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A Comparison of Brain Structural Variables, Neuropsychological Factors, and Treatment Outcome in Early Versus Late Onset Late Life Depression

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Abstract

Objective—To compare differences in grey matter volumes, white matter and subcortical gray matter hyperintensities, neuropsychological factors, and treatment outcome between early and late onset late life depressed (LLD) subjects.

Design—Two-site, prospective, nonrandomized controlled trial.

Setting—Outpatient clinics at Washington University and Duke University.

Participants—126 subjects aged 60 years or older, met DSM-IV criteria for major depression, scored 20 or more on the Montgomery-Asberg Depression Rating Scale (MADRS), received neuropsychological testing and magnetic resonance imaging, excluded for cognitive impairment or severe medical disorders.

Intervention—Twelve weeks of sertraline treatment.

Main Outcome Measure—Subjects' MADRS scores over time, neuropsychological factors.

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Results—Left anterior cingulate thickness was significantly smaller in the late onset depressed group than early onset LLD subjects. The late onset group also had more hyperintensities than the early onset LLD subjects. There was no difference in neuropsychological factor scores or treatment outcome between early onset and late onset LLD subjects.

Conclusions—Age of onset of depressive symptoms in the late life depressed are associated with differences in cortical thickness, and white matter and subcortical gray matter hyperintensities, but age of onset did not affect neuropsychological factors or treatment outcome.

Keywords

late life depression; antidepressant; hippocampus; amygdala; neuropsychological factors; cognitive deficit; age of onset; vascular risk factors; white matter hyperintensities; treatment outcome

Objective

Studies of late life depression (LLD) are important not only for the insights into the underlying pathophysiology of depression, but also because of the clinical significance of an expanding elderly population. LLD is a heterogeneous disorder, with outcome disparities in studies examining structural brain volumes, ischemic lesions, and neuropsychological deficits (1–3). The conflicting results may in part be related to samples that differ in age of depression symptom onset (4–6).

One difference between late onset late life depression (LOD), defined as depression onset age 60 or older, and early onset late life depression (EOD) defined as age of onset <60, may be the contribution from underlying vascular disease. Multiple studies (1, 7) have shown an association between cerebrovascular disease and depression in elderly adults (8). LOD subjects have a higher burden of cerebrovascular disease, which may be an important contributing factor to the later development of depressive symptoms (9). In contrast, EOD may be a more familial disorder with genetic predisposition (10).

Our previous study (11) reported a significant correlation between white matter hyperintensities (WMH), cognitive function, and vascular risk factors (VRF), in support of the vascular depression hypothesis. However, this study did not examine the effect that age of onset of depressive symptoms exerts on white matter hyperintensities, cognitive deficits, region of interest (ROI) gray matter volumes and cortical thicknesses, or treatment outcomes. The purpose of the current study is to compare ROI volumes and cortical thicknesses, deep white matter and non-white matter (subcortical gray matter) hyperintensities, neuropsychological factors, and treatment outcomes between early onset and late onset LLD subjects.

Methods

Participants

Patients were recruited from an ongoing National Institute of Mental Health study, Treatment Outcome in Vascular Depression, through advertising and physician referral to Washington University (WU) Medical Center and Duke University Medical Center. Patients

were at least 60 years of age, met *DSM-IV* criteria for major depression by Structured Clinical Interview for Axis I *DSM-IV* Disorders (SCID-IV) given by a research psychiatrist, and had a Montgomery-Asberg Depression Rating Scale (MADRS) (12) score of 20 or greater. Inclusion criteria, study measures, and study design have been described in detail elsewhere (11). Patients were excluded if they had contraindications to MRI, used psychotropic drugs, or had evidence of severe depression as defined by symptoms requiring hospitalization, risk of suicide, or history of failure to respond to 2 or more antidepressants. In addition, patients were excluded if they had a severe or unstable medical disorder or a known primary neurologic disorder. All participants were screened for dementia using the Clinical Dementia Rating (CDR) (13) and were excluded for CDR score > 0.

There were 217 patients (120 at WU and 97 at Duke) enrolled in a 12-week treatment trial with sertraline. One hundred and ninety participants completed the trial; 168 had complete imaging data. Subjects were divided into two groups: EOD (depression onset before age 60) and LOD (depression onset at age 60 or older). To match groups for age, the youngest 42 EOD participants were removed from the sample. Thus, a total of 126 participants were included in the current analyses, 60 in the EOD group and 66 in the LOD group. Written informed consent approved by the relevant institutional review board was obtained for all subjects.

Comparison Group

For the purpose of creating *a priori* regions of interest, a comparison group was recruited. The comparison group consisted of a sample of non-depressed subjects (n=57) recruited from the community. Comparison subjects did not have a personal history of depression or current major depression. Of these 57 participants, 50 had complete usable MRI scans.

Measures

Data were obtained from evaluations performed by research staff of the clinical research study at each site and included medical, psychiatric, demographic, MRI, and neuropsychological measures. Age of onset of depression was obtained from the subjects, all of whom had no evidence of dementia (CDR 0). For the current study comparing EOD to LOD subjects, demographic variables included age, education, gender, race, and vascular risk factor (VRF) score, as defined by the Framingham study (14). In the current study we used the VRF score minus age in adjusting for VRF so as not to adjust for age twice.

Outcome Measures

MADRS scores were obtained at baseline and weekly for 12 weeks by a research psychiatrist. Participants were administered sertraline for 12 weeks [for details on dosing, adherence, and adverse effects, see (11)]. Response to treatment was measured using the MADRS; participants were administered the MADRS weekly during the duration of their sertraline treatment. For purposes of data analysis, given variable patient schedules for completing the study, completion was defined as more than 8 weeks in the study.

Briefly, all participants were given a neuropsychological test battery examining executive function, processing speed, episodic memory, language processing, and working memory.

Specific tests for each domain include: verbal fluency, Trails B, the color-word interference condition of the Stroop, the Initiation-Perseveration subscales of the Mattis, and categories completed from the Wisconsin Card Sorting Test for executive functioning; Symbol-digit modality, the color naming condition of the Stroop task, and Trails A for cognitive processing speed; word list learning, logical memory, constructional praxis, and the Benton Visual Retention Test for episodic memory; the Shipley Vocabulary Test, the Boston Naming Test, and the Word reading condition of the Stroop for language processing; and digit span forward, digit span backwards, and ascending digits for working memory. For full details of neuropsychological measures, please see our previous studies (11, 15).

Magnetic Resonance Imaging

Image Acquisition—Magnetic resonance images were collected using a MAGNETOM Sonata 1.5 T scanner (Siemens, Munich, Germany) at WU. Three-dimensional, T1-weighted (T1W) scans were acquired with magnetization-prepared rapid acquisition gradient echo: time to repetition (TR), 1900 milliseconds; echo time (TE), 4 milliseconds; time following inversion pulse (TI), 1100 milliseconds; and $222 \times 256 \times 128$ pixels ($1 \times 1 \times 1.25$ mm). To improve signal-to-noise ratio, multiple T1W images were obtained and averaged as part of the image processing stream described below.

Magnetic resonance images were collected using a 1.5 T scanner (General Electric, Schenectady, New York) at Duke University. The equivalent sagittal T1W sequence was conducted using a 3-dimensional inversion recovery–prepared spoiled gradient recalled scan: TR, 8.3 milliseconds; TE, 3.3 milliseconds; TI, 300 milliseconds $256 \times 256 \times 124$ pixels. To correct for magnetic field inhomogeneities, a parametric bias field correction was used to correct both T1W and T2W image intensities.

Image Processing—MRI preprocessing and the delineation of cortical and subcortical gray matter regions on structural images was conducted through a pipeline in the Washington University School of Medicine Central Neuroimaging Data Archive, based on the XNAT processing environment, using FreeSurfer's automated segmentation software (FreeSurfer 4.0.1, <http://surfer.nmr.mgh.harvard.edu>) (16–18). Briefly, this processing includes motion correction, averaging of multiple volumetric T1 weighted images, removal of non-brain tissue, automated Talairach transformation, segmentation of the subcortical white matter and deep gray matter volumetric structures, intensity normalization, tessellation of the gray matter- white matter boundary, automated topology correction, and surface deformation following intensity gradients to optimally place the gray/white and gray/cerebrospinal fluid borders. Once cortical models are complete, further data processing and analysis can include parcellation of the cerebral cortex into gyral and sulcal structure (18) using both intensity and continuity information from the entire 3D MR volume to produce representations of cortical thickness. FreeSurfer morphometric procedures have been demonstrated to show good test-retest reliability (19).

Regions of Interest (ROI)

We compared LLD versus comparison group subcortical volumes and cortical thicknesses to generate a priori ROIs for further analysis between LOD and EOD subjects. There were

significant group differences between LLD and the comparison group in hippocampal and amygdala volumes, as well as the thicknesses of the anterior cingulate, frontal pole, superior frontal gyrus, orbitofrontal gyrus, and middle frontal gyrus. In the current study, we used these ROIs for LOD versus EOD comparison and also compared white/non-white matter hyperintensities in early versus late onset LLD subject comparisons.

Statistical Analyses

There was no difference in age, education, VRF (age excluded), gender, and race across the two groups (Table 1). We tested for EOD/LOD group differences of 18 structural characteristics with significant results reported in Table 1. Since the distribution of brain volume and thickness is often skewed, we used Wilcoxon rank-sum tests to compare cortical thicknesses and white/non-white matter hyperintensities between EOD and LOD cases. To compare ROI volumes between EOD and LOD groups, we adjusted for intracranial volume and implemented a linear regression procedure with robust standard error. This procedure provides stable results even if normality assumptions were violated and/or the variances were not constant (20). For the structural characteristics tests, a Hochberg-Benjamini procedure was conducted for the multiple comparisons adjustment of p-values to control for the false discovery rate of 0.05.

Linear regression was used to examine whether there were group differences on neuropsychological factors and treatment outcomes, controlling for age, education, VRF, gender, race, and location (WU versus Duke). The linear regression assumptions were examined through residual plots and normality tests: residual and Student residual versus predicted value and predictors plots were used to check the constant variance assumption; residual histogram, qq-plot, and Shapiro-Wilk/Kolmogorov-Smirnov tests were used to check the normality assumption; leverage and Cook's D plots were used to identify outliers. In cases where normality assumptions were violated and/or the variances were not constant, we used robust standard errors.

Results

Table 1 shows demographic variables by the EOD and LOD groups. There were no differences in age, education, VRF scores (without age component), gender, or racial composition between the early onset and late onset cohorts. Table 1 also shows comparisons of cortical thickness, and white matter and subcortical gray matter hyperintensities for early onset versus late onset LLD subjects, with the group means, test statistics and unadjusted p-values. Left anterior cingulate thickness was significantly smaller in the late onset LLD group than the early onset subjects (Wilcoxon rank-sum test, $z = 2.31$, $p = 0.02$). There was also a significant difference in white matter and subcortical gray matter hyperintensities between the two groups, with late onset depressed patients having more hyperintensities than those elderly depressed with early onset depressive symptoms (Wilcoxon rank-sum test, $z = -3.49$, $p < .01$ for white matter hyperintensities; Wilcoxon rank-sum test, $z = -2.17$, $p = 0.03$ for subcortical gray matter hyperintensities). When adjusted for multiple comparisons to control the false discovery rate, only white matter hyperintensities remained significant. Notably, there were no differences in hippocampal or amygdala volumes

between early and late onset LLD groups (not shown in Table). Neuropsychological scores (Table 2) are not associated with early onset/late onset groups when we controlled for age, education, VRF (age excluded), gender, race, and location. Therefore, we can conclude that for this adjusted analysis there is no difference between the neuropsychological scores means between the early onset and late onset groups.

Conclusions

The main finding in this study is that LLD subjects with late onset depressive symptoms differ in cortical and subcortical structure from those who first develop depression earlier in life. Those with LOD have smaller left anterior cingulate thicknesses, and more white matter and subcortical gray matter hyperintensities than persons with EOD. The groups did not differ in neuropsychological scores or treatment outcome based on age of onset of depressive symptoms.

In order to generate regions of comparison between LOD and EOD, we compared the entire LLD sample to a non-depressed comparison group. This analysis found smaller volumes in the hippocampus, amygdala, anterior cingulate, frontal pole, superior frontal gyrus, orbitofrontal gyrus, and middle frontal gyrus, but no difference between parahippocampal or caudate volumes. Studies examining specific brain volumes between LLD and non-depressed subjects have had mixed results (see Table 3). While there are discrepancies in differences between brain volumes of LLD versus comparison groups amongst studies, similarities in volumetric reductions provide more evidence supporting a neuroanatomical etiology involving frontolimbic pathways underlying the pathophysiology of LLD.

In contrast to studies comparing LLD and non-depressed subjects, few studies have compared LOD and EOD. In our analyses, the left anterior cingulate was significantly smaller in those with late onset LLD compared to early onset LLD subjects. Previous imaging research has shown smaller anterior cingulate volumes in LLD compared to controls (21). Gunning et al (22) examined the relationship between anterior cingulate volumes and antidepressant treatment in a 12 week study using the antidepressant escitalopram and found that non-remitting depressed subjects had smaller dorsal and rostral anterior cingulate cortices than remitters. Andreescu et al (23) examined the correlation between brain volumes and age of depression onset and duration of depressive illness. Similar to our study, they found a significant correlation with age of onset for anterior and middle cingulate volumes but also reported smaller parahippocampal and parietal inferior area, frontal superior, frontal orbital, frontal middle, frontal medial superior, temporal pole, temporal middle and temporal inferior, and putamen volumes in LOD compared to EOD. In contrast, Delaloye et al (24) found no significant difference in anterior cingulate volumes.

Our study found no significant difference in hippocampal or amygdala volumes in LOD compared to EOD subjects. Other studies have agreed with our results (23–26). Janssen et al (26) found reduced hippocampal volume in EOD compared to controls, but hippocampal volumes in LOD did not differ compared to EOD or from controls. Ballmaier et al (25) reported significantly smaller hippocampal volumes in LLD compared to controls, but found no difference in hippocampal volumes based on age of onset. Interestingly, there were

localized volume reductions in the anterior subiculum and lateral-posterior CA1 subfield in the late onset depressed, areas this study noted were implicated in very early Alzheimer's disease. In contrast, Lloyd et al (27) found significant bilateral hippocampal atrophy in late onset depressed compared to both early onset depressed and controls. Similar to our amygdala volume results, Burke et al (28) reported smaller amygdala volumes in both LOD and EOD compared to controls, but there was no difference between EOD and LOD. Deloloye et al (24) and Andreescu et al (23) also reported no significant difference in amygdala volumes in LOD.

Multiple studies have shown increased gray and white matter hyperintensities in LOD samples compared to EOD subjects. A recent meta-analysis including studies from 1966 to January 2007 concluded that periventricular and deep WMH are more common and more severe in LLD than controls; specifically, there is a 2.57 times greater odds of periventricular WMH in LOD than controls, and 4.51 times greater odds in LOD than EOD (5). Subsequent studies have also had similar results to our study, with a higher prevalence of white matter lesions in LOD than EOD (24, 26). These results provide further support for the vascular depression hypothesis (29–30), and support the idea that late onset late life depression may have a different etiologic pathophysiology than early onset LLD.

Our study found no difference in neuropsychological factors or treatment outcomes between early onset and late onset late life depressed. Salloway et al (9) found poorer performance on memory and executive functioning in LOD compared to EOD. Delaloye et al (24) found neuropsychological functioning was the same between EOD and LOD, except for episodic memory, for which the LOD had lower recall scores than EOD or controls despite exclusion for dementia. One explanation for the discrepancies between these study results and our results showing no difference in neuropsychological factors between early and late onset LLD patients is that other studies may not have formally screened for the mildest incipient dementia. In contrast, our subjects were only included with CDR=0, with no evidence of even very mild dementia. Despite differences in specific ROI volumes and white matter and subcortical gray matter hyperintensities, our study found no difference in treatment outcome between the EOD and LOD subjects. Multiple studies also report no difference in treatment outcome based on age of onset of depressive symptoms (31–33). The current study results are similar to our previous study (11) which also found that WMH did not predict treatment outcome after adjustment for depression severity. Our recent study did report a correlation between white matter integrity and neuropsychological factors in LLD compared to controls but did not examine differences with age of onset, as was the focus of the current study (34). In a study examining change in cognition with antidepressant treatment in a LLD sample, Barch et al (35) found that a later age of onset of depressive symptoms predicted less improvement in executive function, while WMH burden predicted less change in processing speed. This study also found that greater treatment response did not benefit cognitive improvement, with the exception of language.

The importance of reduced anterior cingulate volumes in late onset LLD compared to those elderly depressed with earlier onset of depressive symptoms is potentially of clinical significance. The prodromal dementia hypothesis of LLD proposes that some patients presenting with late life depression represent the prodromal or very early stage of dementia

(36–37). Further, it is now clear that approximately 25% of the cognitively normal elderly population has preclinical Alzheimer's disease by both post-mortem pathological examination (38) and in vivo amyloid PET imaging (39). It is possible that this preclinical AD group may have amyloid-induced damage to regions involved in mood regulation. Several regions, including the anterior and posterior cingulate/precuneus cortices, are the earliest sites of amyloid deposition (39–40) and well known to be involved in affective regulation. Significantly smaller anterior cingulate volumes in late onset LLD subjects may provide additional support to our understanding the unique pathophysiology of LLD and relationship with Alzheimer's Dementia.

In summary, this study used ROI volumetric comparisons between LLD subjects and a non-depressed group and then examined the significance of age of onset on subcortical volumes, cortical thicknesses, white matter and subcortical gray matter hyperintensities, neuropsychological features, and treatment outcome. To our knowledge, this is the largest sample size to address these questions. Comparing LLD subjects to a non-depressed comparison group, we found smaller volumes in the hippocampus and amygdala, with smaller cortical thicknesses in the anterior cingulate, frontal pole, superior frontal gyrus, orbitofrontal gyrus, and middle frontal gyrus, but no difference between parahippocampal or caudate volumes. When further examining the LLD subjects, the late onset LLD patients had significantly smaller left anterior cingulate thickness, and increased deep white matter and subcortical gray matter hyperintensities compared with early onset LLD. The fact that there is no difference between treatment outcome and neuropsychological factors based on age of symptom onset, suggests similar clinical outcome despite different pathophysiological etiologies.

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Table 1

a. Descriptive Statistics	Early Onset Depression (EOD) n = 60		Late Onset Depression (LOD) n = 66	
	Mean (SD)	Mean (SD)	t or χ^2	p
Age ^a	69.42 (6.48)	71.11 (7.35)	-1.36	.18
Education ^a	14.43 (2.97)	13.80 (3.13)	1.16	.25
VRP ^a (no age)	8.15 (3.67)	7.64 (3.58)	.79	.43
Gender ^b	23 M, 37 F	33 M, 33 F	1.73	.19
Race ^c	58 W, 2 B, 0 A	60 W, 5 B, 1 A	2.04	.36

b. Structural Characteristics ^d	EOD		LOD	
	Mean	Mean	z	p (unadjusted)
L Anterior Cingulate Thickness	5.44	5.22	2.31	.02
White Matter Hyperintensities	4496.60	6731.58	-3.49	<.01*
Non-White Matter Hyperintensities	45.43	69.70	-2.17	.03

^a two-sided unpaired t-test with 124 df

^b M = Male, F = Female, $\chi^2(df=1)$

^c W = White, B = Black, A = Asian, $\chi^2(df=2)$

^d Wilcoxon rank-sum test for EOD versus LOD

* significant at $p < .05$ after adjusting for multiple comparisons using the Hochberg-Benjamini procedure to control false discovery rate.

Table 2
Neuropsychological Measures in Early (n = 60) and Late (n = 66) Onset Depression.

Dependent Variables *	Descriptive Statistics			Statistics after Adjusting for Age, Education, VRF (age excluded), Gender, Race, and Location in linear regression model			
	EOD Mean z Score	LOD Mean z Score	Pooled SD	Regression Coefficient (β) Estimates for Group Membership (EOD vs LOD) (Standard Error of Estimates)	t	df	p
Episodic Memory	-.35	-1.08	3.39	-.05 (.60)	-.08	117	.94
Language	.02	-.22	2.34	.09 (.41)	.22		.83
Working Memory	.22	-.48	2.45	-.58 (.46)	-1.27	117	.21
Processing Speed	-.24	-.04	2.65	.40 (.47)	.87	112	.39
Executive Function	-.26	-.54	3.74	.25 (.67)	.37	109	.71

* two-sided t-test with *df* reported in the column next to the t-statistic from the linear regression model

Table 3**Studies Comparing Brain Volumes Between LLD and Comparison Subjects**

Reference	Population	Results
Andreescu et al. ²³	71 elderly depressed subjects, 32 comparison subjects	LLD subjects had significantly smaller volumes in the frontal superior orbital, frontal orbital, frontal inferior, frontal superior medial, gyrus rectus, insula, hippocampus, parahippocampus, amygdala, parietal inferior, putamen, pallidum, thalamus, temporal superior, temporal pole, temporal middle, and temporal inferior ROIs compared to the non-depressed group. No significant difference in caudate volumes between groups. Duration of illness and later age of onset correlated with smaller parahippocampal and parietal inferior volumes, later onset also correlated with smaller cingulum, putamen, frontal and temporal volumes.
Colloby et al. ⁴¹	38 elderly depressed subjects, 30 comparison subjects	This study examined cortical thickness and voxel based morphometric abnormalities, and found no significant difference in frontal cortical thickness or difference in grey matter volumes between LLD subjects and the comparison subjects. An age-related decrease in grey matter regardless of diagnosis.
Goveas et al. ⁴²	1372 post-menopausal women, age 65–79 at baseline enrolled in the WHIMS-MRI study. Late-life depressive symptoms assessed with screening questionnaire, on average 8 years prior to structural brain MRI.	Depressive symptoms at baseline were associated with smaller superior and middle frontal gyral volumes. They did not find differences in hippocampus, amygdala, or ischemic lesions between depressed and non-depressed elderly women. No age of onset or duration of depressive symptoms were available.