal, superior and inferior temporal and fusiform gyri (figure 1A, table 2).

In the KI cohort, depression-related changes were identified in temporal and parietal regions, including bilateral superior temporal, left supramarginal, right posterior cingulate and precuneus (figure 1B, table 2).

Association between depression, CSF biomarkers and cortical thickness

In the KI cohort, a significant difference in the slopes of the cortical thickness/CSF t-τ relationship between depressed and non-

Table 1 Comparison of demographic and clinical data for KI and ADNI cohorts

	KI cohort			ADNI cohort		
	Depressed (n=16)	Non-depressed (n=25)	p Value	Depressed (n=84)	Non-depressed (n=64)	p Value
Age	66.0 (62.5–75)	67.5 (61.5–73)	0.25	76.0 (70.6–80.3)	75.0 (69.5–80.7)	0.64
Gender (% of male)	56%	28%	0.07	53%	52%	0.87
Education(years)	12.0 (9–14.5)	12.0 (9–16.5)	0.29	16.0 (12–18)	15.0 (12–16)	0.7
MMSE	22.0 (20–26)	25.0 (22–27)	0.08	24.0 (23–25)	23.0 (22–25)	0.3
CSDD/GDS	8.0 (7–8)	2.0 (1–3)	0	2.0 (2–3)	0	
% of patients with A/D (n)	12.5% (2)	12% (3)	0.92	–	–	–

Numbers are in median (IQR).
A/D, antidepressants; CSDD, Cornell Scale for Depression in Dementia; GDS, Geriatric Depression Scale.

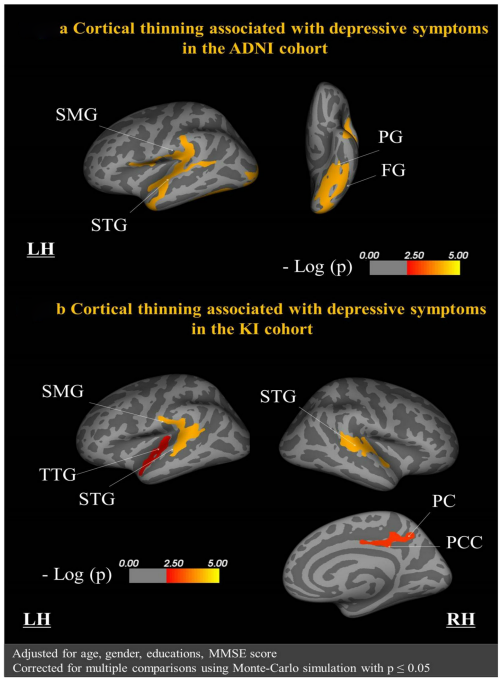

Figure 1 (A) Cortical thinning associated with depressive symptoms in the ADNI cohort. (B) Cortical thinning associated with depressive symptoms in the KI cohort. Regions showing significant between-group differences in cortical thicknesses on the lateral, medial and ventral inflated cortical surfaces. The clusters of depressed<non-depressed are rendered in red. LH, left hemisphere; RH, right hemisphere; STG, superior temporal gyrus; TTG, transverse temporal gyrus; SMG, supramartinal gyrus; PC, precuneus; PCC, posterior cingulated cortex; PG, parahippocampal gyrus; FG, fusiform gyrus.

depressed AD patients was found in several regions (figure 2). Significantly higher negative correlation in the depressed group was observed in the cluster covering right posterior cingulate cortex and precuneus (clusterwise p value (CWP) =0.008) and cluster covering right parahippocampal and fusiform gyri (CWP =0.001). The same regional pattern was observed for the cortical thickness/p-τ relationship. No significant difference between depressed and non-depressed subjects was observed in

Table 2 Clusters of cortical thinning associated with depressive symptoms in the ADNI cohort

Cluster	Size (mm^2)	TalX	TalY	TalZ	CWP
KI cohort					
Left hemisphere					
Superior temporal	1782.91	−50.8	−34.2	9.9	0.0001
Superior temporal	1082.48	−45.0	−19.5	5.4	<0.01
transverse temporal					
Right hemisphere					
Superior temporal	1541.02	60.3	−31.2	5.3	0.0001
Posterior cingulate, precuneus	642.12	6.2	−40.9	40.4	<0.01
ADNI cohort					
Left hemisphere					
Superior temporal	959.55	−55.9	−20.7	−20.7	0.0001
Fusiform	2710.86	−40.4	−52.8	−9.8	0.0001

CWP, clusterwise p value; LH, left hemisphere; TalX, TalY, TalZ, coordinates of maximum in Talairach space.

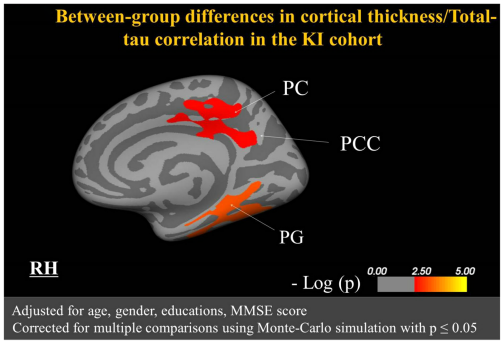

Figure 2 Regions showing significant between-group differences in cortical thicknesses/Total – tau correlation on the medial inflated cortical surface. The clusters where slopes of the correlation were significantly stronger in depressed were rendered in red. RH=right hemisphere. PCC=posterior cingulate cortex; PG=parahippocampal gyrus; FG=fusiform gyrus.

cortical thickness/Ab42 correlation. Next, correlation between cortical thickness and CSF t-τ level was tested in depressed AD separately from non-depressed. Clusters covering right parahippocampal, fusiform, posterior cingulate cortex and precuneus remain significant (CWP=0.0002, 0.0001) and also a cluster of cortical thinning in the right middle temporal gyrus (CWP=0.0001) was identified.

In the ADNI cohort, correlation between cortical thickness and CSF levels of τ protein was more pronounced in the depressed group compared with non-depressed in precuneus bilaterally but did not survive correction for multiple comparisons.

DISCUSSION

We have observed that even mild and subsyndromal depression is associated with cortical thinning in patients with AD. Depression-related cortical changes included temporal and parietal regions. When compared with non-depressed AD, patients with depressive symptoms demonstrated significantly higher negative correlation between CSF levels of τ protein and cortical thickness in the right medial temporal and cingulate regions; this association was also significant in the depressed-only group suggesting a more significant impact of the neurodegenerative process on limbic structures in depressed AD patients.

Our study has several limitations. First, the sample size of the KI cohort was rather small, though it was sufficient to detect significant differences in cortical thickness between groups. Second, CSF data were available only in subgroups for both cohorts, thus reducing the statistical power to detect small associations. Third, our patients did not have a diagnosis of depressive disorder, depressive symptoms were measured using clinical scales and had mild (KI cohort) or subsyndromal (ADNI cohort) levels. Of note, although criteria for depressive disorder in AD have been proposed, there are yet no established consensus criteria available. Different scales for depression were used for the two cohorts considered in this paper, and the definition of depressive symptoms may not be directly comparable. However, both the CSDD used in KI and GDS in ADNI have demonstrated good psychometric properties both in elderly people with and without AD. Differences in the correlations between cortical thickness and CSF level of τ protein between depressed and non-depressed were observed in both cohorts; however, they did not reach significance in ADNI cohort. This might be

due to the subsyndromal level of depressive symptoms in this cohort. Further studies with larger samples of AD with clinical level of depression are needed to confirm this finding. A further issue is that white matter lesions were not measured. Since these have been shown be associated with depression in AD,[30 31] they might also have influenced findings in this study. Finally, since diagnosis of AD was based on clinical evidence without histopathological conformation, misdiagnosis cannot be excluded.

Depression-associated atrophy in the temporal cortex was found in AD patients from both cohorts. These results support recent findings from several structural[32 33] and functional[34] neuroimaging studies focused on depressive symptoms in AD. Thinning in the superior temporal cortex has been described for patients with major depressive disorder.[35] A similar pattern of cortical atrophy including temporal and parietal regions was observed in non-demented subjects with late-life depression (LLD).[36 37] It has also been shown that psychotherapy-resistant patients with LLD compared with responders have thinner cortex in several regions, including paracentral, precuneus and posterior cingulate cortex.[38] However, there are studies that have not found any brain atrophy in LLD patients.[39] Heterogeneity of LLD might be one explanation for this difference. Thus, there may be a subgroup of patients with depression as a first symptom associated with neurodegenerative process that further develop dementia, while another subgroup may represent geriatric depression without association with any specific neurodegenerative disorder. Thus, our findings may have prognostic implications in terms of progression of cognitive decline as well as treatment response.

Thinning in temporal and parietal cortex was recently reported not only for depression but also for apathy and hallucinations in AD.[40] This might be explained by the clinical overlap between neuropsychiatric symptoms, in particular depression and apathy, which might result in similar pattern of structural changes. In addition, it is possible that the same cortical region is involved in several neuronal networks responsible for different neuropsychiatric symptoms. Studies combining structural and functional neuroimaging data are needed to further explore this issue.

We observed that the correlation between cortical thickness and CSF level of τ protein was significantly stronger in depressed compared with non-depressed AD patients in the right posterior cingulate cortex, precuneus, parahippocampal and fusiform gyri. Previously, it has been shown that depressive symptoms in cognitively normal and mild cognitive impairment (MCI) subjects are associated with binding of a tracer specific for τ protein and A-β in posterior cingulate and temporal regions.[13] Taken together, these results suggest that τ pathology might be relevant not only for the development of dementia, but also for the development of depressive symptoms in the elderly. This in turn may depend on the regional distribution of the pathological process.

Areas of observed depression-associated atrophy, that is, precuneus, posterior cingulate cortex and temporal cortex, are parts of the default mode network (DMN), which shows higher neural activity and energy consumption at rest. Functional connectivity within the DMN has been found to be decreased in AD patients compared with healthy aged controls[41] and increased in patients with depressive disorder.[42] Future studies need to clarify the interaction between AD and depression at the functional level, and perform studies in order to understand the relationship between functional abnormalities and cortical atrophy. Disruptions of neural networks containing limbic pathways have been proposed as a model of depression also in other neurologic diseases: stroke, multiple sclerosis, Parkinson's disease and Huntington's disease, and also in primary unipolar depression.[43 44]

Structural changes in temporal, posterior cingulate cortex and precuneus observed in our study are additional evidence for the role of these structures in mood regulation. In order to increase our understanding of the neurobiological interaction between dementia and depression, longitudinal studies focused on the causal relationships between cognitive impairments and depressive symptoms, taking into account brain structure and function, are needed.

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Contributors AL and DA developed study design. L-OW recruited and clinically evaluated the subjects. L-OW and EW contributed substantially to the image acquisition. XL and AL were responsible for data collection for the KI cohort. AS and EW were responsible for for the ADNI cohort. AVL, AS, AL and EW contributed to the image analyses, quality control and preprocessing. All authors participated in preparation and writing of this manuscript.

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Competing interests None.

Patient consent Obtained.

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REFERENCES

1 Plassman BL, Wyse BW, Welsh-bohmer KA, *et al*. Prevalence of depression and its treatment in an elderly population. *Arch Gen Psychiatry* 2013;57:14–18.
2 Katz I, Streim J, Parmelee P. Prevention of depression, recurrences, and complications in late life. *Prev Med* 1994;23:743–50. http://www.sciencedirect.com/science/article/pii/S0091743584711285 (accessed 18 Sep 2013).
3 Katon WJ. Clinical and health services relationships between major depression, depressive symptoms, and general medical illness. *Biol Psychiatry* 2003;54:216–26.

4 Enache D, Winblad B, Aarsland D. Depression in dementia: epidemiology, mechanisms, and treatment. *Curr Opin Psychiatry* 2011;24:461–72.
5 Barnes DE, Yaffe K. The projected effect of risk factor reduction on Alzheimer's disease prevalence. *Lancet Neurol* 2011;10:819–28.
6 Gao Y, Huang C, Zhao K, *et al*. Depression as a risk factor for dementia and mild cognitive impairment: a meta-analysis of longitudinal studies. *Int J Geriatr Psychiatry* 2013;28:441–449.
7 Sapolsky RM. Glucocorticoids and hippocampal atrophy in neuropsychiatric disorders. *Arch Gen Psychiatry* 2000;57:925–35. http://www.ncbi.nlm.nih.gov/pubmed/11015810
8 Maes M, Yirmyia R, Noraberg J, *et al*. The inflammatory & neurodegenerative (I&ND) hypothesis of depression: leads for future research and new drug developments in depression. *Metab Brain Dis* 2009;24:27–53.
9 Corsentino EA, Sawyer K, Sachs-Ericsson N, *et al*. Depressive symptoms moderate the influence of the apolipoproteine epsilon4 allele on cognitive decline in a sample of community dwelling older adults. *Am J Geriatr Psychiatry* 2009;17:155–65.
10 Rapp MA, Schnaider-Beeri M, Grossman HT, *et al*. Increased hippocampal plaques and tangles in patients with Alzheimer disease with a lifetime history of major depression. *Arch Gen Psychiatry* 2006;63:161–7.
11 Kim D, Payne M, Levy R. APOE genotype and hippocampal volume change in geriatric depression. *Biol Psychiatry* 2002;51:426–9. http://www.sciencedirect.com/science/article/pii/S0006322301012720 (accessed 22 Oct 2013).
12 Butters M, Klunk W, Mathis C. Imaging Alzheimer pathology in late-life depression with PET and Pittsburgh Compound-B. *Alzheimer Dis Assoc Disord* 2008;22:261–5. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2636843/ (accessed 16 Oct 2013).
13 Lavretsky H, Siddarth P, Kepe V, *et al*. Depression and anxiety symptoms are associated with cerebral FDDNP-PET binding in middle-aged and older nondemented adults. *Am J Geriatr Psychiatry* 2009;17:493–502. http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2709773&tool=pmcentrez&rendertype=abstract
14 Kramberger MG, Jelic V, Kåreholt I, *et al*. Cerebrospinal fluid Alzheimer markers in depressed elderly subjects with and without Alzheimer's disease. *Dement Geriatr Cogn Disord Extra* 2012;2:48–56.
15 Dotson VM, Davatzikos C, Kraut MA, *et al*. Depressive symptoms and brain volumes in older adults: a longitudinal magnetic resonance imaging study. *J Psychiatry Neurosci* 2009;34:367–75. http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2732743&tool=pmcentrez&rendertype=abstract
16 Ogura A, Morinobu S, Kawakatsu S, *et al*. Changes in regional brain activity in major depression after successful treatment with antidepressant drugs. *Acta Psychiatr Scand* 1998;98:54–9. http://www.ncbi.nlm.nih.gov/pubmed/9696515
17 Li X, Li T-Q, Andreasen N, *et al*. The association between biomarkers in cerebrospinal fluid and structural changes in the brain in patients with Alzheimer's disease. *J Intern Med* 2013. Published Online First: 16 November 2013. doi:10.1111/joim.12164
18 Yesavage JA, Brink TL, Rose TL, *et al*. Development and validation of a geriatric depression screening scale: a preliminary report. *J Psychiatr Res* 1983;17:37–49. http://www.ncbi.nlm.nih.gov/pubmed/7183759
19 Mackin RS, Insel P, Tosun D, *et al*. The effect of subsyndromal symptoms of depression and white matter lesions on disability for individuals with mild cognitive impairment. *Am J Geriatr Psychiatry* 2013;21:906–14.
20 Knapskog A, Barca M, Engedal K. A comparison of the validity of the Cornell Scale and the MADRS in detecting depression among memory clinic patients. *Dement Geriatr Cogn Disord* 2011;32:287–94. http://www.karger.com/Article/FullText/334983 (accessed 16 Oct 2013).
21 Westman E, Simmons A, Muehlboeck J-S, *et al*. AddNeuroMed and ADNI: similar patterns of Alzheimer's atrophy and automated MRI classification accuracy in Europe and North America. *NeuroImage* 2011;58:818–28.
22 Simmons A, Westman E. MRI measures of Alzheimer's disease and the AddNeuroMed study. *Ann N Y Acad Sci* 2009;1180:47–55. http://onlinelibrary.wiley.com/doi/10.1111/j.1749–6632.2009.05063.x/full (accessed 16 Oct 2013).
23 Ségonne F, Dale AM, Busa E, *et al*. A hybrid approach to the skull stripping problem in MRI. *NeuroImage* 2004;22:1060–75.
24 Ségonne F, Pacheco J, Fischl B. Geometrically accurate topology-correction of cortical surfaces using nonseparating loops. *IEEE Trans Med Imaging* 2007;26:518–29.
25 Fischl B, Dale AM. Measuring the thickness of the human cerebral cortex from magnetic resonance images. *Proc Natl Acad Sci U S A* 2000;97:11050–5.
26 Fischl B, Sereno MI, Tootell RB, *et al*. High-resolution intersubject averaging and a coordinate system for the cortical surface. *Hum Brain Mapp* 1999;8:272–84. http://www.ncbi.nlm.nih.gov/pubmed/10619420
27 Desikan RS, Ségonne F, Fischl B, *et al*. An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. *NeuroImage* 2006;31:968–80.
28 Rosas H, Liu A, Hersch S, *et al*. Regional and progressive thinning of the cortical ribbon in Huntington's disease. *Neurology* 2002;05886:695–701. http://www.neurology.org/content/58/5/695.short (accessed 21 Oct 2013).
29 Fischl B, Sereno M, Dale A. Cortical surface-based analysis: II: Inflation, flattening, and a surface-based coordinate system. *Neuroimage* 1999;207:195–207. http://www.sciencedirect.com/science/article/pii/S1053811998903962 (accessed 3 Sep 2013).
30 Starkstein S. Neuroimaging correlates of apathy and depression in Alzheimer's disease. *J Neuropsychiatry Clin Neurosci* 2009;21:259–65. http://neuro.psychiatryonline.org/article.aspx?articleID=103788 (accessed 25 Nov 2013).
31 Clark L, McDonald W. Magnetic resonance imaging correlates of depression in early-and late-onset Alzheimer's disease. *Biol Psychiatry* 1998;3223. http://www.sciencedirect.com/science/article/pii/S0006322398001061 (accessed 26 Nov 2013).
32 Lebedev A, Beyer M, Fritze F. Cortical changes associated with depression and antidepressant use in Alzheimer and Lewy body dementia: an MRI surface-based morphometric study. *Am J Geriatr Psychiatry*. Published Online First: 2013. http://www.sciencedirect.com/science/article/pii/S106474811300122X (accessed 16 Oct 2013).
33 Son J, Han D, Min K, *et al*. Correlation between gray matter volume in the temporal lobe and depressive symptoms in patients with Alzheimer's disease. *Neurosci Lett*. Published Online First: 2013. http://www.sciencedirect.com/science/article/pii/S0304394013004424 (accessed 3 Sep 2013).
34 Kang JY, Lee JS, Kang H, *et al*. Regional cerebral blood flow abnormalities associated with apathy and depression in Alzheimer disease. *Alzheimer Dis Assoc Disord* 2012;26:217–24.
35 Peng J, Liu J, Nie B, *et al*. Cerebral and cerebellar gray matter reduction in first-episode patients with major depressive disorder: a voxel-based morphometry study. *Eur J Radiol* 2011;80:395–9.
36 Ballmaier M, *et al*. 2004. Localizing gray matter deficits in late-onset depression using computational cortical pattern matching methods. *Am J Psychiatry* 2004;161:2091–9.
37 Lim HK, Jung WS, Ahn KJ, *et al*. Regional cortical thickness and subcortical volume changes are associated with cognitive impairments in the drug-naive patients with late-onset depression. *Neuropsychopharmacol* 2012;37:838–49.
38 Mackin R, Tosun D, Mueller S. Patterns of reduced cortical thickness in late-life depression and relationship to psychotherapeutic response. *Am J Geriatr Psychiatry* 2013;21:795–801. http://www.sciencedirect.com/science/article/pii/S1064748113000183 (accessed 16 Oct 2013).
39 Colloby SJ, Firbank MJ, Vasudev A, *et al*. Cortical thickness and VBM-DARTEL in late-life depression. *J Affect Disord* 2011;133:158–64.
40 Donovan NJ, Wadsworth LP, Lorius N, *et al*. Regional cortical thinning predicts worsening apathy and hallucinations across the Alzheimer disease spectrum. *Am J Geriatr Psychiatry* 2013;:1–12.
41 Binnewijzend M. Resting-state fMRI changes in Alzheimer's disease and mild cognitive impairment. *Neurobiol Aging* 2012;33:2018–28. http://www.sciencedirect.com/science/article/pii/S0197458011002703 (accessed 16 Oct 2013).
42 Sheline YI, Barch DM, Price JL, *et al*. The default mode network and self-referential processes in depression. *Proc Natl Acad Sci U S A* 2009;106:1942–7.
43 Mayberg H. Frontal lobe dysfunction in secondary depression. *J Neuropsychiatry Clin Neurosci* 1994;6. http://www.ap.psychiatryonline.org/data/Journals/NP/3823/428.pdf (accessed 16 Oct 2013).
44 Robinson R. Pathophysiology of secondary depressions in the elderly. *J Geriatr Psychiatry Neurol* 1999;12:129–35. http://jgp.sagepub.com/content/12/3/128.short (accessed 3 Sep 2013).

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