

Mapping Callosal Morphology in Early- and Late-Onset Elderly Depression: An Index of Distinct Changes in Cortical Connectivity

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There is some evidence of corpus callosum abnormalities in elderly depression, but it is not known whether these deficits are region-specific or differ based on age at onset of depression. Twenty-four patients with early-onset depression (mean age = 68.00, SD ± 5.83), 22 patients with late-onset depression (mean age = 74.50, SD ± 8.09) and 34 elderly control subjects (mean age = 72.38; SD ± 6.93) were studied. Using 3D MRI data, novel mesh-based geometrical modeling methods were applied to compare the midsagittal thickness of the corpus callosum at high spatial resolution between groups. Neuropsychological correlates of midsagittal callosal area differences were additionally investigated in a subsample of subjects. Depressed patients exhibited significant callosal thinning in the genu and splenium compared to controls. Significant callosal thinning was restricted to the genu in early-onset patients, but patients with late-onset depression exhibited significant callosal thinning in both the genu and splenium relative to controls. The splenium of the corpus callosum was also significantly thinner in subjects with late- vs early-onset depression. Genu and splenium midsagittal areas significantly correlated with memory and attention functioning among late-onset depressed patients, but not early-onset depressed patients or controls. Circumscribed structural alterations in callosal morphology may distinguish late- from early-onset depression in the elderly. These findings suggest distinct abnormalities of cortical connectivity in late- and early-onset elderly depression with possible influence on the course of illness. Patients with a late onset of depression may be at higher risk of illness progression and eventually dementia conversion than early-onset depression, with potentially important implications for research and therapy.

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INTRODUCTION

Studies of elderly depressed patients have repeatedly suggested a potential involvement of the prefrontal cortex and temporal lobe structures, such as the hippocampus, in the disorder (for review see Alexopoulos *et al*, 2005; Steffens *et al*, 2006). In a subset of elderly depressed patients with major depression, the first episode occurs late in life (Alexopoulos *et al*, 1988). This subgroup, frequently referred to as having late-onset depression, exhibits certain unique clinical, biological, and neuroimaging characteristics (Burvill *et al*, 1989; Heun *et al*, 2000; Krishnan *et al*, 1995,

1997; Schweitzer *et al*, 2002), implying that late-onset depression may represent a distinct subtype of depression in the elderly. Along with observations of greater cognitive deficits (Salloway *et al*, 1996) and an increased risk of dementia conversion (Geda *et al*, 2006; Schweitzer *et al*, 2002), there is some evidence that patients with late-onset depression may have more pronounced atrophy in cortical and subcortical regions implicated in the pathophysiology of elderly depression (Almeida *et al*, 2002; Hickie *et al*, 2005; Steffens *et al*, 2000). Using traditional volumetric region of interest analyses and computational cortical mapping methods, we previously found complex structural changes in frontal and temporo-parietal brain regions, which may point to differential patterns of atrophic or neurodegenerative processes that may be influenced by age at illness onset (Ballmaier *et al*, 2004a, b, c).

The corpus callosum is the largest interhemispheric white matter commissure and is known to modulate interhemispheric

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communication and cognitive processes (Gazzaniga, 2000; Sanchez *et al*, 1998). Subregions of the corpus callosum topographically map various cortical areas that have been involved in elderly depression. Therefore, the corpus callosum appears to be an attractive candidate for exploring the neuroanatomical changes underlying the pathophysiology of depressed elders. Here we aimed to identify regional alterations of callosal morphology in elderly depression and to shed light on the hypothesis that early- and late-onset depression may present distinct structural characteristics.

Structural neuroimaging research on regional differences in callosal size are commonly based on the segmentation criteria suggested by Witelson (1989). These subdivision criteria have recently generated some controversy with respect to the assumed topography of callosal fibers (Hofer and Frahm, 2006). Indeed, this method arbitrarily divides the midsagittal corpus callosum into several regions according to maximal length and thus could be biased by local variability in callosal shape. To circumvent the risk of defining the callosal sections with implicit assumptions regarding sectors with consistent fiber distribution and to increase spatial resolution of callosal measurements, we characterized callosal abnormalities by applying anatomical mesh-based geometrical modeling methods, which compute 100 pointwise indicators of callosal thickness across the whole corpus callosum at midline (Luders *et al*, 2006a,b; Narr *et al*, 2000, 2002; Vidal *et al*, 2006). Importantly, these mapping methods detect and visualize the spatial patterns of callosal abnormalities using color-coded statistical maps, revealing any highly localized group differences in callosal thickness.

On the basis of our previous findings, we predicted callosal abnormalities in the genu and the splenium, both of which interconnect cortical regions previously implicated in elderly depression. Owing to the paucity of available data, we did not predict which regions of the corpus callosum would be affected based on age at illness onset. Finally, we examined the relationship between callosal areas and

neuropsychological measures of memory and attention in a subsample of subjects, given that these measures may be affected by interhemispheric communication as well as hemispheric competence.

MATERIALS AND METHODS

Subjects

Subjects were recruited through local newspapers and radio advertisements and through referrals from the geriatric psychiatry ambulatory care programs at the University of California, Los Angeles (UCLA) Medical Center. Tables 1 and 2 show the demographic characteristics of the sample. Forty-six elderly depressed patients 60 years or older with major depression who fulfilled DSM-IV criteria for major depression (and scored 15 or more on the Hamilton Rating Scale for Depression; Hamilton, 1967) were included in the study. The control group consisted of thirty-four similar-aged older people with no past history of depression or current depression. The cohort with depression was subdivided into those with early- and late-onset depression, using onset of the first major depressive episode after age 60 as cutoff (24 subjects with early-onset depression, 22 subjects with late-onset depression). Information on previous episodes and the age of onset was provided by patients and caregivers. Exclusion criteria for both patients and controls were (1) neurologic illness, including history or evidence of stroke, transient ischemic attack and clinical evidence of dementia or suspected dementia; (2) serious or unstable physical illness (eg insulin-dependent diabetes mellitus, uncontrolled heart failure, cancer); (3) illness or medication precluding cognitive testing; (4) alcohol abuse or dependence, and (5) metal in the body precluding magnetic resonance imaging (MRI). In addition, none of the patients had another major psychiatric illness or histories of long-term antidepressant treatment in the past. All patients were free of psychotropic medications for at least 2 weeks

Table 1 Demographic and Clinical Data of Participants with and without Depression with Overall Group Effect

	Comparison subjects N = 34	Subjects with depression N = 46	Analysis		
			t/F	df	P
Age	72.38 (± 6.93)	71.10 (± 7.66)	0.76	78	0.45
Mini-mental state examination score	29.48 (± 0.79)	28.68 (± 1.45)	2.86	75	0.01
Gender (female/male)	19/15	34/12	$\chi^2 = 2.84$	1	0.09
Age of onset, years	—	51.43 (± 22.89)	—	—	—
Hamilton depression score	—	17.73 (± 3.29)	—	—	—
CVRF score	11.19 (± 6.68)	11.00 (± 5.36)	0.14	73	0.89
Total brain volume	1286.93 (± 138.72)	1295.68 (± 129.61)	-0.29	78	0.77
Splenium	203.975 (± 35.22)	183.26 (± 35.90)	F = 8.48	1,75	0.005
Isthmus	65.365 (± 10.70)	60.980 (± 13.95)	F = 2.85	1,75	0.096
Posterior midbody	77.345 (± 11.60)	74.920 (± 11.79)	F = 0.42	1,75	0.519
Anterior midbody	84.145 (± 12.68)	81.200 (± 12.52)	F = 1.06	1,75	0.305
Anterior third	312.895 (± 54.05)	258.89 (± 52.40)	F = 21.02	1,75	<0.001

CVRF, cardiovascular risk factor.

All area measurements, expressed in mm², are shown after correcting for age, gender, and total brain volume. Total brain volumes are shown in cm³.

Table 2 Demographic and Clinical Data of Participants with and without Depression Dichotomized for Age of Depression Onset

	Comparison subjects N = 34	Subjects with depression		Control vs early onset		Control vs late onset		Early vs late onset	
		Early-onset N = 24	Late-onset N = 22	F	P	F	P	F	P
Age	72.38 (± 6.93)	68.00 (± 5.83)	74.50 (± 8.09)	F(1,56) 6.38	0.042	F(1,54) 1.09	0.301	F(1,44) 9.87	0.009
Mini-Mental State Examination score	29.48 (± 0.79)	28.72 (± 1.61)	28.64 (± 1.33)	F(1,53) 5.38	0.024	F(1,53) 5.53	0.004	F(1,42) 0.04	0.839
Gender (female/male)	19/15	20/4	14/8	χ^2 3.647	0.056	χ^2 0.089	0.766	χ^2 1.401	0.237
Age of onset, years	—	33.25 (± 16.05)	71.27 (± 7.23)	—	—	—	—	—	—
Previous episodes of depression	—	4.80 (± 4.13)	0.50 (± 0.90)	—	—	—	—	—	—
Hamilton depression score	—	17.33 (± 2.63)	18.13 (± 3.77)	—	—	—	—	F(1,44) 0.76	0.389
Total brain volume	1286.93 (± 138.72)	1273.98 (± 137.13)	1318.28 (± 119.91)	F(1,56) 0.11	0.746	F(1,54) 0.76	0.388	F(1,44) 1.29	0.262
CVRF score	11.19 (± 6.68)	9.36 (± 4.57)	12.64 (± 5.69)	F(1,51) 1.24	0.271	F(1,51) 0.68	0.414	F(1,42) 4.42	0.041
Splenium	203.975 (35.22)	199.16 (± 28.36)	165.91 (± 35.74)	F(1,53) 0.16	1.00	F(1,51) 15.06	<0.001	F(1,41) 8.73	0.015
Isthmus	65.365 (± 10.7)	64.845 (± 10.26)	56.765 (± 16.05)	F(1,53) 0.01	1.00	F(1,51) 5.60	0.065	F(1,41) 0.91	1.00
Posterior midbody	77.345 (± 11.60)	74.145 (± 9.7)	75.780 (± 13.92)	F(1,53) 0.06	1.00	F(1,51) 0.50	1.00	F(1,41) 0.98	0.985
Anterior midbody	84.145 (± 12.68)	81.320 (± 10.28)	81.065 (± 14.84)	F(1,53) 0.27	1.00	F(1,51) 1.03	0.948	F(1,41) 0.49	1.00
Anterior third	312.895 (± 54.05)	260.185 (± 42.42)	257.475 (± 62.53)	F(1,53) 8.65	0.015	F(1,51) 12.25	0.003	F(1,41) 1.05	0.934

CVRF, cardiovascular risk factor.

All area measurements, expressed in mm², are shown after correcting for age, gender and total brain volume. Total brain volumes are shown in cm³.

before imaging. A neuropsychiatric examination and the structured clinical diagnostic interview for normal subjects were administered to all control subjects to rule out current or past psychopathology. All subjects underwent Mini-Mental State Examination (Folstein *et al*, 1975). A subset of the larger study group completed a small neuropsychological test battery, including two tasks from the California Verbal Learning Test (CVLT) (Delis *et al*, 1987) to capture learning (CVLT trials 1–5) and recall (20 min CVLT delayed recall) and one task from the Stroop paradigm to assess sustained attention with a motor response (Stroop Part 1) (Stroop, 1935).

The study was performed in accordance with the policies of the UCLA Human Subjects Protection Committees, and all subjects gave written consent to participate. We have previously published cortical abnormalities in a smaller sample than reported here (Ballmaier *et al*, 2004a, b, c).

Magnetic Resonance Imaging

All subjects were studied with MRI performed on a 1.5-T Signa magnet (GE Medical Systems, Milwaukee) using a coronal T₁-weighted spoiled gradient/recall acquisition in the steady state (spoiled GRASS) with the following parameters: repetition time = 20 ms; echo time = 6 ms; flip angle = 45 degrees; 1.4 mm slice thickness without gaps; field of view = 22 cm; number of excitations = 1.5; matrix size = 256 × 192 mm; in-plane resolution = 0.86 × 0.86 mm.

Image Preprocessing

Image processing, callosal thickness, and callosal area measurements were performed as detailed previously (Luders *et al*, 2006a, b; Narr *et al*, 2000, 2002; Vidal *et al*, 2006). Each brain volume was corrected for radiofrequency field inhomogeneities (Sled and Pike, 1998) and placed into the standard coordinate system of the ICBM-305 average brain volume using a three-translation and three-rotation rigid-body transformation (Woods *et al*, 1998). This procedure corrects for differences in head alignment between subjects to assure that region of interest measurements are not influenced by different brain orientation. The corpus callosum was traced in midsagittal sections with the upper (top) and lower (bottom) callosal boundaries being delineated separately. To obtain the most accurate possible measure of midsagittal callosal area, the three most medial brain slices were included (1 mm slice thickness). For interrater reliability, two independent investigators contoured the corpus callosum in six different randomly selected brains, achieving intraclass correlation coefficients of $r = 0.97$. The callosal contours were traced by one rater blind to diagnosis.

Callosal Thickness and Area Measurements

Callosal thickness measurements were performed after correcting brains for head position and tilts but preserving original brain size. Callosal top and bottom sections were redigitized, converting them into 100 equidistant points along the midsagittal callosal curve per section. A medial line was then calculated as the average curve between the superior and inferior callosal boundaries in each subject,

followed by computing the pointwise distances from this medial line to the callosal top and bottom traces (Figure 1a). Subsequently, individual pointwise distance values, indexing callosal thickness, were compared across subjects at spatially homologous callosal surface points.

To obtain measures of corpus callosum morphology consistent with regional measurements more typically reported in the literature, the callosal renderings from each brain volume were reoriented to maximize callosal length and divided into five vertical partitions representing (1) the splenium, (2) isthmus, (3) the posterior midbody (4) the anterior midbody and, (5) the anterior third as visualized in Figure 1b (Witelson, 1989). Areas measures were computed in mm² for each callosal segment, as described previously (Narr *et al*, 2002; Vidal *et al*, 2006).

Statistical Analyses

Statistical analyses examined whether differences in callosal thickness and area measures were present in patients compared to healthy comparison subjects, and in patients based on age of illness onset. That is, using either midsagittal callosal area or regional thickness measures as dependent variables, we employed the general linear model to establish the presence of overall diagnostic group effects (controls *vs* all depressed patients), covarying for age, sex, and total brain volume. Significant overall group effects were followed up by examining differences between early-onset depression and controls, late-onset depression and controls, as well as between the two disease groups (early-*vs* late-onset depression). Age, gender, and total brain volume were again included as covariates. *Post hoc* Bonferroni corrections were used to control for potential

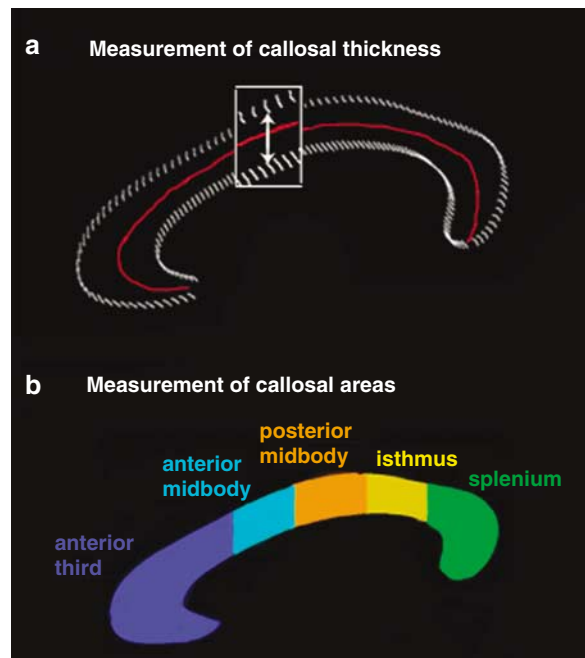


Figure 1 (a) The pointwise distances between the medial curve (in red) and the callosal top and bottom segments are superimposed as color-coded values on each subject's callosal surface model. (b) Subdivision of the corpus callosum in five areas according to the Witelson scheme.

inflated Type I error for analyses of midsagittal callosal areas. Since comparisons of callosal thickness were made at one hundred equidistant callosal surface points and adjacent data points may be correlated, a false discovery rate (FDR) of 0.05 was employed to control for multiple spatial comparisons (Benjamini and Hochberg, 1995; Storey, 2002). Significant group differences in callosal thickness, corrected using FDR, were coded in color and mapped on the callosal surface model.

To assess the relationship between callosal area measures obtained from the partitioning scheme, and neuropsychological scores, we utilized Spearman's rank correlational analyses examining only those callosal areas corresponding to regions for which thickness effects were observed. Spearman's correlations are not influenced by outliers in small samples and the diagnostic groups did not differ by age, education or gender, so bivariate analyses were appropriate. To control for potentially inflated Type I error by examining the relationship between three neuropsychological measures and the two callosal areas showing disease-related changes of callosal thickness, Bonferroni correction was applied and the new threshold of significance was set at $P < 0.01$.

RESULTS

Subjects

Depressed subjects and controls did not differ significantly on demographic variables (Table 1). Patients and controls differed significantly in their Mini Mental State Examination scores. When the depressed group was dichotomized by age at illness onset (Table 2), subjects with early-onset depression were significantly older than the control group. Significant age differences were also observed between the two disease groups. Mini-Mental State Examination scores differed significantly between each disease group and the controls. In addition, the late-onset group showed a significantly higher cardiovascular risk factor score than the early-onset group. There was no significant difference in total brain volume or sex distribution among all groups. The subsample did not show significant differences on CVLT and Stroop measures (CVLT trials 1–5: $F = 1.70$; $P = 0.20$; CVLT long delay: $F = 1.67$; $P = 0.20$; Stroop Part I: $F = 0.10$; $P = 0.90$). Mini-Mental State Examination scores differed significantly between each patient group (early-onset and late-onset depression) and controls in the subsample of study participants for which correlations of callosal area and neuropsychological variables were examined (MMSE, early-onset subgroup = $28.80 (\pm 1.66)$; late-onset subgroup = $28.77 (\pm 1.01)$; controls subgroup = $29.73 (\pm 0.59)$; $P \leq 0.05$).

Group Differences in Callosal Thickness

FDR-corrected statistical maps of group differences in callosal thickness are shown in Figure 2. Significant differences were observed between all patients and controls, with depressed subjects exhibiting thinner callosal regions concentrated in the anterior third and the posterior profile of the corpus callosum (corresponding to the genu and the splenium). When subjects with early-onset depression were

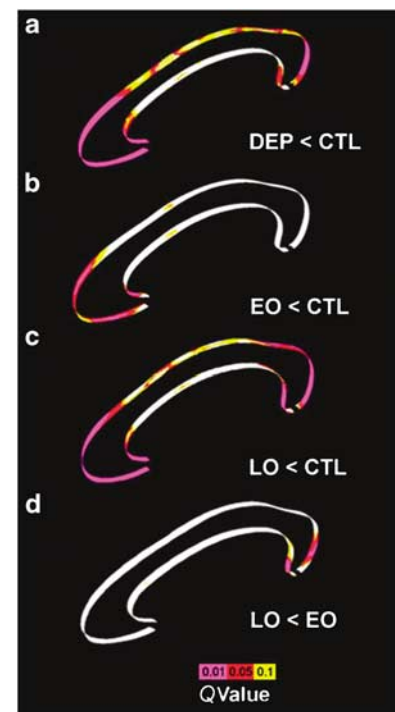


Figure 2 Corrected statistical maps (false discovery rate) showing group differences in callosal thickness between (a) all depressed patients and controls, (b) early-onset depressed patients and controls, (c) late-onset depressed patients and controls, and (d) early- and late-onset depressed patients. DEP = all depressed patients; EO = early-onset depression; LO = late-onset depression; CTL = controls. All statistical maps are corrected for age, gender and total brain volume. For all statistical maps, the color bar encodes the probability values for the observed effects.

compared with the healthy individuals, the regions in which the corpus callosum was thinner in depressed subjects became restricted to the anterior third, whereas comparison between late-onset depression and controls revealed prominent callosal thinning in the anterior third as well as the splenium. Significant group differences were also detected between the two disease groups, with reduced callosal thickness in the splenium in the late-onset depressed group compared to the early-onset depressed group.

Group Differences in Callosal Area Measurements

In traditional area analyses, patients overall had a significant reduction in the anterior third and the splenium when compared to controls (Table 1). Follow-up analyses are reported in Table 2. Early-onset depressed subjects exhibited significantly smaller areas in the anterior third compared to controls. Late-onset depressed patients showed significantly smaller areas in both the anterior third and the splenium than controls. Additionally, the area of the splenium was significantly smaller in late-onset depressed patients compared to the early-onset depressed group. None of the other comparisons resulted in statistically significant results.

Neuropsychological Testing

In the subsample for which neuropsychological measures were available, significant correlations emerged for the

late-onset depressed patients between the CVLT Trials 1–5 and area reduction in the genu ($r=0.75$, $P=0.003$) and splenium ($r=0.61$, $P=0.03$). Late-onset depressed patients also showed associations between attention/processing performance on the Stroop Part 1 and areas of the genu ($r=-0.54$, $P=0.05$) and splenium ($r=-0.74$, $P=0.004$). CVLT long delay was not related to callosal areas among late-onset patients. There were no significant interactions between cognitive performance and callosal areas for early-onset patients or controls. For late-onset patients, the significant correlations between CVLT Trials 1–5 and the genu area and between the Stroop Part 1 and splenium area survived Bonferroni correction.

DISCUSSION

To our knowledge, this is the first study to investigate callosal abnormalities in elderly depression and relate them to age at illness onset. We applied novel computational mesh-based methods to calculate and compare callosal thickness between groups at high spatial resolution. In addition, we also used traditional morphometric methods. Four key findings emerged from our study: (1) significant reduction of callosal thickness mostly pronounced in both the genu and the splenium when the depressed cohort was combined and compared to healthy subjects; (2) significant callosal thinning confined to the genu in early-onset depression compared to controls; (3) prominent decreases of callosal thickness in the genu as well as the splenium when late-onset depressed patients and controls were compared, and (4) significant regional reduction in the area of the splenium in the late-onset depressed group relative to the early-onset depressed group. Computational mapping of highly localized reductions in callosal thickness were confirmed by more traditional area measure analyses based on the Witelson partitioning boundaries.

Previous investigations of callosal morphology in depressed populations have almost exclusively relied on younger adults, with negative results (Brambilla *et al*, 2004; Husain *et al*, 1991; Parashos *et al*, 1998) and positive results (Lacerda *et al*, 2005; Lyoo *et al*, 2002; Wu *et al*, 1993). Some studies found callosal atrophy in patients with secondary (organic) causes of depression, such as multiple sclerosis (Schilling *et al*, 2006) and tumors (Nasrallah and McChesney, 1981; Tanaghow *et al*, 1989). In the context of elderly depression, the present findings of anterior and posterior callosal abnormalities in patients *vs* controls may be consistent with one previous study using magnetization transfer imaging, which reported significantly lower magnetization ratios in the genu and splenium of the corpus callosum (Kumar *et al*, 2004). On the other hand, two diffusion tensor imaging studies have not found evidence of callosal abnormalities (Bae *et al*, 2006; Nobuhara *et al*, 2006) in depressed elders. In addition, one report employing Witelson's segmentation criteria of corpus callosum areas obtained from midsagittal MRI section in a mixed elderly population did not detect an association between callosal atrophy and mood disturbances (Ryberg *et al*, 2007). The lack of consistency in findings may reflect methodologic differences in imaging and sample characteristics, or effects

may be relatively subtle and difficult to detect in small samples.

Indirect support for our results is however provided by the considerable literature linking prefrontal abnormalities and changes in temporal lobe structures to elderly depression (for review see Alexopoulos *et al*, 2005). Monkey and human studies indicate that prefrontal, premotor and motor fibers cross through the anterior part of the corpus callosum, whereas temporal, parietal, and occipital fibers cross through the caudal part (de Lacoste *et al*, 1985; Pandya and Rosene, 1985; Pandya and Seltzer, 1986).

In view of these connectivity patterns, the present finding of callosal thinning restricted to the genu in early-onset depression relative to controls may possibly indicate abnormal connections with prefrontal areas, in line with our own previous findings of frontal gray matter abnormalities in patients with an early onset of illness (Ballmaier *et al*, 2004a, b).

In contrast, reduced callosal thickness in both the genu and splenium in late-onset depression compared to controls may reflect a more widespread compromise in cortico-cortical connectivity. Thinning of the callosal genu may also relate to decreased connectivity in prefrontal areas. Indeed, frontal lobe atrophy has been reported in late-onset depression (Almeida *et al*, 2002; Kumar *et al*, 1998). In addition, an attenuation of the 'normal' volumetric asymmetry in the frontal lobes was found in late-onset depressed subjects compared to healthy controls (Kumar *et al*, 2000).

Moreover, genu as well as splenium thinning may corroborate results from our previous work (Ballmaier *et al*, 2004c), showing widespread decreases in temporal and parietal gray matter in late-onset depression compared to controls, with prominent decreases in sensorimotor regions. Deficits were more pronounced in the right than in the left hemisphere (Ballmaier *et al*, 2004c), implying a possible involvement of abnormalities in inter-hemispheric information transfer in late-onset depression (Kumar *et al*, 2000).

Perhaps of most interest, however, is our finding of differences in callosal morphology between the two disease groups. Several distinctions between these groups have been identified, and subjects with early-onset depression are more likely to have a family history of psychiatric illness (Brodaty *et al*, 2001), while subjects with late-onset depression have greater subcortical ischemic disease (Krishnan *et al*, 1988; Salloway *et al*, 1996; Taylor *et al*, 2004). In addition, late-onset depression has been associated with more pronounced temporal lobe atrophy (Greenwald *et al*, 1997; Kumar *et al*, 1998) and hippocampal volume reductions (Steffens *et al*, 2000; Hickie *et al*, 2005), with specific genotypes possibly mediating this effect (Taylor *et al*, 2005). If these previous investigations are interpreted to be signs of different causes or risk factors for depression based on age at onset, greater splenium thinning in late- than early-onset depression might indeed point to more prominent atrophic or neurodegenerative processes in temporal connections, possibly reflecting higher risk for cognitive impairment and dementia conversion in the future (Geda *et al*, 2006; Salloway *et al*, 1996; Schweitzer *et al*, 2002; van Ojen *et al*, 1995). Indeed, regionally specific posterior callosal atrophy has been reported in mild

Alzheimer's disease (Lyoo *et al*, 1997; Wang *et al*, 2006; Yamauchi *et al*, 2000).

Preliminary data in our subsample indicate a significant relationship between genu volumes and learning scores of the CVLT, and a significant correlation between splenium volumes and attention/motor scores of the Stroop Part 1 in late-, but not early-onset depression or controls. Since neuropsychological measures were in the normal range, these associations may reflect an early indicator of cognitive impairment becoming clinically evident only with further illness progression. On the other hand, callosal abnormalities did not correlate with scores of the CVLT long delay, mostly linked with early Alzheimer's disease (Wang *et al*, 2006). This might argue against the hypothesis that patients with late-onset depression are at increased risk of developing dementia. Such an interpretation, however, requires great caution, because some evidence suggests that callosal changes occur very early in the dementing process before detection with neuropsychological assessments is possible (Wang *et al*, 2006). In addition, interpretations are overall limited by the small size of the subsample for which neuropsychological measures were available.

Other limitations of this study should be noted. The study groups were relatively small, and although corrections for multiple comparisons were performed, negative results must be interpreted with caution. Notwithstanding, since this is, to our knowledge, the first study to identify region-specific callosal abnormalities in elderly depression, replication with a large homogeneous group of subjects may serve to confirm our present findings. However, it should be kept in mind that midsagittal areas of the corpus callosum do not necessarily reflect abnormalities of the whole structure and true loss of connectivity. In addition, other factors, such as ischemic damage and medication effects may have confounded our results and would need to be carefully considered in future studies. Our patient and control groups were not optimally matched for gender, which is an important variable affecting callosal size (Luders *et al*, 2006b; Narr *et al*, 2002). At the same time, all our analyses included age, gender, and total brain volume as covariates, thereby reducing the risk of possible confounding effects. Further studies may be needed to investigate the specific contribution of gender to callosal abnormalities in early- and late-onset depression.

In conclusion, this study reports differentially localized patterns of callosal thinning between early- and late-onset elderly depression. In addition, a tentative association between genu and splenium thinning and learning, and attentional/motor functioning was found in late-onset depression, but not in early-onset depression or controls. Further longitudinal research will be needed to clarify callosal abnormalities in relation to altered cortical disconnections in both disease groups, and how the associations between local callosal abnormalities and neuropsychological functioning may predict later cognitive decline.

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DISCLOSURE/CONFLICT OF INTEREST

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