

Depressive State- and Disease-Related Alterations in Neural Responses to Affective and Executive Challenges in Geriatric Depression

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Objective: Geriatric depression has been associated with a heterogeneous neuropathology. Identifying both depressive state-related and disease-related alterations in brain regions associated with emotion and cognitive function could provide useful diagnostic information in geriatric depression.

Method: Twelve late-onset acutely depressed patients, 15 patients fully remitted from major depression, and 20 healthy comparison subjects underwent event-related functional MRI. Brain activation and deactivation associated with executive and emotional processing were investigated using an emotional oddball task in which circles were presented infrequently as attentional targets and sad and neutral pictures as novel distractors.

Results: Significant changes in brain activation in patients were found mainly in response to attentional targets rather than to sad distractors. Relative to healthy comparison subjects, the depressed patients had attenuated activation in the re-

gions of the executive system, including the right middle frontal gyrus, the cingulate, and inferior parietal areas. Activity in the middle frontal gyrus revealed depressive state-dependent modulation, whereas attenuated activation in the anterior portion of the posterior cingulate and inferior parietal regions persisted in the remitted subjects, suggesting a disease-related alteration. Enhanced deactivation was observed in the posterior portion of the posterior cingulate, which was also state dependent. The remitted group did not show this deactivation.

Conclusions: Our results indicate distinct roles for the right middle frontal gyrus and the anterior and posterior portions of the posterior cingulate cortex in geriatric depression. The deactivation of the posterior portion of the posterior cingulate could be informative for differentiation of cognitive dysfunction related to depression from other conditions, such as mild cognitive impairment.

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Studies using functional MRI (fMRI) in young depressed patients have reported activity changes in the limbic-thalamic-cortical network associated with emotion and cognition (1–5). Several studies have described exaggerated activity in the ventral frontal and limbic regions, including the amygdala (2, 4, 6), in young adults with major depression relative to comparison subjects during negative emotional processing, although this activity is not always found (7). Depending on the degree of task difficulty, depressed patients also show increased or decreased activation in the dorsolateral prefrontal cortex while performing cognitive tasks (5, 8–10). Antidepressant medication normalizes these state-dependent changes in those patients who respond to treatment (2, 6, 11–14).

In contrast to studies of young depressed adults, fMRI studies that evaluate both emotional and cognitive function in geriatric depression are scarce. Elderly patients with depression may show deficits different from those of young depressed adults, given age-related changes such

as cerebrovascular ischemia and white-matter hyperintensities (14). A greater range of adverse outcomes, including cognitive impairment, has been reported in late-onset depression. This may reflect the greater presence of cerebrovascular pathology in geriatric depression, particularly in the frontostriatal regions, leading to cognitive and emotional deficits (15). Aizenstein et al. (16) demonstrated decreased activation in the dorsolateral prefrontal cortex and increased activation in the striatum in depressed older patients relative to comparison subjects during an explicit sequence learning task. However, their study did not investigate the relationship between altered brain activation and clinical status. There has been no comparable study investigating the emotional processing system in geriatric depression. It is likely that abnormal activation in the frontostriatal circuits during a cognitive task is a prominent feature of geriatric depression rather than exaggerated activation in emotion-related regions during a negative emotional task.

This article is featured in this month's AJP [Audio](#) and is discussed in an editorial by Dr. Alexopoulos (p. 790).

TABLE 1. Demographic and Clinical Characteristics and Reaction Time Profiles of Older Participants in an fMRI Study Using an Emotional Oddball Task^a

Characteristic	Group					
	Depressed Patients (N=12)		Remitted Patients (N=15)		Comparison Subjects (N=20)	
	Mean	SD	Mean	SD	Mean	SD
Mean age (years)	69.1	6.0	70.8	5.5	73.1	5.3
Education (years)	14.9	1.9	16.1	2.2	16.8	1.9
Duration of illness (weeks) ^b	104.3	94.1	214.4	127.5		
Age at onset of illness (years)	67.1	6.3	65.8	4.7		
Number of depressive episodes	2.2	1.3	5.1	4.9		
Montgomery-Åsberg Depression Rating Scale score ^c	23.7	5.7	3.5	2.1	0.95	1.5
Mini-Mental State Examination score ^d	28.0	1.7	28.6	1.7	29.4	0.7
Response time to targets in emotional oddball task (msec)	676.3	123.4	698.4	121.9	651.45	104.1
	N	%	N	%	N	%
Female	7	58.3	5	33.3	12	60.0
Taking antihypertensive medication ^e	6	50.0	5	33.3	3	15.0

^a There were no significant between-group differences in age, gender, years of education, number of depressive episodes, and response time to targets.

^b Duration of illness was the duration from the day of initial diagnosis to the day of fMRI scan. Depressed vs. remitted, two-sample t test, $p=0.004$.

^c One-way analysis of variance, $F=202.597$, $p<0.001$; Bonferroni post hoc test, depressed vs. remitted patients, $p<0.001$, depressed patients vs. comparison subjects, $p<0.001$.

^d One-way analysis of variance, $F=5.543$, $p=0.007$; Bonferroni post hoc test, depressed patients vs. comparison subjects, $p=0.01$.

^e Kruskal-Wallis test, $\chi^2=5.806$, $p=0.055$; Mann-Whitney U test, depressed patients vs. comparison subjects, $p=0.016$.

While there have been many neuroimaging studies of young patients during a depressive state, only a few studies of remitted patients have been reported. Decreased activity of the medial and orbital frontal cortices in remitted patients during sad mood induction has been reported, indicating a possible neuroimaging marker of depression (17, 18). This possibility has not been studied in geriatric depression. Decreased activation in the dorsal anterior cingulate cortex during a verbal fluency task has been observed in remitted patients who had multiple depressive episodes (19). However, the study did not include an acutely depressed group for comparison. A systematic comparison of acutely depressed patients, patients with remitted depression, and normal healthy subjects is needed to identify the depressive state-related and disease-related alterations in brain activities in geriatric depression.

In addition to activation, task-induced negative activation (20)—or deactivation—might also have implications in geriatric depression. Greicius et al. (21) recently reported greater resting-state subgenual cingulate and thalamic functional connectivity in young depressed patients relative to healthy comparison subjects. Regions in the posterior cingulate revealed a reduced magnitude of deactivation in mild cognitive impairment and Alzheimer's disease (22, 23). These studies highlight the importance of investigating the association of deactivation in the default-mode network with depressive state and cognition.

In this study, we compared brain activity in acutely depressed patients, patients with remitted depression, and healthy comparison subjects, all over age 60. We used an emotional oddball task during fMRI scanning to evaluate both emotional and executive processing. Given that apathy and cognitive dysfunction might be prominent in geriatric depression, we hypothesized that relative to the comparison subjects, acutely depressed patients would exhibit decreased activation in the executive system to attentional targets.

On the other hand, we hypothesized that they would not show hyperactivity in the emotional system in response to sad stimuli. We also surmised that some of these features might constitute a disease-specific biomarker and would be present in patients whose depression had remitted. Finally, we hypothesized that depressed patients would have enhanced deactivation because of limited attentional resources.

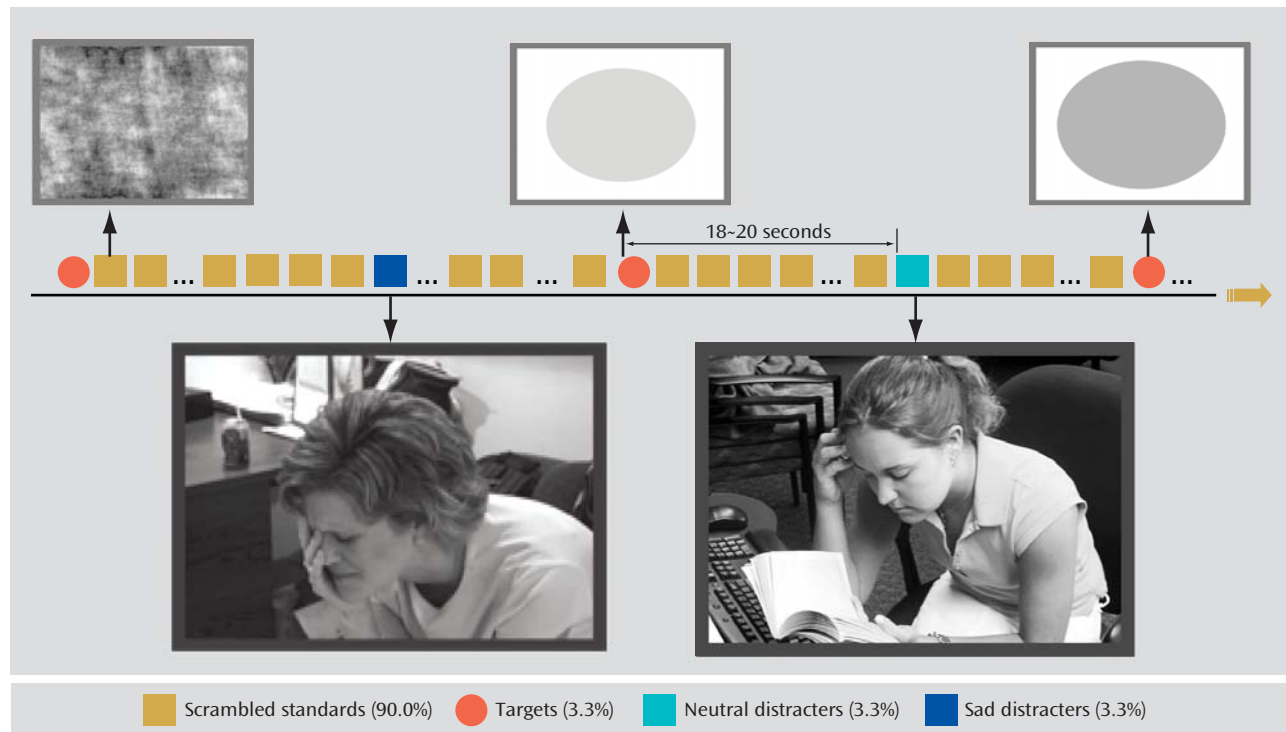
Method

Participants

Twelve patients with an active unipolar major depressive episode, 15 patients with a previous DSM-IV diagnosis of major depressive disorder who were currently in full remission, and 20 healthy comparison subjects participated in the study. All participants were over 60 years of age and were recruited from the Silvio O. Conte Center for the Neuroscience of Depression in Late Life at Duke University Medical Center. We have long used the National Institute of Mental Health's Diagnostic Interview Schedule to either verify (for depressed participants) or rule out (for comparison subjects) major depression and to rule out other major psychiatric illnesses. Age at illness onset for all patients was over age 55, as determined from information obtained in the interview. All acutely depressed patients met DSM-IV criteria for active major depression and had a Montgomery-Åsberg Depression Rating Scale (MADRS; 24) score ≥ 17 . Remission was defined as an absence of symptoms for a minimum of 6 months and a MADRS score less than 8.

Among the 12 acutely depressed participants, nine were receiving antidepressant monotherapy (six with a selective serotonin reuptake inhibitor [SSRI], two with venlafaxine, and one with bupropion), two were receiving combination treatment (an SSRI and bupropion), and one was receiving no antidepressant medication at the time of testing. Among the 15 participants in the remitted group, 11 were receiving antidepressant monotherapy (six with an SSRI, two with bupropion, two with venlafaxine, and one with mirtazapine), one was receiving combination treatment (an

FIGURE 1. Emotional Oddball Task Used in an fMRI Study of Older Patients With Depression or in Remission From Depression and Healthy Comparison Subjects^a



^a The task used three types of rare events: targets (circles varying in size and luminance), sad distractors (scenes of a person crying or scenes depicting despair, grief, internment, incarceration, or poverty), and neutral distractors (scenes matched the sad pictures for the presence and number of human figures, postural features, gaze direction, and gender). All pictures were in gray scale. The three types of rare events were presented randomly in between the standard scramble pictures, separated by 18–20 seconds to isolate the hemodynamic responses associated with them. Participants responded by pressing a button when they detected circles. Figure adapted from references 26 and 30.

Comparison subjects were screened for depression by a geropsychiatrist (25). Exclusion criteria for all three groups included another major psychiatric illness, alcohol or drug abuse or dependence, a neurological illness, a medical illness or disability that would prevent the participant from completing the task, and contraindications to MRI. Depressed individuals who met criteria for comorbid generalized anxiety disorder were not excluded. A complete description of the study enrollment protocol is available elsewhere (25). The MADRS was used to assess symptom severity in the acutely depressed group, residual symptoms in the remitted group, and presence of symptoms in the comparison group prior to fMRI scanning. Demographic and clinical characteristics are listed in Table 1. The study was approved by the Institutional Review Board at Duke University, and all participants provided written informed consent after the procedures had been fully explained to them.

Stimuli and Experimental Design for the Oddball Task

The stimuli and design of the emotional oddball task were identical to those described previously (26). Briefly, the task used four types of pictures (Figure 1): attentional targets (circles), sad distractors, neutral distractors, and standard stimuli (phase-scrambled pictures). All of the distractors were trial unique. The presentation frequency for targets, sad distractors, and neutral distractors was 3.33% each, with scrambled pictures comprising 90% of stimuli. There were 10 runs of 1,500 stimuli in total (stimulus duration=1.5 seconds, interstimulus interval=2 seconds). The interval between successive rare stimuli (targets and/or distractors) was randomized between 18 and 20 seconds to allow hemodynamic responses to return to baseline.

Participants pressed a response button using their right index finger when they detected a target stimulus. Participants rated the distractors on a Likert-type scale of sadness/happiness immediately after scanning (26). The analysis for the sad versus neutral contrast was based on each participant's subjective rating (26). A trial was considered a "sad" distractor if the individual participant rated the image as "sad" or "very sad."

Image Acquisition and Analysis

Functional images were acquired on a 4-T GE scanner using the same acquisition parameters as described previously (26). Briefly, T₁-weighted high-resolution three-dimensional whole-brain structural images were acquired parallel to the anterior commissure-posterior commissure plane (matrix=256×256×68, slice thickness=1.9 mm). Inverse-spiral gradient functional images were acquired with 3.75 mm³ isotropic voxels (matrix=64×64×34, repetition time=2000 msec, field of view=24 cm, flip angle=60°).

Prior to statistical analyses, preprocessing steps, including repetition-time alignment, motion correction, coregistration, normalization, and smoothing (8 mm³ kernel), were performed with custom Brain Imaging and Analysis Center tools. The voxelwise and region-of-interest analyses were conducted using custom MATLAB scripts (27, 28).

For individual analyses, event epochs (sad, neutral, and target) that were time locked to the onset of each event were extracted from 4 seconds before to 20 seconds after the presence of the stimulus. Voxelwise signal percentage change at each time point was calculated after subtracting prestimulus baseline activity (from -4 seconds to 0 seconds). Averaged signal changes at 6–8

TABLE 2. Brain Regions That Revealed a Significant Group Effect on Activation and Deactivation in the One-Way Analysis of Variance of Results of an Emotional Oddball Task in Older Patients With Depression (N=12) or in Remission From Depression (N=15) and a Comparison Group (N=20)

Contrast and Brain Region	MNI Coordinates ^a			Peak F Value	Cluster Size	Post Hoc Region-of-Interest Comparisons ^b
	x	y	z			
Activation						
Sad vs. neutral						
Depressed > comparison						
Left amygdala ^c	-27	-8	-14	4.92	5	Depressed vs. comparison, p=0.013
Right amygdala	32	-7	-11	5.79	5	
Target						
Depressed < comparison and remitted						
Right middle frontal gyrus ^c (Brodmann's area 9)	25	32	35	8.06	8	Depressed vs. comparison, p=0.002; depressed vs. remitted, p=0.013
Left supramarginal gyrus (Brodmann's area 40)	-49	-32	28	10.09	17	
Right supramarginal gyrus (Brodmann's area 40)	49	-46	32	9.73	10	Depressed vs. comparison, p=0.002; remitted vs. comparison, p=0.031
Depressed and remitted < comparison						
Left anterior cingulate cortex (Brodmann's area 24)	-4	-2	33	10.55	14	Depressed vs. comparison, p<0.001; remitted vs. comparison, p=0.008
Left anterior portion of the posterior cingulate cortex (Brodmann's area 23/31)	-14	-39	39	11.81	32	
Left angular gyrus (white matter)	-28	-56	32	13.18	28	Depressed vs. comparison, p<0.001; remitted vs. comparison, p=0.002
Deactivation^d						
Target						
Depressed > comparison and remitted						
Left posterior portion of the posterior cingulate cortex ^c (Brodmann's area 30/31)	-4	-56	32	10.03	34	Depressed vs. comparison, p=0.045; depressed vs. remitted, p=0.001
Left orbitofrontal/inferior frontal area (Brodmann's area 47)	-39	25	-14	11.87	23	
Remitted < comparison and depressed						
Right orbitofrontal/inferior frontal area (Brodmann's area 47)	32	28	-18	12.75	16	Remitted vs. comparison, p=0.007; remitted vs. depressed, p<0.001
Left medial prefrontal cortex ^c (Brodmann's area 10)	-4	46	-11	9.32	37	
Right medial prefrontal cortex ^c (Brodmann's area 10)	7	53	14	15.14	26	Remitted vs. comparison, p=0.017; remitted vs. depressed, p=0.001
Left parahippocampus	-35	-28	-14	12.03	31	

^a Montreal Neurological Institute coordinates.

^b Only the results that were significant in the post hoc tests are shown here.

^c The mean activation in the region (region-of-interest analysis) was significantly correlated with MADRS score ($r>0.4$, $p<0.05$).

^d Larger magnitudes of deactivation are referred to as greater.

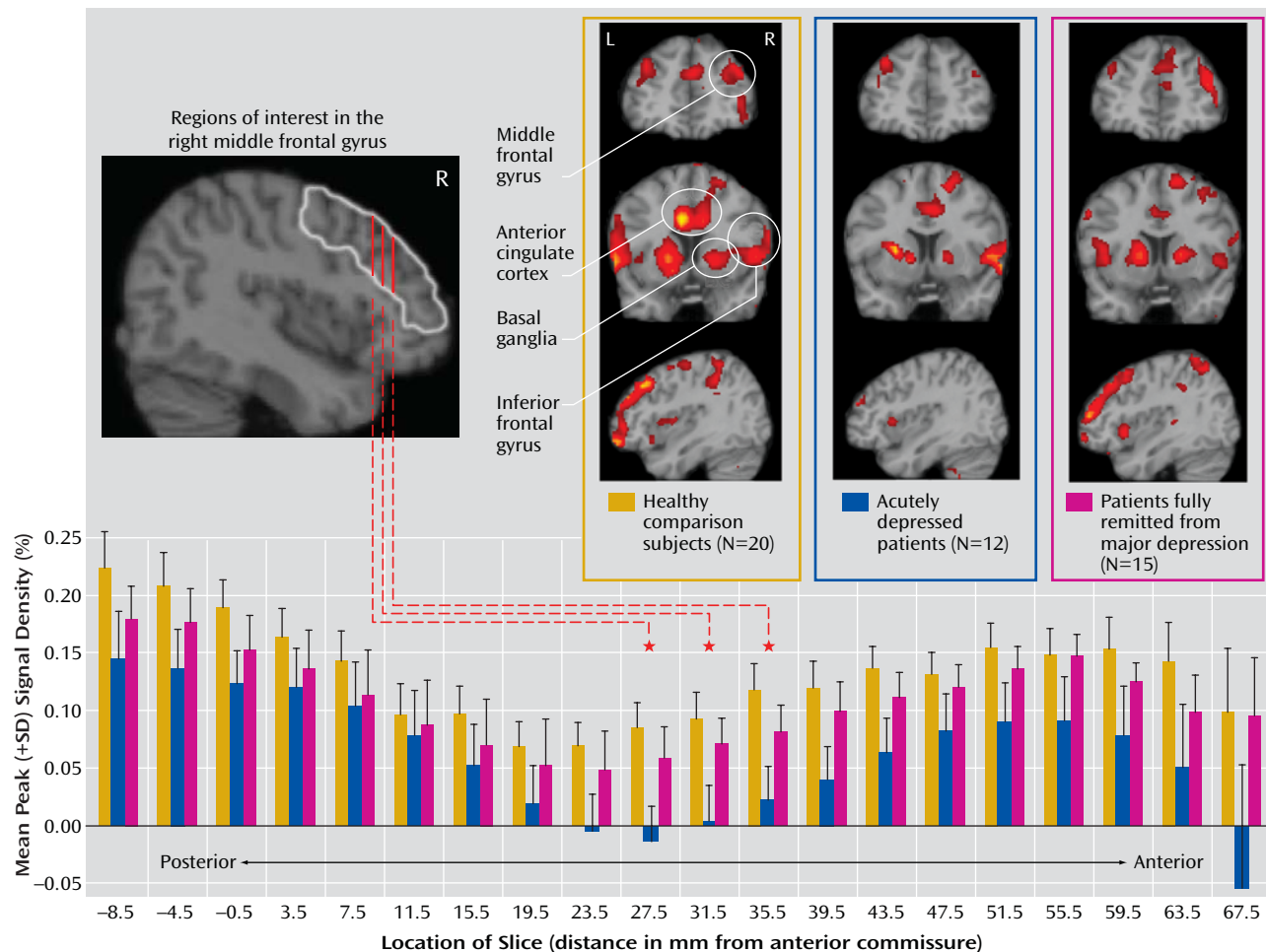
seconds poststimulus for peak activations and at 10–12 seconds for peak deactivations were used for the within- and between-group analyses. The within-group random-effects analyses were computed to generate voxel-based statistical t maps for each event ($p<0.05$, false-discovery-rate-corrected, spatial extent of five contiguous voxels). The between-group analyses were conducted only within those significant voxels identified by the within-group analyses.

Voxelwise one-way analyses of variance (ANOVAs) for studying group effect (depressed, remitted, and comparison groups) were conducted at each contrast (sad versus neutral and target versus baseline), followed by voxelwise post hoc t tests between the groups. To identify the regions that showed common alterations in the acutely depressed and remitted groups relative to the comparison group, a conjunction analysis was performed using the method of Dolcos et al. (29). To identify alterations specific to the acutely depressed group relative to the comparison group, a t test was conducted with an exclusion mask to exclude the regions that showed a significant difference between the remitted and comparison groups. The same logic was applied to the analysis of abnormalities specific to the remitted group. All these analyses were

thresholded at $p<0.001$ uncorrected, with a spatial extent of five contiguous voxels.

Given our primary interest in the dorsolateral prefrontal cortex, we drew structural regions of interest of the middle frontal gyrus bilaterally on a normalized template brain. The regions of interest were drawn on a slice-by-slice basis (4 mm each, indexed relative to the anterior commissure) using an in-house computer program guided by our prior work (26). Other regions of interest beyond this primary interest region were defined on the basis of independent clusters that showed a significant group effect in the ANOVA. To confirm the voxel-based findings, ANOVAs within each region of interest were conducted on the mean peak percent signal change by hemisphere ($p<0.05$, two-tailed). The Bonferroni test was used for the post hoc analyses. Finally, regression analysis was performed to correlate peak signal changes in each region of interest with MADRS scores using a statistical threshold of $r>0.4$ and $p<0.05$ (two-tailed). Age, education, number of episodes, and duration of illness were used as covariates. A similar regression analysis was conducted to investigate the influence of number of depressive episodes on the fMRI results.

FIGURE 2. Voxelwise Within-Group Analysis of the Three Groups in Response to Targets in an Emotional Oddball Task fMRI Study of Older Individuals, With Slice-by-Slice Structural Region-of-Interest Analysis in the Right Middle Frontal Gyrus^a



^a The three panels in the upper right show results of the voxelwise within-group analysis of the three groups in response to targets. The graph at the bottom shows the slice-by-slice structural region-of-interest analysis in the right middle frontal gyrus to illustrate the mean peak activation in response to attentional targets in the three groups. The image in the upper left shows how the region of interest was drawn on 75-mm coronal slices, each 4 mm thick, acquired along the anterior commissure-posterior commissure line. The red lines inside the region of interest indicate the slices that revealed significant attenuation in the depressed group relative to the comparison group, and the dotted red lines link these slices to the bar graph.

Results

Behavioral Results

The ANOVA revealed no significant main group effect on emotional ratings of the distractors in any emotional category (mild happy, neutral, mild sad, sad, or very sad). There was no significant group effect on reaction time to attentional targets during the scan. The mean reaction time to attentional targets for each group is listed in Table 1.

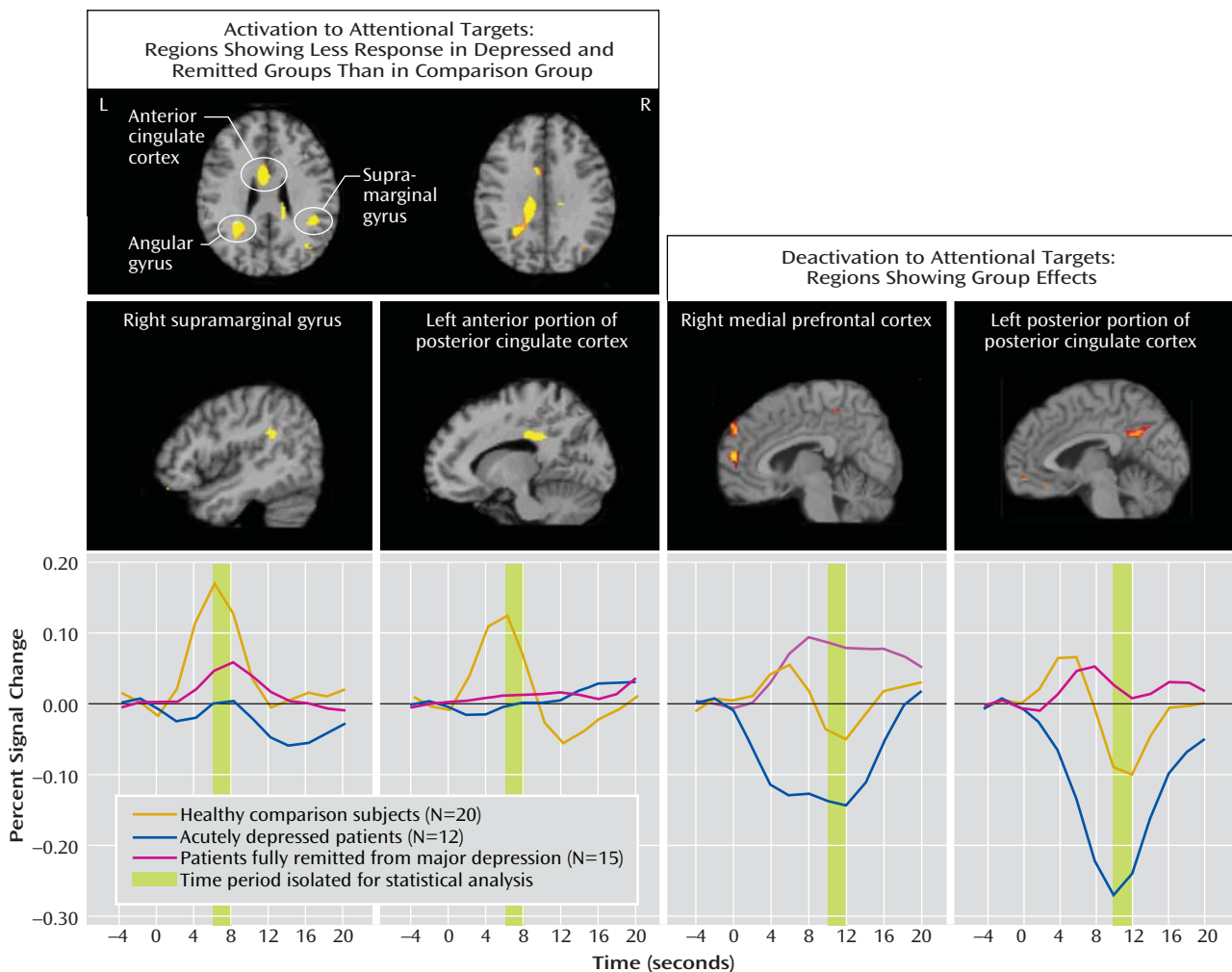
fMRI Results

Activation and deactivation to sad versus neutral distractors. The voxelwise ANOVA of the activation and deactivation in the sad versus neutral contrast did not produce any significant differences among the three groups except two small clusters of the amygdala bilaterally (Table 2). The acutely depressed patients had stronger activa-

tion in the amygdala than the comparison subjects. Given that the clusters were too small (five voxels) and were located on the border of amygdala, we limit our discussion of this finding. In the within-group analysis of this contrast in comparison subjects, our previous finding was repeated, suggesting validation of the data. The within-group results are reported in the data supplement that accompanies the online edition of this article.

Activation to attentional targets. As shown in Figure 2, the comparison group exhibited strong activation to attentional targets in the regions of the executive system, including the middle frontal gyrus bilaterally, the dorsal anterior cingulate cortex, the insula, the superior and inferior parietal lobule, the thalamus, and the striatum. These results are consistent with our previous findings in young healthy adults using the same paradigm (26). The de-

FIGURE 3. Regions Showing Activation or Deactivation to Attentional Targets in an Emotional Oddball Task fMRI Study of Older Individuals^a



^a The images at top left show brain regions that revealed significantly decreased activation in both the depressed group and the remitted group relative to the comparison group in the conjunction analysis. The graphs at bottom left show the signal percentage change in the right supramarginal gyrus (left) and the left anterior portion of the posterior cingulate cortex (right) in the three groups in the region-of-interest analysis. The images in the upper right, showing results of the voxel-based analysis of variance, indicate a group effect on the mean peak deactivation in the right medial prefrontal regions as well as the left posterior portion of the posterior cingulate cortex in response to attentional targets. The two graphs at lower right show the signal percentage change in the right medial prefrontal cortex (left) and the left posterior portion of the posterior cingulate (right) in the region-of-interest analysis.

pressed group revealed a less spatially extensive activation relative to the comparison group.

The voxelwise ANOVA revealed significantly attenuated activation to targets in the right middle frontal gyrus in the acutely depressed group relative to both the remitted group and the comparison group (Table 2). Slice-by-slice region-of-interest analysis revealed significant differences in the slices of the right middle frontal gyrus from 27.5 mm to 35.5 mm anterior to the anterior commissure (Figure 2). There were no significant differences in activation between the remitted group and the comparison group in any of the slices, nor in the whole region of interest. Thus, the attenuation of the middle frontal gyrus activation in the depressed group appears to be depressive state dependent.

The conjunction analysis revealed that both the depressed and the remitted groups had significantly reduced activation relative to the comparison group in the supra-marginal gyrus bilaterally, the left anterior cingulate cortex, the anterior portion of posterior cingulate, and the white matter area of the left angular gyrus (Figure 3). There was no significant difference in activation between the depressed and remitted groups. Of particular note is that some of the regions showing consistent attenuation in patients fall within the white matter area, namely, the superior longitudinal fasciculi (Figure 3).

Deactivation to attentional targets. Compared with baseline, the attentional targets revealed significant deactivation in the comparison group in the dorsomedial pre-

frontal cortex bilaterally, the ventromedial prefrontal cortex, the hippocampal/parahippocampal complex, the posterior portion of the posterior cingulate cortex, the cuneus, and the middle occipital gyrus. The depressed group showed deactivation in a regional distribution similar to the comparison group, whereas in the remitted group no region demonstrated deactivation. The within-group results are summarized in the online supplement (Table S3 and Figure S1).

The ANOVA revealed a significant group effect on deactivation in response to targets in the right lateral orbitofrontal/inferior frontal area (Brodmann's area 47), the medial prefrontal cortex bilaterally, the left parahippocampus, and the left posterior portion of the posterior cingulate (Table 2, Figure 3). The deactivation in the left posterior portion of the posterior cingulate area indicates a depressive state-dependent effect in that the deactivation was enhanced significantly in the depressed group relative to the remitted and comparison groups (Table 2, Figure 3). The remitted group revealed reduced deactivation in the posterior portion of the posterior cingulate, although the magnitude of the activity did not significantly differ from that of the comparison group.

In the lateral orbitofrontal/inferior frontal area bilaterally (Brodmann's area 47), the medial prefrontal area bilaterally (medial prefrontal cortex, Brodmann's areas 8, 9, and 10), and the left parahippocampus area, the depressed and comparison groups showed comparable deactivation, whereas the remitted group showed activation rather than deactivation (Figure 3 and Table 2).

Correlations With MADRS Score

The activities in response to targets in the following regions were correlated with MADRS score across all patients: the activation in the right middle frontal gyrus ($r = -0.44$, $p = 0.021$), the deactivations in the left posterior portion of the posterior cingulate ($r = -0.47$, $p = 0.013$), and the deactivation in the right medial prefrontal cortex ($r = -0.60$, $p = 0.001$). The correlations in the right middle frontal gyrus and the medial prefrontal cortex remained significant after controlling for age, education, number of depressive episodes, and duration of illness. However, the correlation in the left posterior portion of the posterior cingulate was not significant after controlling for education or the number of depressive episodes. Number of episodes tended to be positively correlated with the deactivation in the left posterior portion of the posterior cingulate ($r = 0.37$, $p = 0.06$), which may have been driven by the remitted group (depressed group: $r = 0.018$, $p = 0.96$; remitted group: $r = 0.39$, $p = 0.14$). Interestingly, in the remitted group, the greater the severity of depressive symptoms, the larger the magnitude of deactivation in the left posterior portion of the posterior cingulate, whereas the greater the number of depressive episodes, the less deactivation there tended to be.

Notably, none of the above correlations were significant within the depressed group alone. The scatterplots indicated

that the correlations were driven mainly by depressive state. Thus, the correlations of neural responses with MADRS scores across the depressed and remitted groups confirmed a depressive state-dependent effect in these regions.

Discussion

The major findings of this study of older individuals were several. First, acutely depressed patients showed decreased activation in the right middle frontal gyrus during target detection, which was depressive state dependent. Second, remitted patients demonstrated attenuated activation during target detection comparable to that of the depressed patients in the cingulate and inferior parietal areas, suggesting disease-related alterations in these regions. Third, while the attenuated activation of the anterior portion of the posterior cingulate might be disease related, the enhanced deactivation of the posterior portion was depressive state dependent, which suggests that the anterior and posterior portions of the posterior cingulate appear to have distinct roles in geriatric depression. Finally, the remitted group had diminished deactivation in the default-mode network during target detection. Notably, these significant differences among the three groups were mainly revealed during target detection but not during emotional processing, which suggests that executive dysfunction is a prominent deficit in geriatric depression. The changes in response to emotional stimuli in geriatric depression will need further confirmation in larger samples.

The attenuated activation to targets in the depressed group in the middle frontal gyrus (dorsolateral prefrontal cortex) is consistent with findings from Aizenstein et al. (16) and with our findings in young depressed patients using the same task (30). The significantly increased activation in this region in the remitted group relative to the acutely depressed group is also consistent with some of the studies of young depressed patients (2, 3, 5, 31, 32), which showed normalized activation after medication. Thus, our results confirm the important contribution of the right dorsolateral prefrontal cortex to the depressive state.

The inferior parietal and cingulate regions have been consistently activated during attentional and working memory tasks (26, 28, 33). Alterations in these regions in both patient groups indicate executive dysfunction, which could be related to factors that are primarily associated with pathological changes in geriatric depression, such as those caused by cerebrovascular disease. Although a causal link between ischemic lesions and geriatric depression remains controversial (34), ischemic lesions, particularly white matter hyperintensities, may explain in part the persistently attenuated activation in fully remitted depressed patients. Interestingly, persistent attenuation was also observed in white matter areas (the superior longitudinal fasciculi), which has been related to an indirect effect of white matter hyperintensities. Alternatively, the alteration could be a disease marker reflecting a "scar" left

from prior depressive episodes, even in the absence of clinical symptoms. Further evidence of association between fMRI findings, diffusion tensor imaging findings (35), and the residual symptoms in remitted patients would help to elucidate the significance of the persistently attenuated activation in these regions.

The anterior portion of the posterior cingulate (Brodmann's area 23/31) is heavily interconnected with the dorsal anterior cingulate cortex (Brodmann's area 24) and the dorsolateral prefrontal cortex (Brodmann's area 46) (36) and appears to be one of the key nodes of the attention-cognition component in Mayberg's depressive model (37). Our data suggest a strong link of this anterior portion of the posterior cingulate region with the pathology of geriatric depression. The posterior portion (Brodmann's area 30/31) is more closely connected with the retrosplenial cortex and the hippocampal complex. Together with the precuneus, the region of the posterior portion of the posterior cingulate has been implicated in self-consciousness and memory retrieval (22). The enhanced deactivation of this region in the acutely depressed patients, which is opposite to the changes in mild cognitive impairment and Alzheimer's disease (22, 23), implies that it may be possible to differentiate between cognitive dysfunction in acute depression and cognitive changes seen in mild cognitive impairment. Lack of deactivation in Alzheimer's disease and mild cognitive impairment might suggest less task engagement and impaired memory retrieval processing, whereas the increased deactivation in acutely depressed patients might reflect increased task processing demands due to limited attentional resources or baseline hyperactivity due to an active tendency toward rumination.

The lack of deactivation in our remitted group might reflect a biomarker in this group that might signify the intermediate state, characteristic changes related to antidepressants or depressive episodes, cognitive decline, or a response secondary to vascular change. Our remitted group tended to have more depressive episodes and a longer period of exposure to antidepressants than the acutely depressed group. More depressive episodes tended to be correlated with less deactivation of the posterior portion of the posterior cingulate in the remitted group but not in the acutely depressed group, which suggests a stronger influential effect of remission state than of number of depressive episodes. A preliminary comparison between the six acutely depressed and six remitted patients who were on monotherapy with an SSRI (data not shown) revealed that the differences in activations and deactivations between the two groups remained significant (two-sample *t* test, $p < 0.01$). Thus, the state of depression or remission seemed to have a greater effect on our results than use of antidepressants. However, our sample is too small to support this conclusion. The effect of antidepressant medication on vigilance, arousal, and attention varies greatly among the anti-

depressants (38), and the influence of different antidepressants on deactivation associated with vigilance, arousal, or attention remains to be clarified. The Mini-Mental State Examination score in the remitted group was relatively higher than in the acutely depressed group. Therefore, it is also less likely that the diminished deactivation was due to more severe cognitive dysfunction in the remitted group. In short, the lack of deactivation appeared to be a characteristic change related to the remission state. Nevertheless, further studies with antidepressant medication-free patients, studies of the effects of different antidepressants, and detailed evaluation of cognitive function among the three groups will be important for understanding the deactivation pattern in the remitted subjects.

In addition to antidepressants, antihypertensive medications could affect participants' hemodynamic response. The ratio of participants with to those without antihypertensive medication in the depressed group was higher than in the remitted and comparison groups (Table 1). In future studies, matching hypertension and possibly other medical conditions as well as combining perfusion images in larger samples should be undertaken.

To our knowledge, this is the first fMRI study to evaluate emotional and cognitive function simultaneously in geriatric samples of patients with depression and patients remitted from depression. The attenuated activation in the parietal and cingulate regions, including in white matter areas, in both the depressed and remitted groups seem to be pathology related and warrant further investigation. Notably, this study suggests an important role for the posterior cingulate cortex in geriatric depression. Future studies directly comparing task-induced deactivation in patients with depression and mild cognitive impairment, patients with depression and no mild cognitive impairment, and patients with mild cognitive impairment and no depression may help in clinical differentiation and intervention in geriatric depression.

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