Article

Localizing Gray Matter Deficits in Late-Onset Depression Using Computational Cortical Pattern Matching Methods

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Objective: The authors used magnetic resonance imaging and an image analysis technique known as cortical pattern matching to map cortical gray matter deficits in elderly depressed patients with an illness onset after age 60 (late-onset depression).

Method: Seventeen patients with late-onset depression (11 women and six men; mean age=75.24, SD=8.52) and 17 group-matched comparison subjects (11 women and six men; mean age=73.88, SD=7.61) were included. Detailed spatial analyses of gray matter were conducted across the entire cortex by measuring local proportions of gray matter at thousands of homologous cortical surface locations in each subject, and these patterns were matched across subjects by using elastic transformations to align sulcal topography. To visualize regional changes, statistical differences were mapped at each cortical surface location in three dimensions.

Results: The late-onset depression group exhibited significant gray matter deficits in the right lateral temporal cortex and the right parietal cortex, where decreases were most pronounced in sensorimotor regions. The statistical maps also showed gray matter deficits in the same regions of the left hemisphere that approached significance after permutation testing. No significant group differences were detected in frontal cortices or any other anatomical region.

Conclusions: Regionally specific decreases of gray matter occur in late-onset depression, supporting the hypothesis that this subset of elderly patients with major depression presents with certain unique neuroanatomical abnormalities that may differ from patients with an earlier onset of illness.

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A growing body of evidence from structural neuroimaging research suggests that cortical abnormalities are associated with elderly depression, mainly involving the prefrontal cortex (1–10) and temporal lobe structures such as the hippocampus (11–15).

In a subset of elderly patients with major depression, the first episode occurs late in life (16). This subgroup, frequently referred to as having late-onset depression, exhibits certain unique clinical, biological, and neuroimaging characteristics (17–22). More specifically, late-onset depression patients are less likely to have psychiatric comorbidity (23) or a family history of depression (20, 24) when compared with early-onset depression groups. On the other hand, late-onset depression patients are more likely to have associated medical comorbidity (23, 25–28), greater cognitive deficits (29), and increased risk of developing dementia (22). They also more frequently experience a loss of interest and apathy (19, 21).

Findings from structural magnetic resonance imaging (MRI) studies implicate frontal lobe atrophy among patients with late-onset major and minor depression (2, 3). There is also some evidence that patients with late-onset depression may have more pronounced atrophy patterns than subjects with depressive episodes that started early in life. Greater ventricular size (30) and smaller frontal lobe volumes (7) have been reported in late-onset depression when directly compared with elderly patients with early-onset depression. However, a previous report by our group could not detect a significant linear relationship between age at onset of the first episode and neuroanatomical abnormalities (31). One study has shown that among elderly depressed patients, those with older age at onset had smaller hippocampal volume (14).

In addition, high-intensity lesions in subcortical white matter are more common in late-onset depression than in elderly depressed patients with an earlier onset of illness (32–37). Taken together, these observations suggest that late-onset depression may represent a distinct subtype of depression in the elderly (17, 27, 38).

Previous structural neuroimaging studies that focused on late-onset depression have employed traditional volumetric analyses where regional boundaries must be identified. While these studies have provided some evidence for regional specificity of volume loss in late-onset depression, the question of spatial localization of gray matter deficits over the entire cortical surface in late-onset depression has not been addressed in the literature. Such information could provide more comprehensive insights into the neuroanatomical contributions to late-onset depression.

TABLE 1. Clinical and Neuroimaging Characteristics of Elderly Patients With Late-Onset Depression and a Matched Group of Nondepressed Comparison Subjects

	Depressed Patients (N=17)		Comparison Subjects (N=17)		Analysis	
Item	Mean	SD	Mean	SD	t (df=32)	p
Age (years)	75.24	8.52	73.88	7.61	0.41	0.62
Mini-Mental State Examination score	28.53	1.33	29.59	0.71	0.34	0.74
Age at onset of depression (years)	71.88	7.61				
Previous episodes of major depression	0.35	0.99				
Hamilton Depression Rating Scale score	18.41	4.26				
Brain volume (cm^3)						
Total	1311.76	130.14	1273.71	113.69	0.78	0.43
Gray matter	599.58	48.04	587.27	61.93	0.49	0.57
White matter	458.39	69.05	445.49	55.85	0.44	0.55
CSF	253.78	64.52	240.94	63.50	0.47	0.57

The goal of the present study was to use cortical pattern matching methods in order to perform detailed spatial analyses of gray matter abnormalities on lateral and interhemispheric brain surfaces in subjects with late-onset depression relative to group-matched comparison subjects. These brain mapping methods allow data from each individual to be analyzed with a series of manual and automated procedures that carefully match cortical anatomy across subjects and measure local proportions of gray matter at each of 65,536 anatomically matched points on the cortical surface of each cerebral hemisphere. An advantage of this technique is that subtle as well as spatially diffuse differences in regional gray matter can be identified over the entire cortical surface by closely matching structurally homologous brain regions across subjects. This is made possible through definition of cortical sulcal landmarks on the brain surface of each individual.

We used a similar methodological approach in a previous study of depressed elderly patients with an early onset of illness, which revealed significant brain size reduction in orbitofrontal cortices along with significant gray matter increases adjacent to areas of focal decreases of gray matter in the same anatomical region (9). Results from this previous study also showed significant gray matter increases in parietal cortices as well as the left temporal cortex.

We set out to examine whether regionally specific patterns of gray matter abnormalities are present in late-onset depression patients relative to nondepressed subjects of comparable age and gender, after carefully matching gyral anatomy across subjects. On the basis of the existing literature suggesting that late-onset depression is more likely to be associated with cortical atrophy, and considering our previous findings, we expected that late-onset depression would exhibit gray matter deficit patterns in frontal, temporal, and parietal cortices.

Method

Subjects

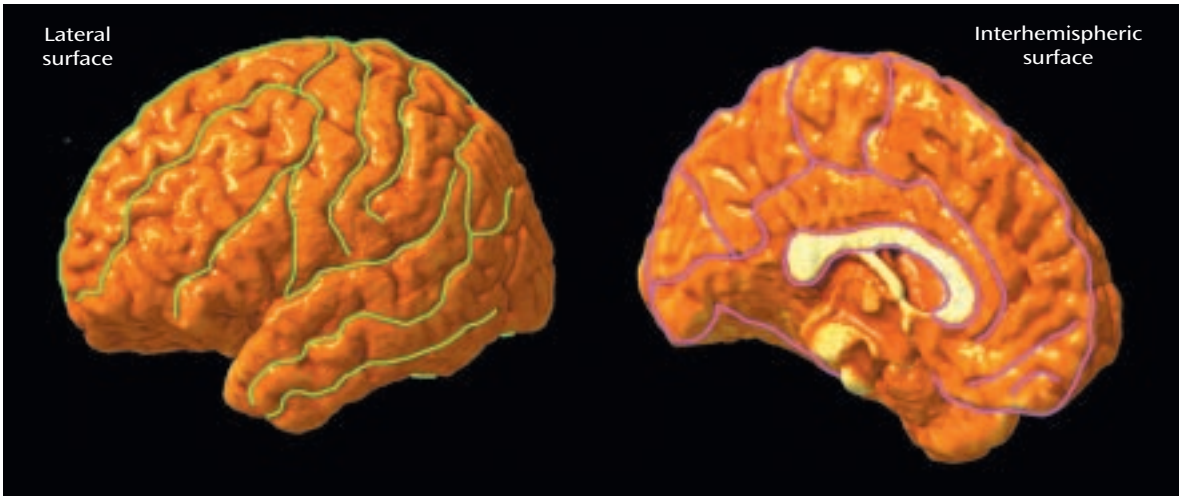
Our study group consisted of 17 patients with major depression (11 women and six men; mean age=75.24, SD=8.52) and 17 nondepressed comparison subjects (11 women and six men; mean age=73.88, SD=7.61) (Table 1). All patients were assessed with the Structured Clinical Interview for DSM-IV (SCID) and met DSM-IV criteria for major depressive disorder. Late-onset depression was defined as onset of the first major depressive episode after age 60. All depressed subjects scored 15 or greater (mean score=18.41, SD=4.26) on the 17-item Hamilton Depression Rating Scale (39). The mean age at onset of depression was 71.88 (SD=7.61). Information on prior depressive episodes and age at onset was obtained from patients and caregivers and corroborated, whenever necessary, with information from the spouse or a close relative. All patients were free of psychotropic medications for at least 2 weeks before imaging. None of the patients had histories of long-term antidepressant treatment or other prolonged psychotropic medications. Patients underwent a thorough medical examination and laboratory testing. Exclusion criteria were 1) another major psychiatric illness, such as bipolar disorder, schizophrenia, or schizoaffective disorder; 2) active alcohol or drug dependence; 3) primary neurologic illness, such as dementia, stroke, Parkinson's disease, seizure disorder, or multiple sclerosis; 4) presence of a medical illness or medication use that could affect cognitive function; 5) physical disability that precluded cognitive testing; and 6) metal in the body that precluded MRI scanning. A psychiatric examination and a structured interview (SCID) for normal subjects were administered to all comparison subjects to rule out current or past psychopathology. Exclusionary conditions for comparison subjects were clinical evidence of dementia, suspected dementia, or any other brain disorder determined from history or mental status examination. None of the patients and comparison subjects had axis II disorders. All subjects had Mini-Mental State Examination (40) scores ≥24 (depressed patients: mean=28.53, SD=1.33; comparison group: mean=29.59, SD=0.71). Several of the depressed patients and comparison subjects had stable comorbid medical disorders such as hypertension, ischemic heart disease, or arthritis.

Patients were recruited through community outreach efforts that included local newspaper and radio advertisements and through referrals from the geriatric psychiatry ambulatory care programs at the UCLA Medical Center. Comparison subjects were recruited from the community through newspaper and radio advertisements. The study was performed in accordance with the policies of the UCLA Human Subject Protection Committees, and written informed consent was obtained from all subjects after the procedures had been fully explained.

Imaging

Subjects were scanned with a 1.5-T Signa magnet (GE Medical Systems, Milwaukee). The imaging protocol was a whole-brain, gradient-echo (spoiled gradient recall acquisition) T_1-weighted series acquired coronally with section thickness of 1.4 mm, no gaps (repetition time=20 msec; echo time=6 msec; flip angle=45°; field of view=22 cm; number of excitations=1.5; matrix size=

FIGURE 1. Sulcal and Gyral Landmarks Traced on the Lateral and Interhemispheric Surfaces of Cortical Surface Models From Elderly Patients With Late-Onset Depression (N=17) and a Matched Group of Nondepressed Comparison Subjects (N=17)



256×192 mm; in-plane resolution=0.86×0.86 mm). Quantification of white matter lesions was not assessed in this study.

Image Processing

We have described the methods for image analysis in detail elsewhere (9, 41, 42), and will briefly summarize them here.

1. We performed automatic whole brain extraction and interhemispheric brain extraction with removal of nonbrain tissue (43). Each brain slice was also manually edited such that only brain tissue and CSF remained in each image volume. Reliability of manual scalp editing was determined by calculating the intraclass correlation coefficients for brain volumes from 10 test brains that were randomly mixed in among a larger data set (42). Intra- and interrater reliability achieved in our laboratory were both >0.99.
2. Each scan was corrected for signal intensity inhomogeneities. A radiofrequency bias field correction algorithm eliminated intensity drifts attributable to scanner field inhomogeneity, using a histogram spline sharpening method (44).
3. Fully automated tissue classification used a partial volume correction method (45) to automatically classify voxels as most representative of gray matter, white matter, and CSF.
4. Brain volumes were transformed into standard International Consortium for Brain Mapping-305 space using a 12-parameter linear, automated image registration algorithm (46).
5. The cortical surface for each MR volume was extracted by using automated software (47, 48).
6. As seen in Figure 1, we traced 17 sulcal and gyral landmarks on the lateral surface and 12 sulci and gyral landmarks on the interhemispheric surface of each hemisphere employing previously validated anatomic delineation protocols (41, 42, 49). In addition to contouring the major sulci, a set of six midline landmark curves bordering the longitudinal fissure were outlined on each hemisphere. Interrater variability of manual outlining was measured as the three-dimensional root mean square difference in millimeters between 100 equidistant points from each sulcal landmark traced in six test brains (H.D.) relative to a gold standard arrived at by a consensus of raters as previously reported (42, 49) (http://www.loni.ucla.edu/~esowell/new_sulcvar.html). Intrarater reliability was computed by comparing the three-dimensional root mean square distance between equidistant surface points from sulcal landmarks from one test brain traced six times by the same rater (H.D.). Three-dimensional root mean square disparities were <2 mm, and on average <1 mm, between points for all landmarks within and between raters.
7. Cortical pattern matching used the sulcal/gyral landmarks and the cortical surface models from each subject to compute a three-dimensional vector deformation field, which reconfigures each subject's anatomy into the average pattern of a given group by matching equivalent landmark points in x, y, and z coordinates (41, 50, 51).
8. Gray matter proportion measurements used the three-dimensional deformation vector fields obtained from the cortical pattern matching methods to allow a local measurement of gray matter to be made at equivalent three-dimensional cortical surface locations in each subject, referencing corresponding point locations in spatially registered tissue classified scalp-edited brain volumes. Cortical gray matter was quantified by measuring the proportion (or density) of voxels segmenting as gray matter within a sphere with a fixed radius of 15 mm at homologous cortical surface points in each individual. Therefore, at each point on the cortical surface, a local measurement of gray matter is made that may be averaged and compared statistically to provide maps indexing very local differences in tissue proportion within and between groups (9, 41, 42, 49).

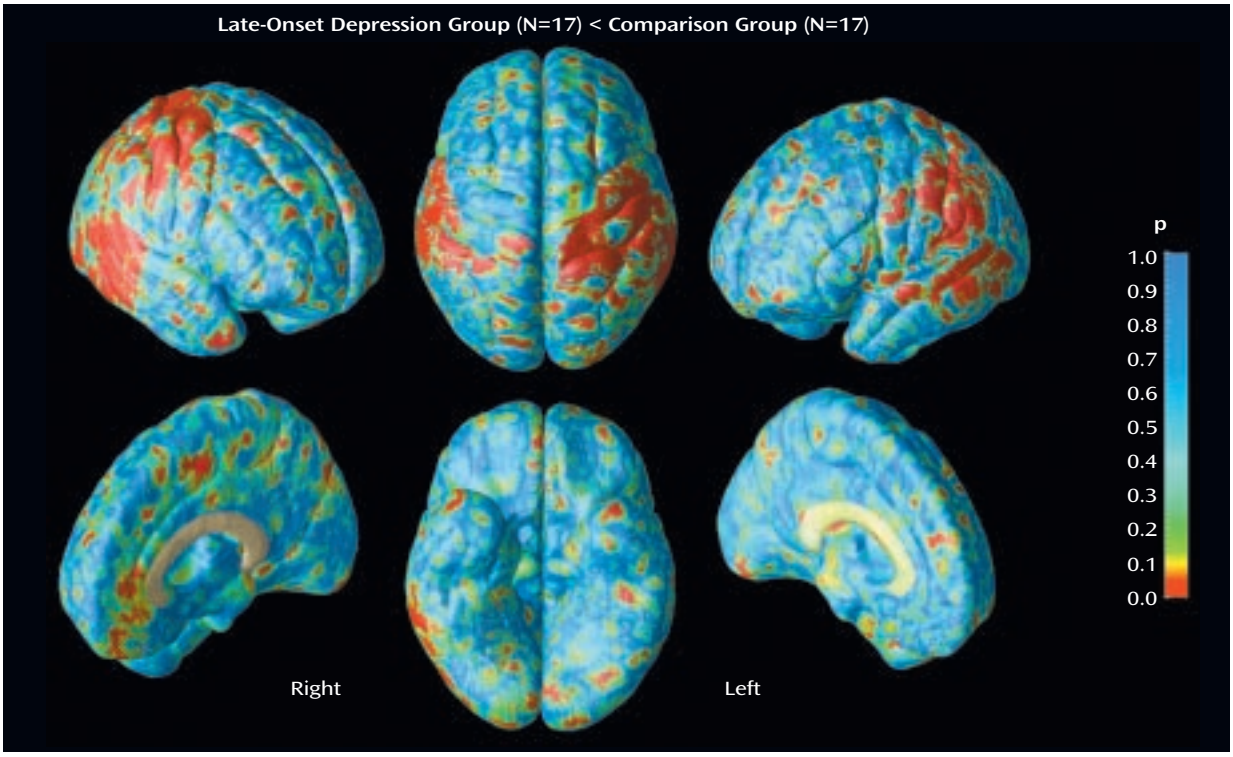
Although patients and comparison subjects were group-matched for age and gender, all gray matter proportion analyses were performed in International Consortium for Brain Mapping-305 space to account for interindividual differences in overall brain size that might be related to demographic variables.

Statistical Analyses

For statistical comparisons, Student's t tests were conducted at each cortical surface location in three dimensions (65,536 surface points) providing spatially detailed maps of gray matter proportion differences between diagnostic groups. In all statistical maps, a surface point significance threshold of $p<0.05$ (two-tailed) was used to visualize the regional specificity of gray matter changes in the cortex.

To correct for multiple comparisons (i.e., statistical tests at each of 65,536 surface points), subjects were randomly assigned to groups of 10,000 new randomized analyses (at each surface point), and the number of significant results (i.e., gray matter pro-

FIGURE 2. Gray Matter Differences Between Elderly Patients With Late-Onset Depression (N=17) and a Matched Group of Nondepressed Comparison Subjects (N=17)[a]



[a] Right-side lateral and interhemispheric, top and bottom, and left-side lateral and interhemispheric views are shown. Regions illustrated in red correspond to significant deficits in the patient group at a threshold of p<0.05 (two-tailed).

TABLE 2. Regional Gray Matter Deficits in Elderly Patients With Late-Onset Depression (N=17) Relative to a Matched Group of Nondepressed Comparison Subjects (N=17) After Correction for Multiple Comparisons[a]

	Analysis of Gray Matter Difference (p)	
Region of Interest	Left	Right
Frontal lobe	0.62	0.73
Temporal lobe	0.07	0.02
Parietal lobe	0.08	0.01
Occipital lobe	0.57	0.64

[a] Permutation analyses were performed in which subjects were randomly assigned to groups of 10,000 new randomized analyses. The p values represent the proportion of randomized group assignments (out of 10,000) in which the number of significant surface points exceeded the number of significant surface points observed in the real group difference test (significance threshold: p<0.05).

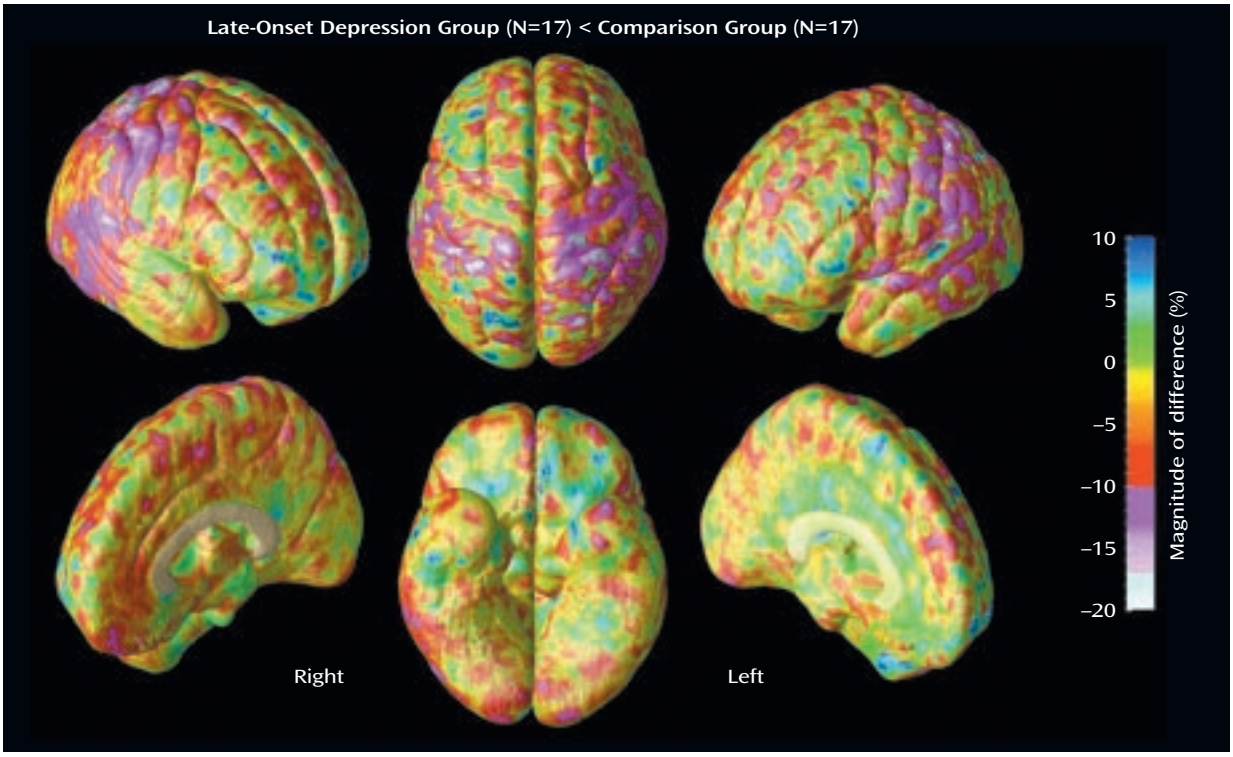
portion at any surface point that significantly differed between groups at the threshold of p<0.05) that occurred in the real group difference test was compared with the null distribution of significant results that occurred by chance in the permutation analyses. In other words, the threshold for assessing significance of statistical maps based on permutation tests was determined objectively by calculating the surface area (number of surface points) of significant effects in the real group difference test. That surface area within any tested region of interest was used as the threshold for comparison with the random tests for that region of interest, and if <5% (i.e., p<0.05) of the results from random tests reached or exceeded the surface area of the real test, the statistical map (within regions of interest) was considered significant (9, 41, 49). The regions of interest used in the permutation analyses were chosen to test our a priori hypothesis that significant group differences would be observed in frontal, temporal, and parietal cortices. Gross frontal lobe, parietal lobe, temporal lobe, and occipital lobe regions of interest were therefore created for each individual from a probabilistic atlas (52).

Finally, t tests were used to examine differences between groups for total gray matter, white matter, and CSF volumes as well as total brain volumes.

Results

Statistical maps show significant differences in gray matter proportions (in International Consortium for Brain Mapping-305 space) at each point on the cortex between diagnostic groups (Figure 2). Probability values from the t tests, indexed in color, are mapped onto the group-averaged cortical surface model at each three-dimensional location. The areas in red reflect significant negative effects (gray matter proportion decreases) at a threshold of p<0.05 (two-tailed). Of note, the p maps reflect two-tailed probability values of signed t values representing negative effects only, since no significant gray matter increases were observed in late-onset depression throughout the cortical surface. The magnitude of differences in gray matter is also shown in percentage (Figure 3), again according to a color scale. In general, a difference greater than approximately –10% corresponded with significant negative effects of depression on gray matter exceeding the threshold of p<0.05.

FIGURE 3. Magnitude of Gray Matter Differences Between Elderly Patients With Late-Onset Depression (N=17) and a Matched Group of Nondepressed Comparison Subjects (N=17)[a]



[a] Right-side lateral and interhemispheric, top and bottom, and left-side lateral and interhemispheric views are shown. Differences greater than approximately –10% correspond with the threshold significance level ($p<0.05$).

In late-onset depression subjects, regional gray matter deficits, mapped at each cortical surface point in three dimensions, appeared spatially diffuse in the right temporal cortex (posterior portions of the superior and inferior temporal gyrus) (Figure 2), where decreases exceeded –10% (Figure 3). Focal patterns of gray matter deficits also appeared in posterior aspects of the left lateral temporal cortex. Significant decreases in right temporal gray matter were confirmed by permutation analyses (Table 2).

Gray matter loss in late-onset depression was also observed in parietal cortices, mainly sensorimotor regions, with most prominent deficits again occurring in the right hemisphere (with 10%–20% loss) (Figure 2 and Figure 3). Permutation analyses (Table 2) showed that the regional patterns of gray matter loss were significant in the right parietal cortex.

No other main effects were detected in any other anatomical region, including the frontal cortex. No significant differences between late-onset depression and comparison subjects were observed for total gray matter, white matter, CSF volumes, or total brain volume (Table 1).

Discussion

Two main positive findings emerged from our study: 1) significant gray matter deficits, confirmed with permutation testing, in the right lateral temporal cortex, mainly the posterior portions of the superior and inferior temporal gyrus, and 2) prominent decreases of gray matter in the right parietal cortex, where deficits were most pronounced in sensorimotor regions, again confirmed with permutation tests. In the same regions, similar patterns of gray matter deficits also appeared in the left hemisphere that approached significance with permutation testing.

Several structural MRI studies have demonstrated hippocampal or temporal lobe abnormalities in late-life depression (11–14), whereas others did not observe significant differences (1, 3, 53). Of all these studies, two focused on patients with first onset of depression after the age of 60 (3, 13), with one showing significantly more left medial temporal atrophy than early-onset patients (13), and the other showing differences in total temporal lobe volume that approached significance between patients with late-onset minor or major depression and comparison subjects (3). Manual delineation of the entire temporal lobe is difficult because the orientation and anatomic boundaries can be unclear. This may at least in part explain why in our previous study decreases in total temporal volume only approached statistical significance and why most region of interest studies examined specific temporal subregions such as the hippocampus, which can be more easily identified. A study by Steffens et al. (14) suggested that hippocampal volume atrophy may be greater in late-onset

depression compared with early-onset depression. It is interesting that the anatomical regions within the temporal lobe where we saw the most pronounced gray matter deficits were the posterior aspects of the superior and inferior temporal gyrus, without any differences in ventral/medial areas. Although our study supports the hypothesis that temporal lobe atrophy is associated with late-onset depression, further studies are clearly warranted to examine which specific temporal subregions are most relevant in the context of late-onset depression.

In addition to our findings of gray matter decrease in lateral temporal regions, the present study is also the first to report gray matter deficits in parietal cortices, mainly sensorimotor regions, in late-onset depression. Lesions in the right temporal or parietal cortices have been shown to impair emotional experience and arousal (54–56) and to impair imagery for emotion (57–60). In addition, patients with tumors affecting temporoparietal cortices have reported pronounced negative mood states after surgery (61). There is evidence that both temporal and parietal cortices contribute to integrating viscerosensory information with affective signals (62, 63). Functional imaging studies in major depression have documented changes in regional cerebral flow or metabolism in the temporal cortex (64–66) as well as in the parietal cortex (67, 68). In geriatric depression, reduced superior temporal and anterior parietal activations have been reported (69).

Using cortical pattern matching methods, we also detected gray matter abnormalities in temporoparietal cortices in our previous report (9) that focused on elderly depressed patients with an early age at onset. However, widespread increases of gray matter instead of decreases were found in these regions. Furthermore, the distribution of gray matter changes in temporal lobe structures differed somehow from the pattern identified in late-onset depression, since gray matter increases were more pronounced in the left hemisphere and observed throughout the lateral surface, including the temporal poles, rather than being more right-lateralized and localized in more dorsal lateral aspects, as observed in late-onset depression.

Whereas gray matter increases may reflect abnormal neurodevelopmental processes, perhaps because of an excess of gray matter early in development that decreases over time yet remains above the normal threshold, the reduction of gray matter in late-onset depression is more likely to be associated with neurodegenerative events. It remains to be clarified whether the region-specific gray matter deficits observed here in late-onset depression are necessary for initiation of the illness or instead represent an epiphenomenon that perhaps appears with progressive accumulation of the number of stressors in later life (i.e., neuronal loss due to the aging process, concomitant medical illness, and grief).

Contrary to our predictions regarding frontal gray matter deficits in late-onset depression, no significant group differences were found throughout this anatomical region. Several previous MRI volumetric studies that implicated structural abnormalities of the frontal lobe, particularly the orbitofrontal cortex, in geriatric depression (1, 5, 8, 70) mainly included patients with long histories of depression, and it is not clear what proportion of their samples had late-onset depression. Of the three previous MRI studies focused on late-onset depression (defined as illness onset after age 60), all examined frontal lobe atrophy using traditional volumetric methods, although results remain mixed (3, 7, 31). Indeed, in an earlier report by our group (3), late-onset depression was associated with greater bilateral frontal atrophy relative to that of nondepressed comparison subjects. However, in a subsequent study (31) we reported that lobar structural abnormalities in the frontal regions did not change with an increasing age at onset of illness. Instead, Almeida et al. (7) found that patients with late-onset depression had significantly more right frontal atrophy than their early-onset counterparts of similar age, without observing significant differences between late-onset depression and nondepressed comparison subjects. However, our results are not fully comparable with previous region of interest studies in late-onset depression, given that these studies examined frontal lobe volumes as a whole and did not specifically address gray matter differences. It is therefore possible that subcortical abnormalities, such as white matter lesions, may have contributed to the evidence of atrophy in total frontal volume in previous reports. For example, one study showed that subcortical lesions may decrease orbitofrontal cortex volume in geriatric depression (70). Although white matter lesions were not specifically addressed in the present study, global white matter volumes did not differ between groups (Table 1). Future studies are needed to understand how subcortical lesions may be related to cortical gray matter changes. Indeed, based on the results of an earlier report (71), comorbid medical disorders may have only a modest impact on brain volume reductions. The differences in the results between our earlier region of interest study in late-onset depression (3) and the present report may additionally arise from differences in the demographic or clinical characteristics of the populations of depressed patients examined. While our earlier study included inpatients, the patients in the study reported here were exclusively outpatients and had an average of less than one prior major depressive episode.

Regarding frontal cortices, it is noteworthy that the results in late-onset depression differ from the pattern identified among elderly patients with early-onset depression in previous research that used computational cortical pattern matching (9). More specifically, the latter study showed a prominent regional size reduction in the orbitofrontal cortex, together with significant increases in cortical gray matter adjacent to focal decreases of gray matter in the same region. In late-onset depression, we expected to find gray matter loss rather than gray matter increase in frontal regions because this subtype of depression is

thought to be associated with greater cortical atrophy than early-onset groups (22).

Although the division between "early" and "late" onset is still considered somewhat arbitrary and not based on reliable clinical and biological data, it remains possible that the patients in the study reported here may not show discernible frontal gray matter deficits because such abnormalities could require more prolonged or intense exposure to potentially neurotoxic events. Whether and to what extent disease severity or longer total history of depression might contribute to frontal abnormalities is yet to be unraveled. On the other hand, there is evidence that the effects of hypercortisolemia in major depression exhibit regional specificity in cortical regions, with intensity of these effects differing according to anatomical site (72). Temporal and parietal cortices of late-onset depression may therefore be, for some reason, more sensitive to the potentially toxic effects of such insults.

There are now a number of studies supporting the view that late-onset depression patients are more likely to have associated cognitive impairment and are more likely to progress to dementia (22). None of our patients had a history of mental status examination results suggesting dementia, although it is possible that some of them will develop progressive cognitive impairment over time (73). Nevertheless, it is noteworthy that the gray matter changes observed here do not show the same patterns as the changes seen in patients with Alzheimer's disease. Indeed, previously published longitudinal Alzheimer's disease studies using cortical pattern matching or voxel-based morphometry demonstrated that gray matter loss appears in ventral/medial regions of the temporal cortex in the earliest stage of the illness (41, 74), whereas here no group differences were detected in these regions. Furthermore, sensorimotor regions are relatively spared in Alzheimer's disease (41, 51), whereas these are the regions within parietal cortices where the gray matter deficit was most pronounced in late-onset depression. This may suggest that the gray matter abnormalities reported here might be indeed disease specific.

Limitations of this study should be noted. The study groups were relatively small, a consideration that suggests caution when interpreting results. That is, it is possible that we did not have sufficient power to detect subtle differences in gray matter that may exist in other cortical regions in late-onset depression. Notwithstanding, since this study is, to our knowledge, the first to identify specific gray matter deficits in temporal and parietal cortices in late-onset depression, replication with a large homogenous group of subjects may serve to confirm the findings reported here. In addition, approximately two-thirds of the subjects were women. We corrected for potential interindividual differences in brain size that might be associated with gender by performing our analyses in International Consortium for Brain Mapping-305 space. However, future studies may be needed to investigate the specific contribution of gender to gray matter abnormalities in late-onset depression. Information on handedness was not available. Future research may further investigate laterality effects, given that larger gray matter differences were observed in the right hemisphere. Our findings in the present context, however, may reflect that power is lacking and not necessarily that laterality effects are present.

Measurements of gray matter obtained after cortical pattern matching algorithms are constrained by size of the sphere used to sample local gray matter proportions. In this study, we chose a 15-mm kernel size to increase signal to noise for local measurements of gray matter (41, 42, 49). Previous studies demonstrated that tissue proportion measurements using this kernel size are comparable to those found with manual delineation procedures. Indeed, Sowell et al. (75) documented that measures of gray matter concentration and gray matter volume are similar when the manually delineated region of interest is small and at the same cortical surface location.

In conclusion, the sensitive cortical pattern methods employed in this study were able to detect prominent local gray matter deficits in the right lateral temporal cortex and parietal cortex, most pronounced in sensorimotor areas, in subjects with late-onset depression relative to nondepressed comparison subjects. These novel findings imply specific neurodegenerative processes in late-onset depression that differ from the pattern commonly seen in dementia. Only longitudinal follow-up evaluations, however, will be able to make this distinction, with important implications from both therapeutic and research standpoints.

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