

Anterior Cingulate, Gyrus Rectus, and Orbitofrontal Abnormalities in Elderly Depressed Patients: An MRI-Based Parcellation of the Prefrontal Cortex

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Objective: To examine structural abnormalities in subregions of the prefrontal cortex in elderly patients with depression, the authors explored differences in gray matter, white matter, and CSF volumes by applying a parcellation method based on magnetic resonance imaging (MRI).

Method: Twenty-four elderly patients with major depression and 19 group-matched comparison subjects were studied with high-resolution MRI. Cortical surface extraction, tissue segmentation, and cortical parcellation methods were applied to obtain volume measures of gray matter, white matter, and CSF in seven prefrontal subregions: the anterior cingulate, gyrus rectus, orbitofrontal cortex, precentral gyrus, superior frontal cortex, middle frontal cortex, and inferior frontal cortex.

Results: Highly significant bilateral volume reductions in gray matter were observed in the anterior cingulate, the gyrus

rectus, and the orbitofrontal cortex. Depressed patients also exhibited significant bilateral white matter volume reductions and significant CSF volume increases in the anterior cingulate and the gyrus rectus. Finally, the depressed group showed significant CSF volume reductions in the orbitofrontal cortex relative to the comparison subjects. None of the other regions examined revealed significant structural abnormalities.

Conclusions: The prominent bilateral gray matter deficits in the anterior cingulate and the gyrus rectus as well as the orbitofrontal cortex may reflect disease-specific modifications of elderly depression. The differential pattern of abnormalities detected in the white matter and CSF compartments imply that distinct etiopathological mechanisms might underlie the structural cortical changes in these regions.

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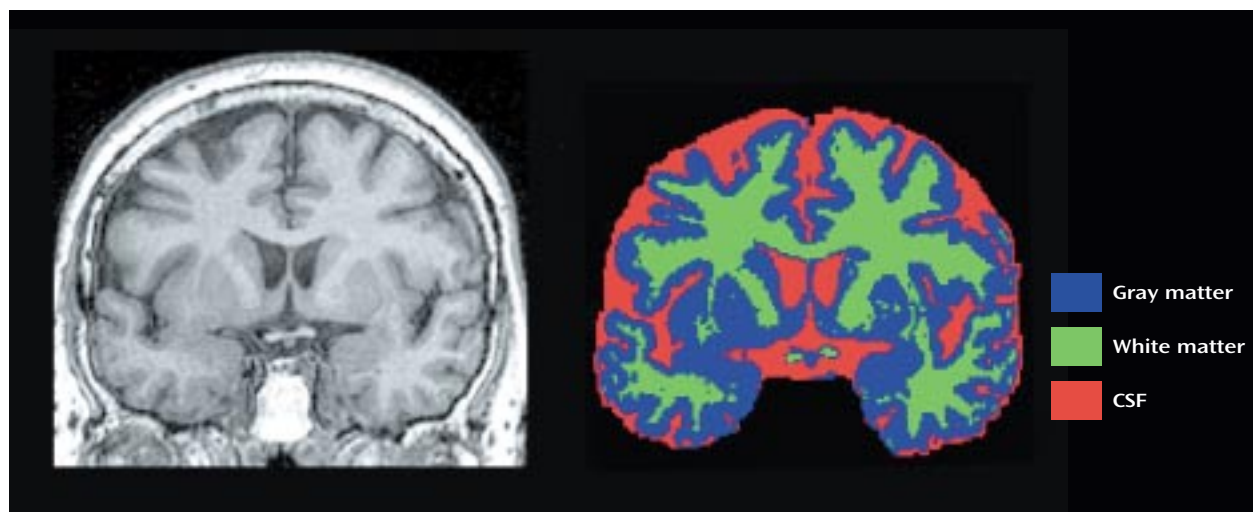
Major depression is conceptualized as a disorder that involves abnormalities of frontolimbic brain regions (1, 2). Efforts to unravel the precise structural and functional impairments underlying major depression have employed neuroimaging and neuropathological procedures. To date, functional imaging studies in adult patients have primarily focused on the prefrontal cortex, showing dysfunction in the dorsolateral prefrontal (3–8), anterior cingulate (9–13), and orbitofrontal cortex (13–15). In geriatric depression, functional imaging studies have also reported decreased blood flow in the orbitofrontal cortex (16) and anterior cingulate (17, 18) as well as biochemical abnormalities in frontal white matter (19). Furthermore, diffusion tensor imaging has shown that microstructural white matter abnormalities in close proximity to the anterior cingulate are associated with lower likelihood of remission in elderly patients with depression (20).

A critical role of the prefrontal cortex in major depressive disorder is further suggested by a number of post-mortem anatomical investigations that have revealed decreases in the density or number of glia and the density and size of some neurons in the orbitofrontal cortex and anterior cingulate (21). In addition, one neuropathologi-

cal study in elderly subjects has described a marked specificity for deep white matter hyperintensities at the level of the dorsolateral prefrontal cortex, consistent with the magnetic resonance imaging (MRI) literature that has suggested high-intensity lesions as one of the primary neurobiological substrates of elderly depression (22). Applying MRI estimates of brain and high-intensity lesion volumes together with clinical indices of cerebrovascular and non-vascular comorbidity, we have proposed that two distinct paths might lead to major depression in the elderly (23). One path might be represented by high-intensity lesions stemming from vascular and nonvascular medical comorbidity. Smaller frontal volumes might reflect another path in which a complex series of interconnected neurobiological events, perhaps influenced by genetic and environmental factors, might provide the changes mediating frontal volume deficits and, ultimately, major depression.

Despite the growing evidence for an involvement of the prefrontal cortex in younger as well as elderly depressed patients, there have been relatively few MRI volumetric studies examining the prefrontal cortex. Two previous structural MRI studies conducted by our group have demonstrated a reduction in whole prefrontal cortical volume

FIGURE 1. Prefrontal Cortex Image and Its Corresponding Image Segmented Into Gray Matter, White Matter, and CSF



in late-onset depression (24, 25). However, the human prefrontal cortex is a large and highly differentiated brain region in which different subregions are associated with specific behavioral and cognitive functions (26). Hence, it is conceivable to argue that specific subregions within the prefrontal cortex might be distinctively involved in the regulation and modulation of affect and emotions deficient in depression.

Two prior MRI studies have reported a left lateralized volume decrease of the subgenual cingulate cortex in patients with a family history of major depression (9, 27), although a more recent investigation could not replicate these findings in familial major depressive disorder (28). A further study in adult depressed patients found a reduction in medial orbitofrontal (gyrus rectus) volume, with no differences in size in the anterior cingulate (29). Possible explanations for the variability in findings may include methodological differences in image acquisition (i.e., slice thickness), region of interest delineation, and patient populations.

To date, two volumetric MRI studies with a focus on a specific region within the prefrontal cortex have been published in geriatric depression. These studies revealed a bilateral decrease in orbitofrontal gray matter (30) and a significant association between smaller orbitofrontal volumes and functional impairment (31).

Volumetric image analysis methods allow assessment of abnormalities in gray matter, white matter, and CSF volumes independently. The investigation of these tissue volumes in frontal subregions might therefore provide additional perspectives toward understanding the pathophysiology of distinct regional abnormalities in major depression.

To this aim, the present study examined differences in gray matter, white matter, and CSF in specific frontal subregions of elderly, depressed, medication-free patients who were compared with healthy volunteers group-matched for

age and gender. Applying a locally developed MRI-based parcellation method of the prefrontal cortex, we subdivided the prefrontal cortex into the following seven functionally relevant subregions: the anterior cingulate, gyrus rectus, orbitofrontal cortex, precentral gyrus, superior frontal cortex, middle frontal cortex, and inferior frontal cortex.

In light of the existing literature (30–33), we predicted that compared with healthy subjects, elderly depressed patients would exhibit gray matter abnormalities in the orbitofrontal cortex. We also hypothesized that we would observe gray matter abnormalities in ventromedial areas on the basis of previous volumetric MRI (9, 34) and post-mortem studies (35) in younger patients that have suggested a crucial role of the cingulate cortex in major depression. No published studies to our knowledge have investigated regional white matter and CSF changes in elderly patients with depression. Nonetheless, we predicted that changes in white matter or CSF would occur in the presence of gray matter reductions after we corrected for intracranial volume.

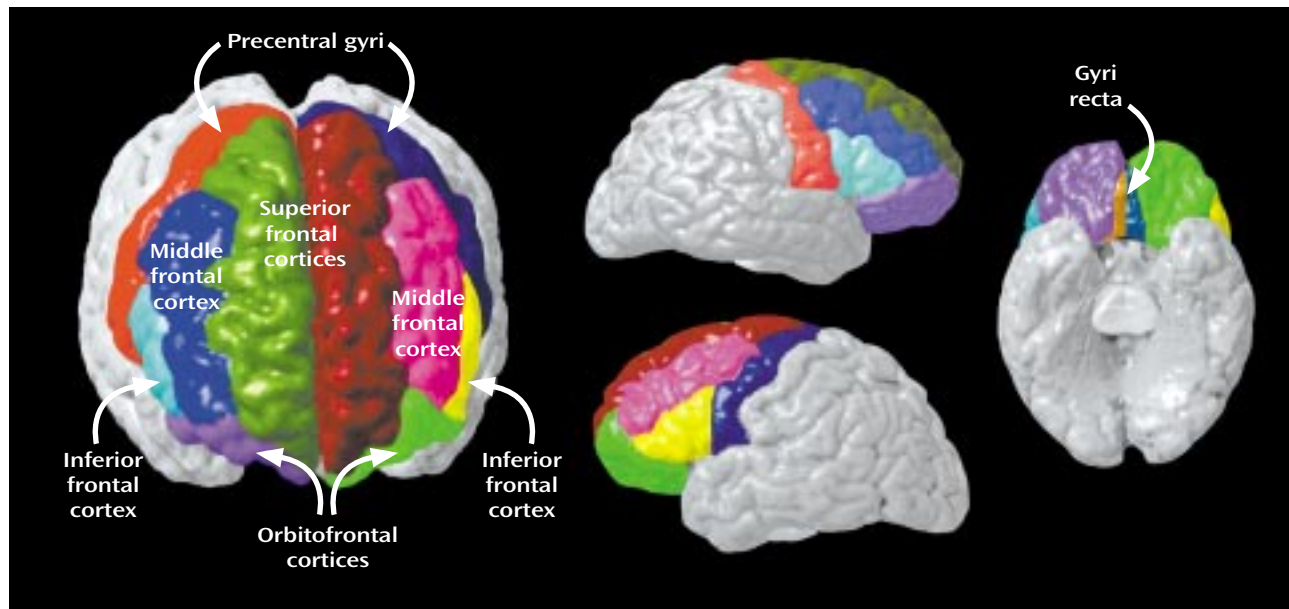
Method

Subjects

Subjects were 24 elderly patients with major depression (18 women and six men; mean age=65.85 years [SD=8.18]) and 19 nondepressed comparison subjects (15 women and four men; mean age=66.24 years [SD=7.25]). All depressed patients met DSM-IV criteria for major depressive disorder and were assessed with a structured psychiatric interview. All patients had scores of 15 or greater on the 17-item Hamilton Depression Rating Scale (36). Depressed patients had an average of two prior episodes of depression (SD=3), with mean age at onset of depression of 35 years (SD=3.45). The purpose of these inclusion criteria was to focus on elderly patients with at least one episode before age 60, in addition to the index episode. Information on prior episodes and the age at onset was obtained from patients and caregivers.

All patients had been free of psychotropic medications for at least 2 weeks before imaging. None of the patients had histories of

FIGURE 2. Three-Dimensional High-Resolution Shape Representations Used to Aid in the Parcellation of Prefrontal Cortex Subregions Measured in 24 Elderly Depressed Patients and 19 Comparison Subjects



long-term antidepressant treatment. Patients received comprehensive medical and neurologic examinations and laboratory testing. None of the subjects had clinical evidence of dementia, suspected dementia, or any other brain disorder according to a review of the subjects' history and a mental status examination. Patients were excluded if they had a history of bipolar disorder, alcohol abuse, or dependence. Mean Mini-Mental Status Examination scores (37) were in the normal range in the major depression group (mean=28.45, SD=1.45) as well as in the comparison group (mean=29.53, SD=0.80).

Patients were recruited through local newspapers 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 newspapers and radio advertisements. All comparison subjects underwent a psychiatric examination and a structured interview (Structured Clinical Interview for DSM-IV) for healthy subjects to rule out current or past psychopathology. The study was performed in accordance with UCLA's policies of the Human Subject Protection Committees, and written informed consent was obtained from all subjects after the procedures had been fully explained.

Imaging Protocol

All subjects were studied with MRI performed on a 1.5-T Signa magnet (GE Medical Systems, Milwaukee) that used a coronal T₁-weighted spoiled gradient/recall acquisition in the steady state with the following parameters: repetition time=20 msec; echo time=6 msec; flip angle=45°; 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=0.859375×0.859375.

Image Analysis

All image data sets were processed with a series of steps in preparation for manual delineation of prefrontal subregions.

First, images were subjected to brain masking with removal of nonbrain tissue (i.e., scalp and orbits) and cerebellum. Brain volumes were corrected for signal intensity inhomogeneities (38), aligned, and placed into stereotaxic coordinates, without scaling. This procedure was used to correct for differences in head posi-

tion and to place data in a common space that was specifically used for group comparisons.

Fully automated tissue segmentation was then applied to the brain volumes, where voxels were automatically classified as most representative of gray matter, white matter, or CSF (39) (Figure 1). Quantification of white matter lesions was not assessed in this study.

The fully automated protocol has been shown valid in comparison with semiautomated tissue segmentation procedures used in our previous reports (40, 41). We assessed 24 subjects with our earlier manual segmentation protocol (40) that used the completely automated classification scheme of Shattuck and colleagues (39) and found Pearson's correlations of 0.96 for white matter volume, 0.94 for gray matter volume, and 0.80 for CSF volume.

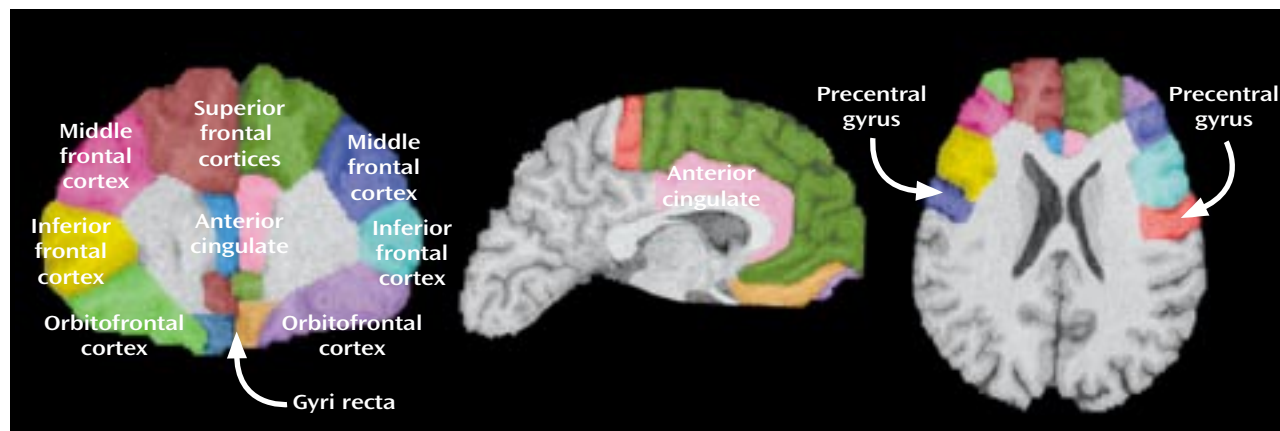
Finally, a high-resolution shape representation of the cortex was extracted for each subject by using automated software (42). By using a three-dimensional active surface algorithm, a spherical mesh surface was created that was continuously transformed to fit a cortical surface tissue threshold intensity value (signal value that best differentiates cortical CSF on the outer surface of the brain from the underlying cortical gray matter) from individual brain volumes. These surface/shape extractions were used to aid in delineation of frontal cortical substructures.

Total intracranial volume including sulcal and subarachnoid CSF but not cerebellum was calculated.

Anatomical Boundaries

The rules applied to achieve parcellation of the prefrontal lobe into seven subregions for each hemisphere are listed in Appendix 1. Complete details of the written anatomical protocols can be found on the World Wide Web (http://www.loni.ucla.edu/protocols/Prefrontal_cortex.html). All anatomical delineations were reconciled using each individual's three-dimensional surface model (Figure 2) and all three planes to corroborate sulcal and subregion identity (Figure 3). Delineations were also verified by using two neuroanatomical atlases (43, 44). For interrater reliability, all anatomical regions were delineated on 10 randomly chosen image data sets. Intraclass correlation coefficients for the reliability of gray matter, white matter, and CSF volumes, as well as total volumes in all subregions ranged between 0.85 and 0.92.

FIGURE 3. Coronal, Sagittal, and Axial Views of the Anatomical Landmarks for the Prefrontal Cortex Subregions Measured in 24 Elderly Depressed Patients and 19 Comparison Subjects^a



^a Subregion identity was defined on the three planes simultaneously.

Statistical Analysis

Gray matter, white matter, CSF, and total region volume in each of the seven prefrontal subregions for each hemisphere were dependent measures in analyses of covariance with diagnosis as a between-group factor. To address potential interindividual differences in brain size that may be associated with demographic variables (i.e., gender and age), region of interest volumes as a proportion of the subject's total intracranial volume (45) were used as dependent variables. Although gender distribution of the two groups was similar, gender was included as a covariate, since earlier investigations (46) have reported differences between male and female subjects in some of the regions measured in the present study. Age did not significantly differ between the groups but was also used as a covariate.

Although multiple tests were performed, we elected to not apply a correction procedure, such as the Bonferroni. Applying a Bonferroni correction would have protected our results from type I error, but this approach would have made the results highly prone to type II errors, given that a large number of comparisons were done. The significance level adopted was $\alpha=0.05$ (two-tailed).

Results

The results are presented in Table 1 and in Figure 4. Group effects are described after correction for total intracranial volume, with age and gender as covariates. Table 1 also documents raw volumes before correction for intracranial volume. Depressed patients exhibited highly significant gray matter volume reductions in the left and right anterior cingulate (differences of 18% and 20%, respectively), the left and right gyrus rectus (differences of 19% and 24%), and the left and right orbitofrontal cortex (differences of 12% in both).

In the anterior cingulate, significant bilateral white matter volume reductions (left: 14% difference; right: 21% difference) and CSF volume increases (left: 18% difference; right: 24% difference) were observed in the depressed patients. In the gyrus rectus, elderly patients with major depression showed significant bilateral white matter volume reductions (left: 15% difference; right: 18% difference) and

CSF volume increases (left: 22% difference; right: 25% difference). Significant CSF volume decreases were seen in the left and right orbitofrontal cortex (differences of 21% and 20%, respectively), with no significant difference in white matter volume.

White matter and CSF volume abnormalities were not as pronounced as the gray matter volume reductions. Total anterior cingulate, gyrus rectus, and orbitofrontal volumes were significantly smaller in patients relative to comparison subjects. We did not detect evidence for gender or age effects in any of the volumes analyzed.

There were no significant differences between the depressed patients and the comparison group in gray matter, white matter, and CSF volumes of the precentral gyrus, superior frontal cortex, middle frontal cortex, and inferior frontal cortex. There were also no significant differences between patients and comparison subjects in total brain volume ($t=0.68$, $df=39$, $p=0.50$), total gray matter volume ($t=0.71$, $df=39$, $p=0.50$), total white matter volume ($t=0.23$, $df=39$, $p=0.80$), or total CSF ($t=0.83$, $df=39$, $p=0.40$).

Discussion

To our knowledge, this is the first study to use a volumetric MRI-based parcellation method of the prefrontal cortex to examine structural abnormalities in major depression. The main findings of this study were 1) a pronounced reduction in left and right gray matter volumes in the anterior cingulate, the gyrus rectus, and the orbitofrontal cortex; 2) significant bilateral decreases in white matter volume and significant increases in CSF volume in the anterior cingulate and the gyrus rectus; 3) a significant bilateral reduction in CSF volume in the orbitofrontal cortex of depressed patients relative to comparison subjects. In sum, the present study shows that volumetric abnormalities occur in distinct tissue compartments of specific frontal subregions in elderly patients with depression.

TABLE 1. Prefrontal Cortex Subregions With Significant Volume Differences Between Elderly Depressed Patients (N=24) and Group-Matched Healthy Comparison Subjects (N=19)^a

Region and Volume Measurement	Raw Volume (mm ³)				Corrected Volume				Analysis		
	Depressed Patients		Comparison Subjects		Depressed Patients		Comparison Subjects				
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	F (df=1, 39)	p	
Anterior cingulate											
Gray											
Left	4391	1064	5472	869	0.0032	0.0005	0.0039	0.0005	15.41	0.0001	
Right	4433	1195	5676	1003	0.0032	0.0006	0.0040	0.0005	19.55	0.00007	
White											
Left	1695	552	2002	456	0.0012	0.0003	0.0014	0.0004	6.18	0.02	
Right	1526	636	1955	536	0.0011	0.0004	0.0014	0.0003	11.60	0.002	
CSF											
Left	1173	272	997	204	0.00087	0.0002	0.00071	0.0002	5.45	0.02	
Right	1146	403	901	374	0.00082	0.0002	0.00062	0.0002	8.51	0.006	
Total											
Left	7259	1567	8471	1013	0.0052	0.0008	0.0060	0.0007	12.53	0.001	
Right	7105	1936	8532	1475	0.0051	0.0008	0.0060	0.0007	16.56	0.0002	
Gyrus rectus											
Gray											
Left	1771	499	2340	523	0.0013	0.0003	0.0016	0.0003	17.89	0.0002	
Right	1838	518	2487	612	0.0013	0.0003	0.0017	0.0004	15.58	0.0001	
White											
Left	687	201	828	183	0.00050	0.0001	0.00059	0.0001	4.21	0.04	
Right	727	213	926	337	0.00053	0.0001	0.00065	0.0002	5.34	0.02	
CSF											
Left	766	242	624	177	0.00055	0.0001	0.00043	0.0001	7.61	0.009	
Right	713	276	547	164	0.00051	0.0002	0.00038	0.0001	9.54	0.004	
Total											
Left	3225	808	3793	770	0.0023	0.0004	0.0027	0.0004	7.88	0.008	
Right	3278	833	3961	938	0.0024	0.0004	0.0028	0.0006	7.65	0.009	
Orbitofrontal cortex											
Gray											
Left	10956	1344	12797	1072	0.0080	0.001	0.0091	0.001	10.21	0.003	
Right	10778	1559	12234	1142	0.0079	0.0009	0.0090	0.001	11.52	0.002	
White											
Left	5519	1025	5336	929	0.0040	0.0007	0.0038	0.0008	0.42	0.51	
Right	6979	1592	7227	1174	0.0051	0.001	0.0051	0.001	0.09	0.76	
CSF											
Left	3026	837	3865	966	0.0022	0.0008	0.0028	0.0008	5.44	0.02	
Right	2772	806	3364	849	0.0020	0.0006	0.0025	0.0006	4.64	0.04	
Total											
Left	20133	2338	22640	2075	0.014	0.002	0.016	0.003	5.27	0.02	
Right	20530	2748	22825	2184	0.015	0.002	0.016	0.003	4.95	0.03	

^a Group effects are described after correction for total intracranial volume, with age and gender as covariates.

On the basis of the structural imaging literature to date, the orbitofrontal cortex, anterior cingulate, and gyrus rectus have been previously identified as critical regions involved in major depression (9, 29, 31, 34, 47), but this is the first time that cingulate volume abnormalities are reported in elderly depressed patients.

The present findings support the results of a prior report that found reduced gray matter volumes in the orbitofrontal cortex of elderly patients with major depression (50). The present findings also contribute to the suggestive evidence that dysfunction of the orbitofrontal cortex may yield a characteristic state of depressed mood in which the ability to interrupt perseverative melancholic thoughts and anxious responses to ordinarily nonthreatening stimuli seems impaired (48).

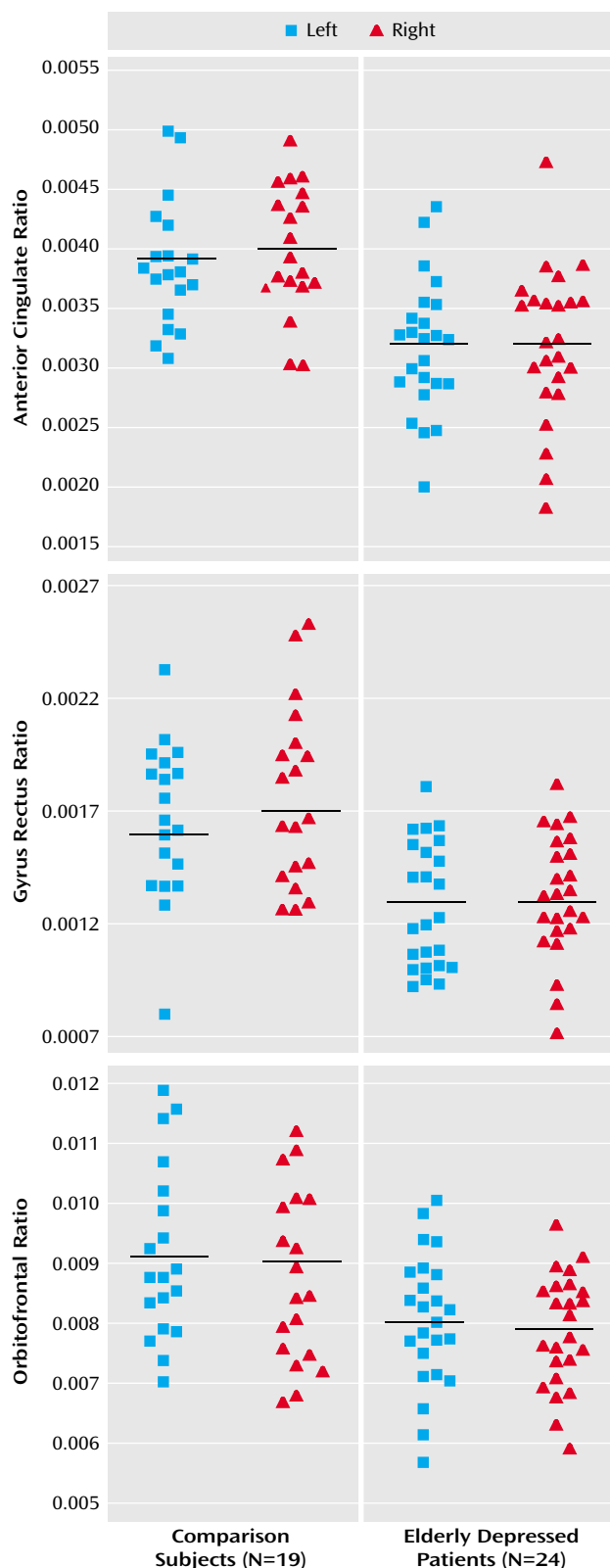
It is of interest that our results show a reduction of CSF volumes in the depressed patients relative to the comparison subjects in the orbitofrontal cortex. The mechanism of this CSF volume decrease is unclear. However, decreased

CSF volumes may suggest that orbitofrontal cortical volume reduction is indicative of hypodevelopment rather than atrophy even in elderly depressed patients. Thus, it may be hypothesized that the individuals studied here were born with smaller volumes of the orbitofrontal cortex and, perhaps, with specific neuroanatomical changes in this region that over time led to exaggerated stress responses and aversive thought and emotion. Longitudinal studies, perhaps among those at risk for developing depression, may help clarify whether the abnormalities are static during the course of the illness (and more likely to be neurodevelopmental) or progressive (and more likely to be neurodegenerative) in nature.

In this context, it is also interesting to discuss our findings in the anterior cingulate and the gyrus rectus. In contrast to previous reports in younger patients (9, 34), our results reveal bilateral abnormalities in these regions.

The present study reveals bilateral volume decreases of gray and white matter, along with significant bilateral CSF

FIGURE 4. Gray Matter Volume Distribution in the Anterior Cingulate, Gyrus Rectus, and Orbitofrontal Cortex of 24 Elderly Depressed Patients and 19 Comparison Subjects^a



^a Gray matter volumes are presented as proportion measures of the subject's total intracranial volume. Horizontal bars represent group means.

volume increases, in the anterior cingulate and the gyrus rectus. This pattern of findings might suggest that distinct neuroanatomical changes are occurring in these regions relative to the findings in the orbitofrontal cortex. Perhaps the increase in CSF is reflective of neurodegenerative processes rather than a neurodevelopmental abnormality in depressed patients with a later age at onset. Of note, glial pathology could play a primary role, given that reduced density and number of glia in the anterior cingulate have been reported in a neuropathological study of mood disorder (49). It is possible, therefore, that the overall cortical changes observed in this region might point to a loss of fiber pathways that connect different brain regions participating in mood regulation. Indeed, the anterior cingulate is a critical area of integration between brain regions that have been implicated in the cognitive/affective and somatic/vegetative symptoms of depression. More specifically, the anterior cingulate is the origin of the anterior cingulate frontal-subcortical circuit (2). It is interesting that this circuit receives major afferents from the hippocampus (2), which communicates with higher-order association cortical regions through the entorhinal, perirhinal, and parahippocampal cortices (50, 51). In addition, the anterior cingulate is interconnected with the amygdala through efferents to the lateral nucleus and through afferents from the basal nucleus, which also project to many higher-order areas (52). The cingulate gyrus is reciprocally connected with the orbitofrontal cortex (48). Stress and clinical depression are often associated with hypercortisolemia, which has neurotoxic properties (53). It has been suggested that stress-induced reductions in neurotrophins may also play a role in the structural changes observed in patients with major depression (54). Thus, if hypodevelopmental phenomena underlie the abnormalities in the orbitofrontal cortex, it could be speculated that a complex set of interrelated neurobiological events, perhaps mediated through these early structural changes, may constitute the path that leads to progressive cingulate damage over time.

Bilateral anterior cingulate abnormalities in elderly patients with depression may be supported by two previous functional neuroimaging studies: one study found a significant bilateral blood flow reduction in the anterior cingulate cortex in elderly depressed patients that persisted after electroconvulsive therapy (17); de Asis and colleagues (18) reported bilateral activation deficits in the anterior cingulate in a study that used brain activation paradigms. Of interest is that abnormalities of the anterior cingulate are thought to be associated with executive and psychomotor symptoms (55), often prominent in geriatric depression (18). On the other hand, a proton magnetic resonance spectroscopy study conducted by our group did not find any changes in *myo*-inositol/creatine, choline/creatine, and *N*-acetylaspartate/creatine ratios in the anterior cingulate of elderly patients with major depression (19). Since the present investigation included

some of the patients of the latter study (19), the current findings may suggest that structural abnormalities and specific biochemical events might occur independent of one another.

It is noteworthy that the gyrus rectus shows structural abnormalities similar to those observed in the anterior cingulate, and it is important that the gyrus rectus is considered to be an extension of the anterior cingulate onto the frontal lobe (56). This may help explain the similarity of the structural changes in both regions. It could also complement and strengthen our results, which propose bilateral anterior cingulate abnormalities as critical neurobiological features in elderly patients with depression. Bremner and colleagues (29) found decreased gray matter volumes of the gyrus rectus in adult depressed patients without any structural changes in the anterior cingulate. To our knowledge, in the two volumetric MRI studies of elderly depressed patients with a focus on a specific region within the prefrontal cortex, the orbitofrontal cortex and gyrus rectus were combined into one single region of interest (30, 31). However, the gyrus rectus might merit further investigation in major depression. Indeed, it may be of interest to note that functional imaging studies in schizophrenia have shown a clear distinction between the gyrus rectus and the orbitofrontal cortex during several cognitive tasks, suggesting that the gyrus rectus may be part of a circuit that mediates some specific emotional functions in humans (57).

It might be argued that accelerated aging or increased vulnerability to the general effects of age could have contributed to the structural abnormalities detected in our study. Actually, there is controversy about which subregions of the prefrontal cortex are particularly affected by the aging process. Age effects reported in the anterior cingulate have been dependent on the method applied (58). A selective preservation of the orbitofrontal cortex has been found in very old healthy elderly subjects (59), while other investigations detected an age-associated volumetric reduction in this region (58, 60). Although the application of different methods has been proposed as a possible explanation for these discrepancies, this issue may clearly warrant further investigation, also in view of the fact that previous studies revealed left-lateralized gray matter reduction in the anterior cingulate in younger patients, whereas here we report bilateral abnormalities in an elderly depressed population.

The present findings may be limited by small study group size, although the highly significant results in gray matter volumes are noteworthy for a relatively small sample.

A further limitation of this study concerns the potential for inflated type I error in comparisons of white matter and CSF changes in elderly patients with depression

relative to healthy comparison subjects. Therefore, statistically less pronounced differences, such as the bilateral white matter and CSF abnormalities observed here, should be interpreted with caution. However, since this is the first study that explores white matter and CSF volumetric differences in addition to gray matter differences between depressed patients and healthy volunteers, we were willing to tolerate a higher chance of type I error rather than miss a true positive finding. Indeed, our results in the white matter and CSF compartments may provide a valuable complement to previous investigations of gray matter abnormalities in major depression (9, 29–31, 34), giving rise to new hypotheses regarding possible etiopathological mechanisms underlying structural cortical abnormalities.

It has been argued that white matter abnormalities should be interpreted with caution, given the lack of clear anatomical landmarks to define white matter subregions within the frontal lobe. In the present study, white matter was generally defined as tissue next to a straight line connecting the deepest point of the sulci that were considered as anatomical landmarks of a given subregion. The high interrater reliability for all segmented volumes may, however, support the notion that white matter measures interpreted in conjunction with gray matter offer a more appropriate and meaningful approach, even given limitations in defining white matter boundaries. Finally, future studies may be needed to specifically investigate the contribution of gender to structural abnormalities in elderly depression.

Conclusions

Highly pronounced robust gray matter deficits were observed in three brain regions, namely the anterior cingulate, the gyrus rectus, and the orbitofrontal cortex, abnormalities consistent with our predictions based on the neuroimaging and neuropathological literature. The extent to which the aforementioned abnormalities might be specifically related to elderly depressed patients remains to be clarified.

Further clinicopathological work, with imaging both in vivo and after death, will be needed to carefully examine radiopathological correlations and to draw further insights into the purported neuroanatomical hallmarks of elderly depression. In addition, future investigations should address the question to what extent age at illness onset, regardless of age, might be relevant to specific neuroanatomical disease markers. This consideration may be of special interest also in light of previous evidence revealing strikingly more severe white matter lesions in subjects with an onset of depression after age 60 years than in individuals who had an onset before age 60 (61).

APPENDIX 1. Parcellation Procedure for the Seven Prefrontal Lobe Subregions Measured in Elderly Depressed Subjects (N=24) and Healthy Comparison Subjects (N=19)**Anterior Cingulate Gyrus**

The anterior cingulate gyrus was traced in both sagittal and coronal slices. The anterior cingulate gyrus was defined with boundaries encompassing the cingulate sulcus (anterior, superior, and inferior boundaries); the paracentral sulcus (posterior boundary); and the pericallosal sulcus (inferior and posterior boundaries). The posterior boundary of the anterior cingulate gyrus is similar to that described by Rademacher and colleagues (62). Tracing started on the most midsagittal image that best illustrated its course, and its most anterior point was identified on that image. Moving laterally, tracing continued in the coronal plane connecting the deepest point of the pericallosal sulcus to the deepest point of the cingulate sulcus. Tracing ended in the coronal plane where the paracentral sulcus appeared. The sagittal plane was used to identify the posterior boundary.

Gyrus Rectus

The gyrus rectus was traced in the coronal plane. It was defined with boundaries encompassing the olfactory sulcus (anterior and lateral boundaries); the olfactory trigone (posterior boundary); and on the medial wall, cortex inferior to a line connecting the deepest point of the olfactory sulcus to the nearest point on the midline on every coronal slice was defined as gyrus rectus. Tracing began in the coronal plane where the most anterior extreme of the olfactory sulcus could be visualized. Axial planes and the three-dimensional surface model were used to aid in corroborating gyrus rectus anatomy. Moving posteriorly, mainly sagittal and axial views were used to identify the olfactory trigone. Tracing ended on the coronal plane when the olfactory trigone was no longer visible.

Orbitofrontal Cortex

The orbitofrontal cortex was traced in the coronal plane. The orbitofrontal cortex included all of the orbital gyri and excluded the gyrus rectus. The orbitofrontal cortex was defined with boundaries encompassing the frontomarginal sulcus (anterior and lateral boundaries); the frontomarginal sulcus, the lateral orbital sulcus, and the circular sulcus of the insula (lateral boundary); and the olfactory sulcus (medial boundary). Before tracing began, the lateral orbital sulcus was identified in the coronal plane. In more anterior slices, the orbitofrontal cortex was traced following the frontomarginal sulcus to its intersection with the midline. Moving posteriorly, the orbitofrontal cortex was defined as cortex between the olfactory sulcus and the sulcus defined as the lateral anatomical boundary. Tracing ended on the coronal plane when the olfactory sulcus and the circular insular sulcus were no longer visible.

Precentral Gyrus

The precentral gyrus was traced in both axial and sagittal slices. The precentral gyrus was defined with boundaries encompassing the precentral sulcus (anterior boundary); the central sulcus (posterior boundary); the lateral fissure and the cingulate sulcus (inferior boundary); and in more lateral portions, a line connecting the deepest points of the precentral sulcus and the central sulcus was defined as the inferior boundary. Tracing started on the most superior axial slice in which the precentral sulcus could be delineated and the precentral gyrus first appeared. The most superior point of the precentral gyrus on the three-dimensional surface model was used to identify this slice. When the precentral sulcus appeared as a broken sulcus, the tip of the sulcus was connected to the midline using the shortest distance. Moving inferiorly, the sagittal plane was mainly used to identify the anatomical landmarks. Since the central sulcus rarely reaches the lateral fissure (42), the three-dimensional surface model was used to draw a vertical line from its inferior extremity to the lateral fissure to complete the course of the gyrus.

Superior Frontal Cortex

The superior frontal cortex was traced in axial, sagittal, and coronal slices. The superior frontal cortex was defined with boundaries encompassing the frontomarginal sulcus (anterior boundary); the precentral sulcus (posterior boundary); and the superior frontal sulcus (lateral boundary). The frontomarginal sulcus, orbitofrontal cortex, and gyrus rectus (in anterior portions) were used as the inferior boundary as was a line connecting the deepest points of the superior frontal sulcus and the cingulate sulcus in the posterior regions. Tracing started on the most superior axial slice in which the superior frontal sulcus could be delineated and the superior frontal cortex first appeared. The most superior point of the superior frontal cortex on the three-dimensional surface model was used to identify this slice. When the precentral sulcus and the midline did not meet, a straight line was drawn from the most medial point of the precentral sulcus to the nearest point of the midline. Moving inferiorly, sagittal, coronal, and axial planes were used in delineating the inferior boundary of the superior frontal cortex. With the corroboration of the sagittal view, tracing ended on the most posterior coronal plane where the border between the superior frontal cortex and the precentral gyrus could be defined.

Middle Frontal Cortex

The middle frontal cortex was traced in the axial plane. The middle frontal cortex was defined with boundaries encompassing the frontomarginal sulcus and lateral orbital sulcus (anterior boundary); the precentral sulcus (posterior boundary); the inferior frontal sulcus (inferior and posterior boundary); and the superior frontal sulcus (superior boundary). The medial boundary of the middle frontal cortex was defined by a line connecting the deepest points of the inferior frontal sulcus and the superior frontal sulcus. Tracing began on the most superior axial slice in which the superior frontal sulcus could be delineated and where the middle frontal cortex first could be seen. The most superior point of the middle frontal cortex on the three-dimensional surface model was used to aid in defining the first slice. In more inferior regions of the middle frontal cortex, the three-dimensional surface model was used to locate regions posterior to the frontomarginal sulcus and the lateral orbital sulcus. Tracing ended on the most inferior axial slice in which the middle frontal cortex could be identified.

Inferior Frontal Cortex

The inferior frontal cortex was traced in the axial plane. The inferior frontal cortex was defined with boundaries encompassing the lateral orbital sulcus (anterior boundary); the precentral sulcus (posterior boundary); and the lateral orbital sulcus and the circular sulcus of the insula (inferior boundary). The medial boundary was a line connecting the deepest points of the inferior frontal sulcus with the deepest points of the precentral sulcus. Tracing began on the most superior axial slice in which the inferior frontal sulcus could be delineated. To find this slice, the most superior point of the pars opercularis on the three-dimensional surface model was identified. Tracing ended on the most inferior axial slice in which the inferior frontal cortex could be distinguished.

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