

A longitudinal study of differences in late- and early-onset geriatric depression: Depressive symptoms and psychosocial, cognitive, and neurological functioning

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Objectives: Studies suggest early-onset depression (EOD) is associated with a more severe course of the depressive disorder, while late-onset depression (LOD) is associated with more cognitive and neuroimaging changes. This study examined if older adults with EOD, compared with those with LOD, would exhibit more severe symptoms of depression and, consistent with the glucocorticoid cascade hypothesis, have more hippocampal volume loss. A second goal was to determine if LOD, compared with EOD, would demonstrate more cognitive and neuroimaging changes.

Method: At regular intervals over a four-year period non-demented, older, depressed adults were assessed on the Mini-Mental Status Examination and the Montgomery–Asberg Depression Rating Scale. They were also assessed on magnetic resonance imaging.

Results: Compared with LOD, EOD had more depressive symptoms, more suicidal thoughts, and less social support. Growth curve analyses indicated that EOD demonstrated higher levels of residual depressive symptoms over time. The LOD group exhibited a greater decrement in cognitive scores. Contrary to the glucocorticoid cascade hypothesis, participants with EOD lost right hippocampal volume at a slower rate than did participants with LOD. Right cerebrum gray matter was initially smaller among participants with LOD.

Conclusions: EOD is associated with greater severity of depressive illness. LOD is associated with more severe cognitive and neurological changes. These differences are relevant to understanding cognitive impairment in geriatric depression.

Keywords: late-onset depression; early-onset depression; cognition; hippocampus

Introduction

Among older adults, there is a strong relation between depression and cognitive impairment (CI; Lopez et al., 2003; Zubenko et al., 2003). At least two theories, which are not mutually exclusive, have been formulated to account for this association. First, in early-onset depression (EOD), repeated depressive episodes over an individual's lifetime are posited to lead to damage to the hippocampus (Sapolsky, 1996). Second, among older adults (60+ years of age), neurological changes that give rise to cognitive deficits are posited to produce depressive symptoms (Janssen et al., 2007). For example, some have proposed a subtype of depression arising in later life that is characterized by a cerebrovascular disease associated with subcortical neurological dysfunction (Baldwin & O'Brien, 2002). Indeed, over a decade ago, Alexopoulos et al. (1997) noted that elderly patients with vascular depression had greater overall CI than those with non-vascular depression.

In most psychiatric disorders, earlier onset is associated with a more severe course of the disorder over the lifetime. Depressive episodes in childhood and

adolescence, rather than those at older ages, predict more episodes and longer duration of depression in adult life (Kendler et al., 1993; Mondimore et al., 2006; Parker, Wilhelm, & Asghari, 1997; Piccinelli & Wilkinson, 2000) and, thus, a more chronic course of illness (Zisook et al., 2007). Additionally, there is longitudinal evidence supporting the formulation that EOD is a risk factor for CI. For instance, a history of depressive symptoms was found to be associated with Alzheimer's disease (AD), even when the onset of depressive symptoms preceded the onset of AD by more than 25 years (Green et al., 2003). The Whitehall II study examined the association between history and frequency of depressive symptoms and cognition over an 18-year period. They found individuals with an early history of depressive symptoms were at a greater risk of cognitive deficits in late midlife (Singh-Manoux et al., 2010).

EOD is thought to be a risk factor for CI in that prior depressive symptoms are thought to lead to damage to the hippocampus, an essential brain structure for the formation of new memories. Sapolsky (1996) proposed a glucocorticoid cascade hypothesis in

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which depression or chronic stressors lead to chronic, prolonged activation of the hypothalamic–pituitary–adrenal axis (HPA axis). The HPA axis involves the hypothalamus, as well as the pituitary and adrenal glands. In response to stress, the hypothalamus releases hormones that stimulate the pituitary gland to release adrenocorticotrophic hormone (ACTH). ACTH then stimulates the adrenal gland to release corticosteroids, such as cortisol. Initially, the release of cortisol in response to stress is helpful in producing physiological changes that facilitate the fight or flight response. However, prolonged and repeated cortisol release is thought to cause damage to the hippocampus. Thus, the glucocorticoid cascade hypothesis contends that depression initiates neurological changes that in turn lead to prolonged activation of the HPA axis, and ultimately to hippocampal damage and neuronal death, which in turn places depressed individuals at greater risk for developing dementia. In this regard, studies have found that many depressed people have high circulating levels of glucocorticoids (Sapolsky, 1996) and that HPA dysregulation and decreased hippocampal volumes are associated with cognitive decline in studies of humans and rodents (Laakso et al., 1998; Lupien et al., 1998).

The glucocorticoid cascade hypothesis describes a specific process that stems from a much broader literature, namely that of allostatic load. More generally, the body is thought to restore balance and stability in response to a stressor through the process of allostasis. The HPA axis is an example of a specific mediator that produces allostasis (McEwen, 1998, 2002). When an individual is exposed to repeated stressors, or when these mediators are activated for longer than necessary, damage can result to the brain and body. This process is known as ‘allostatic load’ (McEwen, 1998).

Recently, it has been shown that hippocampal damage is associated with CI (Steffens, McQuoid, Payne, & Potter, 2011). Depression has been associated with changes in left and right hippocampal volume (Sheline, Sanghavi, Mintun, & Gado, 1999; Videbech & Ravnkilde, 2004). In accordance with the glucocorticoid hypothesis, we might expect hippocampal volume to be reduced in both EOD and LOD, but we would expect EOD to be more strongly affected because these individuals are likely to have more repeated episodes of depression over the lifetime than individuals with LOD. However, this was not unequivocally supported by the literature. In fact, researchers have found reduced hippocampal volumes to be most pronounced in LOD (Gerritsen et al., 2011). It is possible that although EOD and LOD both are associated with hippocampal atrophy, these two types of depression may differ with respect to the cause of the atrophy.

Others suggest that it is LOD that primarily accounts for the association between depression and CI. Several studies have shown an association between LOD and subsequent dementia in older adults (Wilson

et al., 2002; Yaffe et al., 1999). In a cohort of 3410 participants (age 65+) followed for approximately seven years, those with LOD were at increased dementia risk, but EOD had no association with dementia risk. However, the study was limited in that it relied on the brief Center for Epidemiological Studies Depression Scale (CES-D; Radloff, 1977) to assess current depression rather than a thorough assessment of DSM-IV depression (APA, 2000) and only used a brief interview to assess a history of past depression. Thus, they may have underestimated cases of current or past depression, resulting in restricted range of risk ratios (particularly for EOD) for dementia.

In this study, in addition to focusing on the hippocampus, we compare EOD and LOD on other neurological areas associated with CI. Specifically, volume changes in white and gray matter and changes in size and number of white and gray matter lesions (for both hemispheres) have been associated with cognitive functioning (Ferro & Madureira, 2002; O’Brien et al., 2002; Salat et al., 2009; Thompson et al., 2003). The literature, however, to our knowledge has only identified white matter lesions as an area in which LOD has more deficits than EOD (Koga et al., 2002). Finally, the majority of studies have found that **LOD** participants score lower and exhibit more severe impairment in tests of different memory domains than **EOD** participants (Dillon et al., 2009; Salloway et al., 1996; van Reekum, Simard, Clarke, Binns, & Conn, 1999).

In this study, we analyzed data from the neurocognitive outcomes of depression in the elderly (NCODE) study (Steffens, McQuoid, & Potter, 2009). Depressed participants (age 60+) were assessed on study measures over a four-year period. Based on the literature reviewed above, we predicted that participants with EOD would exhibit more severe symptoms of depression (e.g., depressive symptoms and suicidal thinking), less social support, and, consistent with the glucocorticoid cascade hypothesis, more hippocampal volume loss. While we would expect both groups to show cognitive decline over time, we expected that LOD participants would show more cognitive decline and more neurological pathology, as assessed by magnetic resonance imaging (MRI) of the brain.

Methods

Participants

Participant recruitment for the NCODE study began in 1994 and continues to the present. Participants underwent naturalistic treatment using the Duke somatic treatment algorithm for geriatric depression approach developed by clinicians in the **Duke mood disorders program**. The algorithm consists of five stages and is based on their history of antidepressant use, severity of depression and participant’s treatment history. The treatment protocol is described by

Steffens, McQuoid and Krishnan (2002). Additionally, never-treated participants were initially prescribed selective serotonin reuptake inhibitors, with augmentation or change if response was not sufficient (Steffens, McQuoid, et al., 2002).

All participants provided written informed consent to participate, and the research protocol was reviewed and approved annually by the Duke University Institutional Review Board. Secondary data analysis was performed at Florida State University (FSU) and was approved by the Institutional Review Board at FSU.

Non-demented adults age 60 and older who presented for inpatient or outpatient psychiatry services at Duke University Medical Center or the Duke General Internal Medicine Clinic in Durham, North Carolina and met DSM-IV criteria for a current episode of major depression were recruited into the NCODE study. Participants were excluded from the study if they met criteria for another major psychiatric illness that would influence cognitive functioning (i.e., schizophrenia, schizoaffective disorder, bipolar disorder, lifetime alcohol or substance dependence, and dementia). For this study, we included those participants who we could demarcate as having EOD (onset by age 30) or LOD (first onset at age 60+).

In studies comparing EOD and LOD, previous researchers' definitions of early onset have been defined by somewhat arbitrary ages. The vast majority of studies appear to have defined early onset in relationship to the 'opposite of late onset', that is, onset occurring before age 60. We argue that early onset should be represented by the age before which the average individual has had the first episode of depression. Or, as in the case of the current clinical sample, we selected the average age at which the depressed individual in the general population first reported depressive symptoms to a health care provider. Thus, we identified the average age of onset in the National Comorbidity Survey (Kessler, McGonagle, Swartz, Blazer, & Nelson, 1993) for first reporting depressive symptoms to a health professional. The mean age was 29.92 (SD=9.2). Second, we observed that 25% of our sample had their first episode by the age of 31. From this information, for this study we defined early onset as occurring before age 31. We used the definition of late onset as 60+, the same age used in the majority of studies examining LOD.

At baseline, there were 135 depressed older adults who had either EOD (48.1%, $n=65$) or LOD (51.9%, $n=70$). Retrospective reports on the Diagnostic Interview Schedule (DIS) have been shown to be accurate (Knäuper, Cannell, Schwarz, Bruce, & Kessler, 1999; Robins, Helzer, Croughan, & Ratcliff, 1981). Thus, we were assured of a clear demarcation between EOD and LOD, a factor that has been largely overlooked in previous research. Some of the 135 participants failed to complete scheduled assessments or left the study; thus, for a number of analyses that used follow-up data, there were missing data due

to attrition. Attrition was carefully analyzed, and possible effects of attrition were considered within the context of the growth curve analyses (statistical analyses of attrition effects are explained in greater detail in the analyses section below).

Attrition in relation to each measure was as follows. There were 135 participants (EOD=65, LOD=70), assessed at baseline on the Montgomery-Asberg Depression Rating Scale (MADRS; Baudic, Tzortzis, Barba, & Traykov, 2004; Parker, Elizabeth, Hayden, Carl, & David, 2003). We assessed the MADRS every three months over the four-year period; by year 1 there were 129 participants (EOD=62, LOD=67). By year 2 there were 117 participants (EOD=57, LOD=60), by year 3 there were 103 participants (EOD=51, LOD=52), and by year 4 there were 87 participants (EOD=47, LOD=40). For the Mini-Mental Status Examination (MMSE), we assessed participants every six months over the four years. We had 135 assessments on the MMSE at baseline (EOD=65, LOD=70). By year 1 there were 114 participants (EOD=54, LOD=60), at year 2 there were 96 participants (EOD=46, LOD=50), by year 3 there were 68 participants (EOD=32, LOD=36), and by year 4 there were 63 participants (EOD=36, LOD=27).

For the MRI, to allow time for more neurological changes to occur, we included data examining volume changes over six years. We obtained participants' MRI at baseline and every two years. However, there were some participants who failed to come to their MRI assessments at follow-up (scheduled at a time separate from the other assessment appointments). In this study, we present data from the MRI at baseline ($n=133$), year 2 ($n=98$), year 4 ($n=58$), and year 6 ($n=29$). The MRI assessment sample size for EOD was as follows: baseline ($n=63$), year 2 ($n=50$), year 4 ($n=35$), and year 6 ($n=19$). The LOD sample size was as follows: baseline ($n=70$), year 2 ($n=45$), year 4 ($n=23$), and year 6 ($n=10$).

Measures

Baseline demographic and depression assessment

Trained interviewers administered the Duke Depression Evaluation Schedule (DDES), a structured interview that includes sections on demographic information, current life stress, and social support. The DDES also includes the Diagnostic Interview Schedule (DIS; Robins et al., 1981), which allows for an assessment of DSM-IV current and lifetime major depression. Its accuracy has been evaluated in a test-retest design comparing independent administrations by psychiatrists and lay interviewers with inpatients, outpatients, former patients, and non-patients (Robins et al., 1981), and it has been found to have good validity and reliability for participants of all ages (Robins et al., 1981). It is widely used in research in aging populations (see, e.g., Beekman et al., 2000;

Cole et al., 2006; Farrell & Ganzini, 1995; Koenig et al., 1998).

DIS total number of depressive symptoms at baseline

In addition to diagnostic results, the DIS also provided a total symptom count across diagnoses. It should be noted that for each DSM-IV symptom there were several items that assessed each symptom criteria (Cronbach's $\alpha = 89$).

DIS suicidal thoughts and behaviors scale

We created a separate scale from the DIS to record the number of current suicidal thoughts and behaviors based on the following four items coded (No '0' or Yes '1'): thinking a lot about death, thinking I would like to die, thinking about committing suicide, and have attempted suicide (Cronbach's $\alpha = 0.94$).

Social support

At baseline, social support was measured as a continuous variable on a 10-item scale, with higher levels indicating greater social support (Cronbach's $\alpha = 0.83$). This scale has been well validated and used extensively in epidemiological studies of older adults (Blazer & Hughes, 1991; Landerman, George, Campbell, & Blazer, 1989).

Severity of depression

A geriatric psychiatrist used the MADRS to assess severity of depression at baseline (Baudic et al., 2004; Parker et al., 2003). All 10 MADRS items had good inter-rater reliability (Williams & Kobak, 2008). Williams and Kobak (2008) report the intraclass correlation (ICC) for raters using the Structured Interview Guide for the MADRS as $ICC = 0.93$, $p < 0.0001$. The MADRS had good internal reliability (baseline Cronbach's $\alpha = 0.83$). MADRS assessments were then obtained every three months over the next four years.

Cognitive functioning

The MMSE (M. Folstein, S. Folstein, & McHugh, 1975) assesses cognitive functioning in five areas (orientation, registration, attention and calculation, recall, and language) and provides an objective measure of global cognitive functioning. Scores range from 0 to 30. The MMSE has been used extensively in epidemiologic research of older adults. At baseline, reliability was acceptable (Cronbach's $\alpha = 0.70$). MMSE scores were obtained every six months for four years. We should note that we did not measure the categorical diagnosis of mild CI or dementia. Rather, we observed the growth in errors on the MMSE over time.

Magnetic resonance imaging

The differences between the EOD and LOD groups at baseline and changes in volumes over time were examined for hippocampal volume, cerebrum gray matter without lesions, cerebrum white matter without lesions, gray matter lesions, and white matter lesions for both hemispheres. The methodology of MRI measurement has been reported previously (Chen, McQuoid, Payne, & Steffens, 2006; Steffens, Payne, et al., 2002; Taylor et al., 2007a). Tissue segmentation and brain volume measurements were performed using a modified version of MRX software created by GE Corporate Research and Development and originally modified by Brigham and women's hospital for image segmentation (Chen et al., 2006; Hajcak & Simons, 2002; Taylor et al., 2007b). The ICCs for lesion volumes were high: left cerebral gray matter lesions, 0.995; right cerebral gray matter lesions, 0.996; left cerebral white matter lesions, 0.988; and right cerebral white matter lesions, 0.994. The ICC for the total cerebrum volume was 0.998.

Data analytic plan

Demographics

First, we described the participants' demographics and the mean and standard deviation of relevant variables. We then compared the EOD and LOD groups on indices of depression severity, suicidal thoughts and behaviors, and social support.

Hierarchical linear growth curve modeling

Using baseline and follow-up measures (MADRS, MMSE, and MRI volumes), we constructed growth curve models that examined initial scores at baseline (intercept) and change over time (slope). Each model controlled for gender, age, and cerebrum volume at baseline. Hierarchical growth curve modeling is robust to missing data, which were rigorously examined for selective attrition. If we were to find from the attrition analysis that there were non-ignorable missing data, we planned to add dummy variables for having incomplete data and test for differences in participants who left the study compared to participants who did not on our effects of interest. This procedure would involve testing the interaction of participants who left with those who did not and type of depression (EOD vs. LOD) at intercept and over time. This is a recommended method of handling non-ignorable missing data in mixed model effects (Singer & Willett, 1993).

Attrition

To examine the potential effects of selective attrition, we analyzed the data using a discrete-time hazard model. This analysis fit a logistic regression whereby a dummy variable was created with '1' being given for the last time period the participant contributed data,

all prior time points being given a '0', and then all observations after that are censored (Singer & Willett, 2003). We found the depression assessments (MADRS), cognitive functioning assessments (MMSE), and the demographic variables were not related to attrition. We also examined the data at baseline for any baseline hazard probability patterns by group. There was a wide variance but no clear pattern. We tested a linear time attrition variable with group and a group by time interaction. The interaction was not significant, and model fit was reduced in comparison to the full discrete-time model. In sum, therefore, we can analyze the data for the MADRS and for the MMSE over time without concern for selective attrition.

Next, we considered the attrition related to the neuroimaging data. There was only one significant unique effect, which was found for increased left white matter lesions predicting attrition, $\beta(1,130) = -3.69$, $SE = 2.22$, $F = 4.6$, $p = 0.03$. Therefore, we added the dummy code for attrition to all growth curve models as described earlier. Finally, we conducted a regression analysis comparing participants who gave complete neuroimaging data compared with those who did not. No individual discrete-time point approached significance. Missing data did not predict if participants gave complete baseline neuroimaging data. This suggests the groups were not different in relation to attrition on any neurological variables at baseline. Thus, we did not need to interpret the individual effects (Cohen, Cohen, West, & Aiken, 2003).

Results

Demographics

We assessed 135 depressed older adults at baseline who had either EOD (48.1%, $n = 65$) or LOD (51.9%, $n = 70$). Consistent with higher rates of depression among women (Sachs-Ericsson & Ciarlo, 2000), only 31% were male. Participants were almost entirely Caucasian, non-Hispanic (87.4%) and had 13.5 ($SD = 3.1$) years of education. More than half (54.1%) were married at baseline. There were no gender differences in the composition of the EOD and LOD groups. The LOD group was significantly older ($M = 73.4$ years, $SD = 7.1$) than the EOD group ($M = 67.5$ years, $SD = 6.4$), $F(1,134) = 25.6$, $p < 0.001$.

Baseline differences

As predicted, the EOD participants reported more current symptoms of depression on the DIS ($M = 9.7$, $SD = 3.6$) than did the LOD group ($M = 8.3$, $SD = 3.4$), $F(1,133) = 5.19$, $p = 0.024$. Those with EOD endorsed more suicidal ideation and behavior compared to LOD ($M = 1.4$, $SD = 1.23$ vs. $M = 0.87$, $SD = 1.04$), $F(1,133) = 7.3$, $p < 0.01$. As predicted, the EOD participants reported having less social support

($M = 21.37$, $SD = 4.6$) than did the LOD participants ($M = 24.12$, $SD = 3.5$), $F(1,131) = 14.9$, $p < 0.001$.

Growth curve analyses

Table 1 summarizes each effect for each dependent variable of interest by early versus late onset, time, the interaction of depression group by time, the interactions of depression group by attrition, and the three-way interaction with time.

Depressive symptoms over time

MADRS scores were initially high at intake and followed a pattern of rapid decline. To fit this function we used a log transformation. There was a significant group by intercept interaction; LOD was associated with less severe initial score on the MADRS, $\beta(1,130) = -3.58$, $SE = 1.64$, $F = 4.75$, $p = 0.031$. Consistent with the findings on the DIS, MADRS ratings were higher at baseline for EOD compared to LOD, and the LOD advantage did not change over time, as the group by slope interaction was not significant, $\beta(1,03) = 0.34$, $SE = 0.76$, $F = 0.20$, $p = 0.65$. This suggests that LOD participants presented with less severe depressive symptoms and maintained that small advantage throughout the follow-up.

Cognitive functioning over time

The MMSE was assessed at baseline and every six months for four years. Controlling for age, education, and baseline cerebrum volume, there was no baseline difference related to EOD or LOD, $\beta(1,132) = -0.50$, $SE = 0.43$, $F = 1.34$, $p = 0.25$. Controlling for age, education and baseline cerebrum volume, analyses showed the LOD group experienced more cognitive decline throughout the four-year period than did the EOD group, $\beta(1,90) = -0.18$, $SE = 0.06$, $F = 9.24$, $p < 0.01$; the decline is illustrated in Figure 1. We repeated the growth curve analysis and this time controlled also for the four measurements of hippocampal volumes for both hemispheres. LOD still predicted greater decline in MMSE scores, $\beta(1,82) = -0.333$, $SE = 0.131$, $p = 0.011$. Thus, there appears to be a neurological mechanism in addition to hippocampal atrophy that contributes to these cognitive changes. However, we should note that we were unable to identify this mechanism in this study data.

MRI over time

In a series of growth curve analyses, we examined differences between EOD and LOD in relation to neurological differences at baseline and changes over time. All of these analyses controlled for age, education, and baseline cerebrum volume. The analyses and associated statistics are presented in Table 1.

Table 1. Growth curve analyses: Summary of effect of age of depression onset on intercept and slope and the interactions with attrition ($N=135$).

Variable	Group		Group \times Time		Group \times Attrition		Group \times Time \times Attrition	
	β	SE	β	SE	β	SE	β	SE
MADRS	-3.58*	1.64	0.34	0.76	-1.14	2.48	1.27	1.30
MMSE	-0.50	0.43	-0.18**	0.06	-0.43	0.63	>0.01	0.11
RNONLGM	-15.07*	7.11	0.26	0.89	8.68	10.65	0.14	2.15
LNONLGM	-12.49	6.71	0.35	0.92	9.94	10.10	-0.86	2.13
RWMLES	-0.13	1.05	0.04	0.08	-0.09	0.11	0.18	0.15
LWMLES	-0.28	0.90	>-0.01	0.11	1.21	1.34	0.25	0.19
RGMLLES	0.02	0.09	>0.01	>0.01	-0.13	0.15	>-0.01	0.01
LGMLLES	0.04	0.08	0.01	0.01	-0.13	0.12	>-0.01	0.01
RHIPPOC	0.02	0.09	-0.03*	0.01	-0.04	0.15	-0.01	0.03
LHIPPOC	0.05	0.10	-0.02	0.02	0.04	0.15	0.01	0.04
RNONLWM	9.62	7.66	-1.52	0.89	-10.61	11.49	3.66	2.08
LNONLWM	-7.09	8.08	-1.26	0.93	-10.62	12.11	4.71*	2.13

Notes: Group=early compared to LOD, MADRS=Montgomery Asberg Depression Rating Scale, MMSE=Mini-Mental State Examination, R (Right), L (left), NONLGM=gray matter excluding lesions, WMLES=white matter lesions, GMLES=gray matter lesions, HIPPOC=hippocampal volume, NONLWM=white matter excluding lesions, LNONLWM=white matter excluding lesions.

The first column 'Group' shows if, at baseline, the dependent variables differed between EOD and LOD participants. The second column 'Group \times time' reports the interaction of depression group (LOD vs. EOD) over time and indicates if one group changed more than the other group over time. The third column labeled 'Group \times attrition' shows if the effect of group differs based on if the participant left the study early. The final column labeled 'Group \times time \times attrition' shows if the interaction of group and time was different among participants who left the study early.

* $p < 0.05$, ** $p < 0.01$.

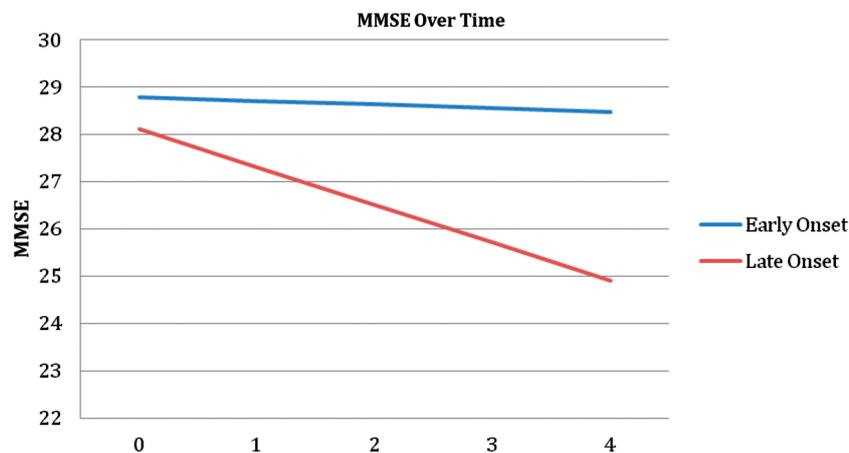


Figure 1. Interaction of early compared to late-onset depression on the MMSE over four years. Note: LOD lost cognitive functioning at a faster rate than did EOD.

Right cerebrum gray matter (excluding lesions) was initially smaller among participants with LOD, $\beta(1,127) = -10.29$, $SE = 4.77$, $F = 4.7$, $p = 0.033$. However, the growth in volume loss did not differ between the two groups.

There were no differences between the groups for left or right hippocampal volume at baseline. Inconsistent with the glucocorticoid cascade hypothesis, LOD lost hippocampal volume at a faster rate than did participants with EOD, $\beta(1,123) = -15.07$, $SE = 7.11$, $F = -3.98$, $p = 0.047$; the LOD group lost an extra 0.03 mL in hippocampal volume each year.

Finally, it does not appear that the effect of group (EOD vs. LOD) over time differed between participants who left the study early and those who stayed. There was, however, one three-way interaction involving left cerebrum white matter excluding lesions with time and attrition, $t(135) = 2.13$, $p = 0.035$. Because this is not moderating a significant effect of depression group (e.g., early vs. late), it does not alter the interpretation of the results.

Inconsistent with predictions, there were no significant differences in baseline white matter lesions or in growth of white matter lesions over time between the EOD and LOD groups (Table 1). As also reported in

Table 1, there were no other significant effects for the MRI data.

Discussion

There is a high comorbidity between depression and cognitive CI among older adults (Lopez et al., 2003; Zubenko et al., 2003). It is not clear if EOD is a risk factor for later cognitive decline (Sapolsky, 2000), if LOD is responsible for the association (Janssen et al., 2007), or if both EOD and LOD are risk factors for CI but perhaps operate through different mechanisms. According to one theory, neurological changes among older adults lead to cognitive deficits that may, in turn, produce depressive symptoms (Janssen et al., 2007). Based on this theory, we expected that LOD would be more strongly associated with CI and neurological dysfunction than would EOD, as depression in late adulthood may co-occur as part of, or in response to, prodromal neurological changes leading to CI.

In this study, the LOD group exhibited several deficiencies relative to the EOD group in relation to cognition and neurological markers. Notable over the four-year period, the LOD group showed more cognitive decline on the MMSE than did the EOD group. Our findings are supported by other researchers who have found that LOD participants score lower and exhibit more severe impairment in memory domains than do EOD participants (Dillon et al., 2009; Salloway et al., 1996; van Reekum et al., 1999). Importantly, a recent longitudinal study found EOD had no association with dementia and confirmed that LOD is associated with an early manifestation of dementia rather than increasing risk for dementia (Li et al., 2011). Our findings demonstrate that late-life depression is a marker for subsequent cognitive decline.

Moreover, even though the LOD group was found to have more hippocampal volume loss than EOD, growth curve analyses controlling for hippocampal volume changes over time still found LOD compared to EOD to predict a greater decrease in cognitive functioning. Thus, neural mechanisms in addition to hippocampal atrophy are affecting cognitive functioning in the LOD group. Further exploration of cognitive processes among individuals with late-life depression is necessary to better understand these mechanisms. For example, some have proposed a subtype of depression arising in later life that is characterized by a cerebrovascular disease that is associated with subcortical neurological dysfunction (Alexopoulos, 2006; Baldwin & O'Brien, 2002). However, we should note we were unable to identify the other neural mechanisms that may have contributed to the LOD group having a greater decrease in cognitive functioning. The decrease in cognitive functioning among the LOD participants is not inconsistent with the glucocorticoid hypothesis; nonetheless, in accordance with the hypothesis, one

would have expected the EOD participants who had more severe depressive symptoms over the lifetime to have shown more cognitive decline. This was not the case.

The LOD group also exhibited lower gray matter volume at baseline than did the EOD group, though there were no differences between the two groups in changes in volume over time. Although, to our knowledge, no investigators have compared gray matter volume in EOD and LOD individuals, researchers have found greater gray matter volume loss in multiple brain regions in older adults with mild AD than in older adults without AD (Baron et al., 2001; Thompson et al., 2003). This finding may represent the possibility that LOD has a greater negative influence on neurological changes in gray matter and should be investigated in subsequent studies.

One other area in which LOD participants showed greater neuroimaging changes than did EOD participants was the hippocampus. We found participants with LOD lost hippocampal volume at a faster rate than did participants with EOD. In a theory of how EOD may be related to CI, repeated depressive episodes over the individual's lifetime are posited to lead to damage to the hippocampus (a brain structure essential to memory) through a glucocorticoid cascade (Sapolsky, 2000). Thus, we had expected that hippocampal volume would be most affected for the EOD participants because their brain had a longer exposure to the neurological effects of depression on the hippocampus. Indeed, the EOD group was also found to have more severe depressive symptoms and a significantly higher number of lifetime episodes. Instead, the LOD group showed more neuroimaging changes on hippocampal volume than did the EOD group. Other cross-sectional studies have also shown that hippocampal volume reduction is more pronounced in LOD than EOD. One study (Ballmaier et al., 2008) found that even in the absence of differences in hippocampal volume between EOD and LOD groups, there are important group differences in brain morphology. Using three-dimensional mapping techniques, the authors found that hippocampal surface contractions were significantly correlated with memory measures in LOD participants, but not in EOD participants or comparison adults. Future research is necessary to explore the mechanisms by which depression, and specifically EOD and LOD, confer risk for hippocampal atrophy. EOD may still contribute to hippocampal atrophy. Pathological processes other than exposure to hypercortisolemia of depression may underlie hippocampal atrophy in depression of late life.

We did not observe differences between the EOD and LOD groups in other brain regions. Surprisingly, there was a lack of findings for white matter lesions, given that others have identified more white matter loss in LOD compared to EOD (Herrmann, Le Masurier, & Ebmeier, 2008). One possibility is

that recent episodes in older EOD participants may sometimes involve hyperintensities. That is, while an individual may have had an episode of depression early in life, the current depressive symptoms may be related to vascular events. Indeed, similar to this study, Lloyd et al. (2004) did not find any differences between LOD and EOD groups in white and gray hyperintensities. In another report using the same dataset, white matter lesions were not associated with later dementia when controlling for other factors (Steffens, MacFall, Payne, Welsh-Bohmer, & Krishnan, 2000).

We also predicted that EOD would be associated with more severe indices of depressive disorder, poorer social support, and more suicidal thoughts and behaviors than would LOD. As predicted, those with EOD had more depressive symptoms at baseline than those with LOD. This was found on both the DIS and on the MADRS. Moreover, the EOD group had more residual symptoms of depression over time. Other studies have found EOD to be associated with more depressive symptoms (Burvill, Hall, Stampfer, & Emmerson, 1989), with a longer index episode, and with higher rates of recurrent major depressive episodes (Klein et al., 1999). We also found that those with EOD had more suicidal thoughts and behaviors than did those with LOD. In the STAR*D study (Zisook et al., 2007) of depressed individuals 18–75 years of age, the authors observed a gradient, with earlier ages at onset associated with more suicidal thoughts and behaviors compared to those with later ages at onset. In a large epidemiological sample (Thompson, 2008), researchers found the earlier the age of first symptoms of major depressive episode, the higher the degree of suicidal intent. We also found that the EOD group reported poorer social support than did the LOD group. Other studies have also found that those with EOD have poorer social support than those with LOD. Overall, the results are consistent with the view that EOD is distinguished from LOD by more frequent association with persistent disturbances in behaviors and attitudes.

We should note a number of limitations of this study. First, the fact that the participants were almost entirely Caucasian, non-Hispanic, and highly educated may limit the generalizability of the results. It will be important for future research to examine differences between EOD and LOD in more heterogeneous samples. Second, a longer time period may be needed to observe volume changes in neurological structures. Additionally, we had considerable missing data over time, though analyses carefully showed attrition did not affect findings. Nonetheless, we may have lacked sufficient power to identify some effects. The use of the MMSE is a limited measure of cognitive functioning. More clear differences may have been identified with a more sensitive measure of cognitive functioning.

Finally, because of our focus on comparing EOD and LOD participants, we are unable to draw any conclusions regarding the effects of depression in

comparison to non-depressed healthy controls on variables examined in this study. Despite these limitations, however, we were able to identify a number of significant differences between EOD and LOD with respect to their associated features, CI, and neuroimaging changes. Finally, we should be cautious in making causal inferences from the results of this study. Although experimental investigations are nearly impossible in this type of research, it will be important for future research to try to elucidate causal factors in EOD and LOD on CI.

This study also has a number of notable strengths. First, we compared LOD participants to EOD participants and assessed their functioning over time. Second, we used a clear demarcation between EOD and LOD. By excluding participants who reported their first episode during middle age, the results of this study represent clear differences that emerged between participants with truly early or late depression. Further, we excluded participants from participating in this study if they had possible prodromal dementia or other psychological illness that would influence their neurological functioning. We also examined cognitive changes over time rather than the dichotomous diagnosis of dementia. This allowed us more power to detect the relative rate of cognitive decline between LOD and EOD. Finally, we used a comprehensive measure of current and past major depression based on DSM-IV criteria (APA, 1994) whereas some other studies have relied on the CES-D and brief interviews.

In conclusion, the primary goal of this study was to examine differences between geriatric participants with EOD and LOD at baseline and over a period of four years. Results indicated that at baseline, participants with EOD reported more depressive symptoms, suicidal thoughts and behaviors, and less social support than did participants with LOD. Longitudinal growth curve analyses revealed that participants with EOD had higher levels of residual symptoms over four years. The LOD group was characterized by greater decrement in cognitive scores over the four years than was the EOD group. Contrary to predictions, participants with EOD lost hippocampal volume at a slower rate than participants with LOD. Overall, right cerebrum gray matter was initially smaller among participants with LOD, but the groups did not differ in volume changes over time. Taken together, these results provide evidence that EOD is associated with more indices of depressive illness severity, whereas LOD is associated with more severe indices of cognitive and neurological dysfunction. These findings are relevant to understanding the established comorbidity between CI and depression.

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