

# Ventromedial Prefrontal Cortex and Amygdala Dysfunction During an Anger Induction Positron Emission Tomography Study in Patients With Major Depressive Disorder With Anger Attacks

Darin D. Dougherty, MD, MSc; Scott L. Rauch, MD; Thilo Deckersbach, PhD; Carl Marci, MD; Rebecca Loh, BS; Lisa M. Shin, PhD; Nathaniel M. Alpert, PhD; Alan J. Fischman, MD, PhD; Maurizio Fava, MD

**Context:** Although a variety of functional neuroimaging studies have used emotion induction paradigms to investigate the neural basis of anger in control subjects, no functional neuroimaging studies using anger induction have been conducted in patient populations.

**Objective:** To study the neural basis of anger in unmedicated patients with major depressive disorder with anger attacks (MDD+A), unmedicated patients with MDD without anger attacks (MDD-A), and controls.

**Design:** We used positron emission tomography, psychophysiological measures, and autobiographical narrative scripts in the context of an anger induction paradigm.

**Setting:** Academic medical center.

**Participants:** Thirty individuals, evenly divided among the 3 study groups.

**Interventions:** In separate conditions, participants were exposed to anger and neutral autobiographical scripts during the positron emission tomography study. Subjective self-report and psychophysiological data were also collected.

**Main Outcome Measures:** Voxelwise methods were used for analyses of regional cerebral blood flow changes for the anger vs neutral contrast within and between groups.

**Results:** Controls showed significantly ( $P < .001$ ) greater regional cerebral blood flow increases in the left ventromedial prefrontal cortex during anger induction than patients with MDD+A, whereas these differences were not present in other between-group analyses. Also, in controls, an inverse relationship was demonstrated between regional cerebral blood flow changes during anger induction in the left ventromedial prefrontal cortex and left amygdala, whereas in patients with MDD+A there was a positive correlation between these brain regions during anger induction. There was no significant relationship between these brain regions during anger induction in patients with MDD-A.

**Conclusion:** These results suggest a pathophysiology of MDD+A that is distinct from that of MDD-A and that may be responsible for the unique clinical presentation of patients with MDD+A.

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From the Departments of Psychiatry (Drs Dougherty, Rauch, Deckersbach, Marci, Shin, and Fava and Ms Loh) and Radiology (Drs Dougherty, Rauch, Alpert, and Fischman), Massachusetts General Hospital and Harvard Medical School, Boston, Mass; and the Department of Psychology, Tufts University, Medford, Mass (Dr Shin).

**M**AJOR DEPRESSIVE DISORDER (MDD) is a clinical syndrome characterized by affect dysregulation, neurovegetative symptoms, autonomic disturbances, and endocrine abnormalities. Freud<sup>1</sup> theorized that depression resulted from anger turned inward. In fact, numerous studies<sup>2-8</sup> have demonstrated that depressed patients have higher rates of anger and aggression than controls. One study<sup>9</sup> even found that the degree of anger expressed inward in depressed patients correlated with the severity of depressive symptoms.

The concept of "anger attacks" in patients with MDD was introduced by Fava and colleagues<sup>10</sup> in 1990. These anger at-

tacks are characterized by sudden spells of anger that are inappropriate to the situation in which they occur and are uncharacteristic of the patient's usual behavior. In addition, clinical characterization of this depressive subtype reveals that patients with MDD with anger attacks (MDD+A) have higher scores on measures of hostility, anxiety, and somatization than patients with MDD without anger attacks (MDD-A).<sup>11</sup> The prevalence of anger attacks in depressed patients is approximately 30% to 40%,<sup>4,5,11-14</sup> and the attacks resolve after successful treatment of the depressive episode.<sup>5,11,12</sup>

Studies<sup>15</sup> have demonstrated that symptoms of anger or aggression may have a prevalence as high as 50% in outpatient psychiatric populations, indicating that an-

**Table 1. Demographic Characteristics of the 30 Study Participants**

Characteristic	MDD + A Group (n = 10)	MDD - A Group (n = 10)	Control Group (n = 10)
Sex, M/F, No.	5/5	4/6	5/5
Age, mean ± SD, y	35.40 ± 14.62	36.90 ± 9.33	33.90 ± 11.85
HAM-D score, mean ± SD	20.90 ± 4.72	17.50 ± 3.37	NA

Abbreviations: HAM-D, Hamilton Depression Rating Scale; MDD + A, major depressive disorder with anger attacks; MDD - A, MDD without anger attacks; NA, not applicable.

ger or aggression may be as common as symptoms of depression and anxiety in this population. Anger and aggression are especially common in patients with diagnoses of MDD, bipolar disorder, intermittent explosive disorder (IED), and cluster B personality disorders. Despite the high prevalence of anger and aggression in psychiatric populations and the obvious public health impact of these symptoms, the role of anger and aggression in psychiatric illness has been understudied. In addition, anger and hostility are associated with higher rates of coronary artery disease,<sup>16-18</sup> myocardial infarction,<sup>19-22</sup> and abnormal glucose metabolism.<sup>23-27</sup> Given that depression itself is a significant risk factor for heart disease<sup>28-30</sup> and diabetes mellitus,<sup>31,32</sup> it would seem that individuals with MDD+A would be especially at risk for medical consequences. Thus, the societal costs of anger and aggression in psychiatric illness stem from the consequences of violence and the medical sequelae associated with anger and hostility. In patients with MDD+A, these costs to society are above and beyond the already staggering financial burden of depression.<sup>33</sup> These findings underscore the importance of elucidating the pathophysiology of anger and aggression in psychiatric illness and of conducting clinical trials in the search for effective treatments.

Converging data implicate a network of brain regions in the pathophysiology of MDD. These regions include, but are not limited to, territories of the prefrontal cortex (PFC), anterior cingulate cortex, and medial temporal lobe structures, including the amygdala and hippocampus.<sup>34-38</sup> Current conceptualization of the underlying neuroanatomy of anger and aggression implicates the amygdala and related temporolimbic structures, the hypothalamus, the anterior cingulate cortex, and the PFC (most notably the ventral PFC) as brain regions involved in mediating aggression.<sup>39-41</sup> Although a variety of functional neuroimaging studies<sup>42-46</sup> have used emotion induction paradigms to investigate the neural basis of anger in control subjects, no functional neuroimaging studies have been conducted in individuals who are diagnosed as having MDD and who have a predilection for anger, aggressive behavior, or both. The present study uses positron emission tomography (PET) and autobiographical narrative scripts to study the neural basis of anger, particularly the relationship between the ventral PFC and the amygdala, in unmedicated patients with MDD+A, unmedicated patients with MDD-A, and control sub-

jects. There is especially strong evidence that anger and aggression seen in a multitude of diagnoses are associated with hypofunctionality of the ventral PFC and amygdala.<sup>47-52</sup> In contrast, numerous studies<sup>36,53,54</sup> have demonstrated greater activity in the ventral PFC and amygdala in patients with MDD compared with control subjects. These results strongly suggest that ventral PFC and amygdala function should differentiate patients with MDD+A and patients with MDD-A from each other and from control subjects and form the basis for our a priori hypotheses. Specifically, we predicted (1) that, based on previous results from our laboratory<sup>44</sup> and others,<sup>42,43,45,46</sup> the control group would exhibit activation of the ventral PFC with corresponding deactivation of the amygdala during anger induction, (2) that the MDD+A group would exhibit diminished activation in the ventral PFC and amygdala during anger induction relative to the control group and the MDD-A group, and (3) that the MDD-A group would have greater activation in these same brain regions during anger induction relative to the control group and the MDD+A group.

## METHODS

### PARTICIPANTS

The study sample was composed of 30 individuals divided evenly among 3 study groups: MDD+A, MDD-A, and controls. All 3 study groups were matched for age and sex; the 2 MDD groups were also matched for depression severity (**Table 1**). The study was conducted in accordance with the guidelines of the Human Subjects in Research Committee of the Massachusetts General Hospital. Written informed consent was obtained from each participant. All participants were right-handed (Edinburgh Inventory<sup>55</sup>) and had normal hearing and normal/corrected-to-normal vision. Exclusion criteria included pregnancy, a history of a major medical or neurologic disorder, a history of head injury, a history of seizure disorder, and current use of psychotropic medications.

#### Patients With MDD

All patients participating in this study were recruited through the Depression Clinical and Research Program at Massachusetts General Hospital. All patients underwent comprehensive evaluation by the Depression Clinical and Research Program staff. A full medical and psychiatric history was performed by a study psychiatrist. During the screening visit, the patients were administered the *Structured Clinical Interview for DSM-IV Disorders*,<sup>56</sup> the Anger Attacks Questionnaire,<sup>4</sup> and the 17-item Hamilton Depression Rating Scale.<sup>57</sup> Inclusion criteria were a DSM-IV diagnosis of major depression, single or recurrent, of at least 4 weeks' duration at the time of the screening visit. Exclusion criteria included current or past Axis I diagnoses other than MDD and a history of mood congruent or mood incongruent psychotic features.

In addition, patients had a diagnosis of MDD+A subtype based on the Anger Attacks Questionnaire,<sup>4</sup> a 7-item self-rating instrument designed to assess the presence or absence during the previous month of anger attacks, defined as spells of anger inappropriate to the situation.

#### Control Subjects

Controls were recruited by advertisements in the community. Subjects participated in a screening, including administration

of the *Structured Clinical Interview for DSM-IV Disorders*,<sup>56</sup> to ascertain their relevant psychiatric, medical, and neurologic history. None of the controls had a history of major neurologic, medical, or psychiatric disorders.

## SCRIPTS

Scripts of participants' past personal events were prepared according to a previously published procedure.<sup>44,58-61</sup> Each participant provided a written description of the 2 life events corresponding to when they were the most and second most angry. Two autobiographical neutral scripts (eg, going for a walk and cooking dinner) were likewise developed. After describing each event, the participant examined a list of bodily responses (eg, "heart racing" and "labored breathing") and circled those responses (if any) that they experienced at the time. Based on the material furnished by the participants, an investigator (D.D.D.) composed a script in the second person, present tense and then audiotaped it in a neutral voice for playback in the laboratory. All scripts were 30 to 40 seconds in duration.

## PET STATE INDUCTION PARADIGM

After habituation to the PET suite environment, participants were scanned 8 times as part of a larger study. Two scans corresponded to the anger condition, 2 scans corresponded to the neutral condition, and 4 scans corresponded to other script-induced emotions. Neutral conditions were performed first and last, whereas the order of the remaining 3 conditions (anger and the other induced emotions) was counterbalanced across participants. Before each scan, the participant was instructed as follows: "Close your eyes, listen carefully to the script, and imagine the event portrayed as vividly as possible, as if you are actually participating in the event rather than just 'watching yourself' in it." Then the audiotape was played. During the 60 seconds immediately after the script audiotape, as per instructions, participants continued to recall and imagine the event while PET data were acquired. The <sup>15</sup>O-carbon dioxide administration and PET data acquisition were then terminated, and the participant was instructed to stop imagining the event. Positron emission tomographic scans were separated by at least 10 minutes to allow for radiation decay to negligible levels. In addition, psychophysiological measures were required to return to within 10% of baseline values before beginning the next PET scan.

## EMOTIONAL STATE ANALOG SCALES

After scanning, the participants rated their emotional responses (ie, happiness, sadness, anger, fear, disgust, surprise, guilt, and shame) to each script on separate subjective 0- to 10-point analog scales,<sup>44,59-61</sup> where 0 indicated the "complete absence of a response" and 10 indicated the "maximum possible response" for the specified emotion. The participants also completed similar analog scales for difficulty recalling the event, vividness of imagery, and strength of visual, auditory, tactile, olfactory, and gustatory imagery. Paired *t* tests were used to compare differences in analog scale scores between conditions.

## PSYCHOPHYSIOLOGIC ASSESSMENT

Psychophysiological assessment was performed during the PET study using equipment from ADInstruments (Sydney, Australia). Measured parameters included heart rate and galvanic skin response (GSR). Psychophysiological parameters were recorded continuously during the PET study. For purposes of data analyses, data were calculated during 2 epochs associated with each scan: 30 seconds before the reading of the script (baseline) and 1 minute during each scan (imagery). Within the baseline and imagery pe-

riods (within each scan), heart rate values were averaged, whereas GSR values were calculated using area under the curve (AUC) methods. For each scan, the values of the baseline period were subtracted from the values of the imagery period. Paired *t* tests, analyses of variance, and independent *t* tests were used, where appropriate, for psychophysiological data analyses.

## PET FACILITIES AND PROCEDURES

### PET Camera

A 15-slice whole-body tomograph (model PC4096; Scanditronix/General Electric Medical Systems, Milwaukee, Wis) was used in its stationary mode to acquire the PET data.<sup>62</sup> The slice geometry consists of contiguous slices with center-to-center distance of 6.5 mm (axial field equal to 97.5 mm) and axial resolution of 6.0-mm full width at half maximum. Image reconstruction was performed using a computed attenuation correction and a Hanning-weighted reconstruction filter set to yield 8.0-mm in-plane spatial resolution full width at half maximum. Additional corrections were made in the reconstruction process to account for scattered radiation, random coincidences, and counting losses due to dead time in the camera electronics.

### Participant Positioning

Head alignment was made relative to the canthomeatal line using projected laser lines whose positions were known with respect to the slice positions of the scanner. An individually molded thermoplastic mask was used to minimize head motion. Once the head was in place, the patient was fitted with a pair of nasal cannulae and an overlying face mask, which were attached to radiolabeled gas inflow and vacuum, respectively.

### Image Acquisition

The participants were studied while continuously inhaling tracer quantities of <sup>15</sup>O-carbon dioxide mixed with room air. The concentration of the delivered gas was 2960 MBq/L (80 mCi/L), with a flow rate of 2 L/min, further diluted by free mixture with room air within the face mask, resulting in a rapidly rising count rate in the brain, reaching terminal count rates of 100 000 to 200 000 events per second. Previous work at Massachusetts General Hospital using radial artery cannulation has demonstrated that the integrated counts over inhalation periods up to 90 seconds are a linear function over the flow range of 0 to 130 mL/min per 100 g (N.M.A., unpublished data, 1991). Therefore, for data to be produced with units of flow relative to the whole brain, no arterial access was necessary.

### PET Data Analysis

Statistical analysis of the PET data was conducted following the theory of statistical parametric mapping.<sup>63,64</sup> Data were analyzed using a software package (SPM99; Wellcome Department of Cognitive Neurology, London, England). Positron emission tomographic images were motion corrected, spatially normalized to the standardized normalized space established by the Montreal Neurological Institute (MNI) (available at: <http://www.bic.mni.mcgill.ca>), and smoothed to 10-mm full width at half maximum. At each voxel, the PET data were normalized by the global mean and fit to a linear statistical model by the method of least squares. Planned contrasts at each voxel were conducted; this method fits a linear statistical model, voxel by voxel, to the data, and hypotheses were tested as contrasts in which linear compounds of the model parameters were evaluated using *t* statistics, which were then transformed to *z* scores.

Region of interest (ROI) definition for interregional correlation analyses (described in the "VMPFC ROI-Based Interregional Correlation Analyses" subsection) was conducted using MarsBaR software.<sup>65</sup>

We report regions containing foci of activation with  $z$  scores  $\geq 3.09$  (corresponding to  $P \leq .001$  [1-tailed], uncorrected for multiple comparisons). Note that the data were inspected in a hierarchical manner: first, regions from the a priori hypotheses were inspected, then the entire brain volume was inspected, and post hoc findings are reported using a comparable threshold to obviate bias.

## RESULTS

All values are reported as mean  $\pm$  SD.

### SUBJECTIVE SELF-REPORT DATA

Analyses of the self-report data revealed that compared with the neutral condition, the anger condition was associated with a higher rating of anger in all 3 groups. The mean difference in anger between the anger and neutral conditions was  $7.06 \pm 1.85$  ( $t_{17} = 16.18$ ) for patients with MDD+A,  $7.11 \pm 2.32$  ( $t_{19} = 13.70$ ) for patients with MDD-A, and  $6.91 \pm 2.57$  ( $t_{10} = 12.04$ ) for control subjects ( $P < .001$  for all). In addition, the anger self-report score difference between the anger and neutral conditions was significantly larger than any of the other emotional self-report score differences ( $t_{55} = 3.36$ ;  $P = .02$  compared with disgust, the self-report score with the next largest difference between the anger and neutral conditions). All patients confirmed that the emotional state achieved was reflective of an anger state and that visual and auditory modes represented its most prominent imagery components.

### PSYCHOPHYSIOLOGIC DATA

Psychophysiologic data were successfully collected in 7 patients with MDD+A, 7 patients with MDD-A, and 10 control subjects; missing data were attributable to technical difficulties.

#### Within-Group Observations

The average change in heart rate for patients with MDD+A from the neutral condition to the anger condition was  $3.53 \pm 5.72$  bpm, which was a significant increase ( $t_{12} = 2.23$ ;  $P = .046$ ). These patients also experienced an increase in GSR AUC of  $72.69 \pm 112.75$  microsiemens during the anger condition, which was significant ( $t_{12} = 2.32$ ;  $P = .04$ ).

In patients with MDD-A, the average change in heart rate from the neutral condition to the anger condition was  $0.50 \pm 8.24$  bpm, which was not significant ( $t_{13} = 0.23$ ;  $P = .82$ ). However, these patients experienced a significant decrease in GSR AUC of  $-55.27 \pm 62.71$  microsiemens during the anger condition ( $t_{13} = -3.30$ ;  $P = .006$ ).

The average change in heart rate for control subjects from the neutral condition to the anger condition was  $5.83 \pm 7.57$  bpm, which was a significant increase ( $t_{10} = 3.44$ ;  $P = .003$ ). These subjects also experienced an increase in GSR AUC of  $81.80 \pm 96.99$  microsiemens dur-

ing the anger condition, which was significant ( $t_{10} = 3.77$ ;  $P < .001$ ).

#### Between-Group Observations

Analysis of variance revealed that a significant difference exists between groups in GSR AUC ( $F_{2,44} = 10.114$ ;  $P < .001$ ) but not in heart rate ( $F_{2,44} = 2.173$ ;  $P = .13$ ). Further analyses confirmed that although no difference existed between the control and MDD+A groups in GSR response ( $t_{31} = 0.27$ ;  $P = .96$ ), a significant difference was detected between patients with MDD-A and control subjects ( $t_{32} = -4.22$ ;  $P < .001$ ) and between patients with MDD-A and those with MDD+A ( $t_{25} = -3.56$ ;  $P = .003$ ).

### PET DATA

#### Within-Group Analyses

In the control group, the anger vs neutral comparison demonstrated increased regional cerebral blood flow (rCBF) in the left ventromedial PFC (VMPFC) (**Table 2**). Regarding the a priori territories of interest, no significant activations were found in within-group analyses involving the MDD+A and MDD-A groups.

#### Between-Group Analyses

Regarding a priori hypotheses, the between-group analyses revealed greater rCBF increases in the control group than in the MDD+A group in the left VMPFC during the anger vs neutral comparison (**Table 3** and **Figure 1**). These differences were not present in other between-group analyses. Last, there were no between-group differences in rCBF changes in the amygdala during the anger vs neutral comparison.

#### VMPFC ROI-Based Interregional Correlation Analyses

Interregional correlation analyses examining the relationship between rCBF responses in the left VMPFC and those in the rest of the brain were conducted in each group for the anger vs neutral comparison (**Table 4** and **Figure 2**). We defined a functional ROI in the left VMPFC (MNI coordinates = -8, 62, -10) based on the anger vs neutral comparison in the control group. We then extracted rCBF values from the ROI and conducted a correlational analysis between these ROI values and whole-brain, voxelwise rCBF changes in the anger vs neutral comparison for each group. Based on known bidirectional connections between the PFC and the amygdala and evidence that these 2 structures are mutually inhibitory, we hypothesized that these interregional correlation analyses would demonstrate an inverse correlation of rCBF changes during anger induction between the left VMPFC and the left amygdala in the control group. The analysis confirmed this hypothesis (Table 4 and Figure 2). Identical interregional correlation analyses of rCBF changes during anger induction did not demonstrate any significant relationship between the left VMPFC and the left amygdala in the MDD-A group (Table 4). However, interregional correlation analyses of rCBF changes

**Table 2. Results of Voxelwise Within-Group Analyses of Anger Induction**

Brain Region (BA)	Maximum Voxel z Score	MNI Coordinates
<b>Control Subjects</b>		
Anger-neutral		
A priori		
Ventromedial prefrontal cortex	3.57	-8, 62, -10
Post hoc		
Medial prefrontal cortex (10)	3.89	2, 60, 26
	3.32	16, 50, 12
Superior temporal cortex (42)	3.93	52, -30, -2
Cerebellum	3.34	10, -62, -20
Neutral-anger		
A priori		
None	...	...
Post hoc		
Anterior temporal pole (38)	3.44	34, 10, -30
Basal forebrain	3.35	8, 6, -12
Inferior temporal cortex (37)	4.09	54, -56, -12
Parietal (40)	3.93	-58, -32, 34
	3.37	58, -24, 26
<b>Patients With MDD + A</b>		
Anger-neutral		
A priori		
None	...	...
Post hoc		
Hippocampus	4.27	-12, -38, 0
Medial prefrontal cortex (10)	4.00	-26, 66, 8
Insula	3.45	-30, 12, 2
Cerebellum	3.51	18, -54, -24
	3.21	12, -74, -18
Neutral-anger		
None	...	...
<b>Patients With MDD - A</b>		
Anger-neutral		
A priori		
None	...	...
Post hoc		
Anterior cingulate cortex (24)	3.40	4, 18, 20
Middle temporal cortex (21)	4.13	-48, -12, -10
Posterior thalamus	3.76	-12, -24, 16
Neutral-anger		
A priori		
None	...	...
Post hoc		
Hippocampus	3.64	18, -42, -4
Middle temporal cortex (21)	5.61	62, -26, -16
	3.55	54, -52, 8
Posterior cingulate cortex (23)	4.05	-6, -58, 14
Brainstem	3.42	6, -12, -12
Superior temporal cortex (38)	3.30	48, 6, -12
Parietal (40)	3.28	58, -34, 28

Abbreviations: BA, Brodmann area; MNI, Montreal Neurological Institute; MDD + A, major depressive disorder with anger attacks; MDD - A, MDD without anger attacks.

during anger induction in the MDD + A group revealed a positive correlation between the left VMPFC and the left amygdala (Table 4 and Figure 2).

Last, to perform a statistical comparison of these correlations between groups, we defined functional ROIs in the left amygdala based on the interregional correlation analyses. One functional ROI corresponded to the left

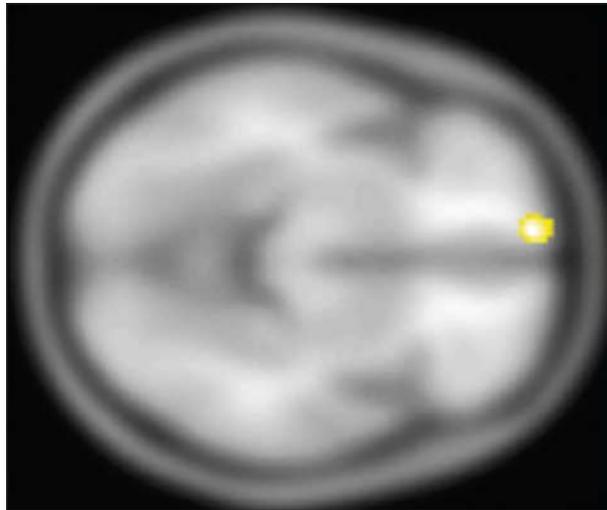
**Table 3. Results of Voxelwise Between-Group Analyses of Anger Induction**

Brain Region (BA)	Maximum Voxel z Score	MNI Coordinates
<b>MDD + A vs Controls</b>		
Anger-neutral; MDD + A > controls		
A priori		
None	...	...
Post hoc		
Insula	3.25	-32, 12, 2
Middle temporal cortex (37)	3.41	48, -60, -6
Cerebellum	3.26	44, -70, -22
Anger-neutral; controls > MDD + A		
A priori		
Ventromedial prefrontal cortex	3.92	-10, 62, -10
Post hoc		
Medial prefrontal cortex (10)	3.36	4, 58, 24
<b>MDD - A vs Controls</b>		
Anger-neutral; MDD - A > controls		
A priori		
None	...	...
Post hoc		
Middle temporal cortex (21)	4.32	-50, -12, -6
Anger-neutral; controls > MDD - A		
A priori		
None	...	...
Post hoc		
Middle temporal cortex (21)	5.20	62, -26, -16
<b>MDD + A vs MDD - A</b>		
Anger-neutral; MDD + A > MDD - A		
A priori		
None	...	...
Post hoc		
Hippocampus	3.97	-12, -36, 2
Middle temporal cortex (21)	4.05	56, -26, -16
	3.29	52, -50, 8
Anger-neutral; MDD - A > MDD + A		
A priori		
None	...	...
Post hoc		
None	...	...

Abbreviations: BA, Brodmann area; MNI, Montreal Neurological Institute; MDD + A, major depressive disorder with anger attacks; MDD - A, MDD without anger attacks.

amygdala locus from the interregional correlation analyses in the control group (MNI coordinates = -22, 2, -12) (Table 4), and the other functional ROI corresponded to the left amygdala locus from the interregional correlation analyses in the MDD + A group (MNI coordinates = -22, -12, -22) (Table 4). Then, separate within-group analyses were conducted to determine the degree of correlation between rCBF values from the left VMPFC ROI and the 2 amygdala ROIs. As expected, there was a significant inverse correlation between left VMPFC ROI rCBF values and rCBF values from the left amygdala ROI derived from the control group interregional correlation analyses in the control group ( $r = -0.87$ ;  $P < .001$ ) but not in the MDD + A ( $r = -0.08$ ;  $P = .83$ ) and MDD - A ( $r = -0.07$ ;  $P = .85$ ) groups. As would also be expected, there was a significant positive correlation between left VMPFC ROI rCBF values and rCBF values from the left amygdala ROI derived from the MDD + A group interregional

correlation analyses in the MDD+A group ( $r=0.90$ ;  $P<.001$ ) but not in the MDD-A ( $r=-0.14$ ;  $P=.69$ ) and control ( $r=0.31$ ;  $P=.38$ ) groups. Fisher  $z$  transformation of the within-group correlation coefficients was used to perform a statistical comparison of these correlations between groups. The correlation coefficient arising from the comparison of left VMPFC ROI rCBF values and rCBF



**Figure 1.** A statistical parametric map of positron emission tomography data corresponding to a between-group comparison of the anger vs neutral conditions is superimposed over a nominally normal magnetic resonance image in Montreal Neurological Institute space for gross anatomic reference. Voxels exceeding the  $z$  score threshold of 3.09 are shown in yellow. This image is an axial section demonstrating that control subjects have a significantly greater regional cerebral blood flow increase in the left ventromedial prefrontal cortex than patients with major depressive disorder with anger attacks.

values from the left amygdala ROI derived from the control group interregional correlation analyses in the control group ( $r=-0.87$ ) differed significantly from the identical comparisons in the MDD-A and MDD+A groups ( $P=.02$  for both), whereas the MDD-A and MDD+A groups did not differ significantly from one another ( $P=.99$ ). The correlation coefficient arising from the comparison of left VMPFC ROI rCBF values and rCBF values from the left amygdala ROI derived from the MDD+A group interregional correlation analyses in the MDD+A group ( $r=0.90$ ) differed significantly from the identical comparisons in the MDD-A ( $P=.002$ ) and control ( $P=.03$ ) groups, whereas the MDD-A and control groups did not differ significantly from one another ( $P=.38$ ).

#### COMMENT

Previous functional neuroimaging studies conducted with individuals predisposed to anger or aggression have principally used neutral-state or pharmacologic challenge studies. In contrast, the present study represents an initial symptom provocation PET study in patients with MDD predisposed to anger or aggression and yields several important findings. First, this study replicated findings from our laboratory<sup>44</sup> and others<sup>42,43,45,46</sup> of increased ventral PFC (specifically, the left VMPFC in this study) rCBF during anger induction in controls. Second, the control subjects demonstrated statistically significantly greater left VMPFC rCBF increases than the patients with MDD+A during anger induction. There was no corresponding difference in left VMPFC rCBF during anger induction when comparing the patients with MDD-A with either the patients with MDD+A or the control sub-

**Table 4. Results of Interregional Correlation Analyses of Left VMPFC rCBF Changes and rCBF Changes in the Rest of the Brain During Anger Induction\***

Control Group			MDD + A Group			MDD - A Group		
Brain Region (BA)	$z$ Score	MNI Coordinates	Brain Region (BA)	$z$ Score	MNI Coordinates	Brain Region (BA)	$z$ Score	MNI Coordinates
<b>Negative Correlation</b>								
<b>Amygdala</b>	<b>3.29</b>	<b>-22, 2, -12</b>	Insula	4.66	44, -16, 8	Lingual gyrus	3.99	-18, -52, -6
Anterior temporal pole (38)	3.97	-30, 6, -20	Orbitofrontal cortex (11)	4.04	34, 56, -16	Parietal cortex	3.68	66, -28, 32
Inferior temporal cortex (20)	3.97	-40, -16, -36	Occipital cortex	3.99	26, -80, 8		3.44	44, -46, 38
Orbitofrontal cortex (11/47)	3.61	-42, 28, -12	Parietal/occipital cortex	3.34	20, -66, 14			
	3.38	-16, 20, -18	Cerebellum	3.23	26, -78, -22			
Brainstem	3.33	2, -20, -16						
<b>Positive Correlation</b>								
Ventromedial prefrontal cortex	4.01	16, 60, -16	Putamen	4.18	14, 8, -4	Inferior frontal cortex (44)	4.60	-58, 18, 20
Insula	3.96	40, -14, -2		4.09	18, -4, 8	Lingual gyrus	4.37	14, -60, -12
Superior temporal cortex (22)	3.51	62, -16, 6	Orbitofrontal cortex (11/47)	4.11	-14, 46, -26	Insula	4.19	-38, -10, -6
				3.59	-14, 32, -14	Superior temporal cortex	4.04	-58, -18, 6
				3.26	8, 24, -22	Middle temporal cortex	3.71	-66, -52, -12
			Insula	3.68	-32, 18, 10	Ventromedial prefrontal cortex	3.25	-58, -32, 6
			<b>Amygdala</b>	<b>3.59</b>	<b>-22, -12, -22</b>	Occipital cortex	3.38	-24, -98, 12
			Anterior cingulate cortex (24/32)	3.54	4, 12, 38			
			Hippocampus	3.44	26, -32, -10			
			Occipital cortex	3.26	-44, -78, 24			

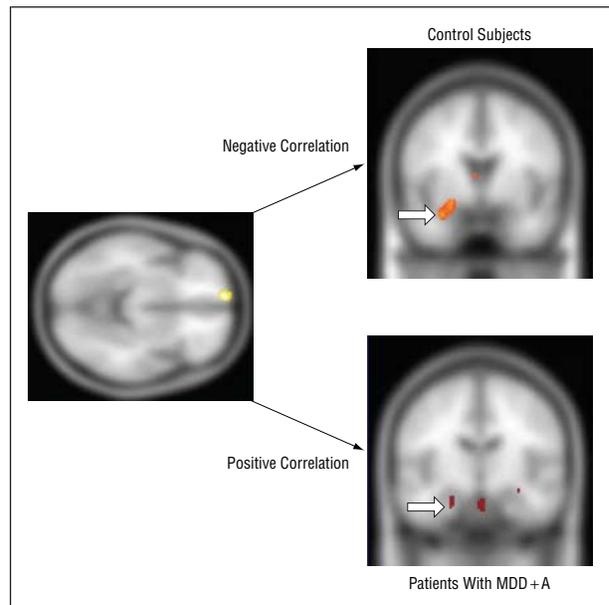
Abbreviations: MDD + A, major depressive disorder with anger attacks; MDD - A, MDD without anger attacks; BA, Brodmann area; MNI, Montreal Neurological Institute; rCBF, regional cerebral blood flow; VMPFC, ventromedial prefrontal cortex.

\*Boldfaced entries indicate a priori regions; all other reported regions represent post hoc findings.

jects. Third, in the control subjects, interregional correlation analyses found an inverse correlation between left VMPFC rCBF changes and left amygdala rCBF changes during anger induction. However, patients with MDD+A demonstrated rCBF changes in the left VMPFC and the left amygdala in the same direction during anger induction, suggesting an aberrant functional relationship between these brain regions in the MDD+A group. Last, whereas patients with MDD-A demonstrated blunted autonomic responses during anger induction, those with MDD+A had autonomic responses that were comparable to the responses of controls. Thus, autonomic response during anger induction clearly differentiates the MDD+A subtype from the MDD-A subtype.

Electroencephalographic<sup>66,67</sup> and functional neuroimaging<sup>42-46</sup> studies have used emotion induction paradigms to investigate the neural basis of anger in control subjects. Although these studies used different techniques to induce anger, all of them demonstrated the involvement of common anterior paralimbic structures during anger states. All of the studies found that the ventral PFC was recruited during anger states. This finding makes sense in the context of multiple lines of evidence indicating that the ventral PFC plays a crucial role in constraining impulsive outbursts.<sup>40</sup> Thus, it is proposed that individuals who exhibit excessive impulsive behavior (including aggression) do so because they cannot mobilize the ventral PFC in this manner. In fact, many studies<sup>68-81</sup> using neuropsychologic tests to assess frontal functional integrity have found deficits in functions mediated by the frontal lobes in violent and antisocial personality disordered (APD) individuals. One structural magnetic resonance imaging (MRI) study<sup>82</sup> demonstrated that a group of patients with APD and a history of violent crimes had an 11% reduction in PFC gray matter volume compared with a control group, and another<sup>83</sup> found that patients with temporal lobe epilepsy and IED had a 17% reduction in PFC gray matter compared with patients with temporal lobe epilepsy without IED. A growing number of functional neuroimaging studies<sup>84-93</sup> of individuals with a predisposition to anger and aggression have found that these individuals (groups have included murderers, violent offenders, and those with APD) exhibit decreased activity in the PFC compared with control subjects. Postmortem studies of individuals completing violent suicide have revealed a variety of serotonergic abnormalities in the PFC.<sup>94-96</sup> In addition, recent [<sup>18</sup>F]fluorodeoxyglucose PET studies have demonstrated that, unlike controls, patients with impulsive aggression do not show activation of the left VMPFC in response to administration of fenfluramine<sup>49,50</sup> or meta-chlorophenylpiperazine.<sup>51</sup> Taken together, these studies provide strong evidence that dysfunction of the PFC, particularly the ventral PFC, is common to the pathophysiology of impulsive aggression seen in a multitude of diagnoses.

Consistent with our hypothesis, correlational analyses examining the relationship between a functionally defined left VMPFC ROI and the rest of the brain in controls demonstrated a negative correlation with the ipsilateral (left) amygdala. A growing literature suggests that the amygdala plays a prominent role in anti-



**Figure 2.** The image on the left corresponds to the within-group comparison of the anger vs neutral conditions in the control subjects; it demonstrates increased regional cerebral blood flow (rCBF) in the left ventromedial prefrontal cortex during anger induction. On the right are statistical parametric maps of positron emission tomography data corresponding to the interregional correlation analyses of changes in rCBF during anger induction in the left ventromedial prefrontal cortex and the rest of the brain. The data are superimposed over a nominally normal magnetic resonance image in Montreal Neurological Institute space for gross anatomic reference. Voxels exceeding the z score threshold of 3.09 are shown in orange. The upper image is a coronal section showing that control subjects demonstrate a significant inverse correlation between changes in rCBF in the left ventromedial prefrontal cortex and the left amygdala (white arrows) during anger induction. In contrast, the lower image is a coronal section showing that patients with major depressive disorder with anger attacks (MDD+A) demonstrate a significant positive correlation between changes in rCBF in the left ventromedial prefrontal cortex and the left amygdala (white arrows) during anger induction.

social behavior.<sup>47</sup> Patients with APD show reduced potentiation of the startle reflex following exposure to threatening visual stimuli<sup>97</sup> and impaired aversive conditioning.<sup>98,99</sup> These impairments are also found in patients with amygdala lesions.<sup>100-102</sup> Patients with amygdala lesions and those with APD also exhibit impairments in the processing of fearful (and possibly sad) facial expressions.<sup>103-107</sup> Neuropsychologic studies<sup>108</sup> have shown similar deficits in decision making in patients with amygdala and VMPFC lesions. In addition, one structural MRI study<sup>109</sup> of patients with temporal lobe epilepsy found that those with comorbid IED had substantially higher rates of amygdala atrophy or amygdala lesions than those without comorbid IED, and another structural MRI study<sup>110</sup> found that levels of antisocial behavior in violent offenders was inversely correlated with amygdala volume. These findings are especially relevant given the role of the amygdala in one model of antisocial behavior, the violence inhibition mechanism model, which suggests that antisocial individuals are less likely to activate the violence inhibition mechanism in the context of fearful and sad facial expressions of others.<sup>42,105,111</sup> A functional MRI study<sup>112</sup> using a memory task demonstrated that participants who scored higher on a scale of antisocial behavior demonstrated reduced amygdala activation while pro-

cessing negatively valenced words compared with individuals who scored lower on the scale. Another recent functional MRI study<sup>113</sup> of patients with APD using a differential aversive-delay conditioning task found blunted activation of the orbitofrontal cortex, anterior cingulate cortex, insula, and amygdala compared with control subjects. Thus, multiple lines of evidence suggest that in addition to dysfunction of the PFC, amygdala dysfunction is also common to the pathophysiology of impulsive aggression seen in a variety of diagnoses.

It has been suggested that APD and IED may be associated with “dual brain pathology” in which abnormalities in the amygdala result in dysfunctional aroused states and those in the PFC result in dyscontrol states.<sup>114</sup> There are known bidirectional connections between the PFC (especially the medial PFC) and the amygdala,<sup>115-120</sup> and there is evidence<sup>121,122</sup> that in control subjects these 2 structures are mutually inhibitory in that increased activity in one structure inhibits activity in the other structure. Because the controls in the present study demonstrated a reciprocal (or inverse) relationship between left VMPFC and left amygdala rCBF during the anger vs neutral comparison, we examined this relationship in the MDD groups. We did not demonstrate any statistically significant relationship for rCBF changes during anger induction between the left VMPFC and left amygdala in the MDD–A group. In contrast, for the MDD+A group the rCBF changes during anger induction in the left VMPFC and the left amygdala were in the same direction (ie, they demonstrated a positive correlation). This suggests that, at least in the context of anger induction, the normal (inverse) functional relationship between the VMPFC and the amygdala is absent in the MDD–A group and is reversed in the MDD+A group. Therefore, this profile of VMPFC and amygdala activity and their interactions may distinguish MDD+A and may be responsible for the unique clinical presentation of patients with this subtype of MDD. Last, the differential abnormalities in VMPFC and amygdala function in the MDD+A group are consistent with the dysfunction of both of these regions found in other impulsively aggressive patient populations.

There are some limitations of the present study. First, this study was not designed to assess sex differences during anger induction. Second, formal assessment for Axis II diagnoses was not performed in the study populations. Future studies that address these issues would be desirable. Last, structural MRIs were not used for anatomic localization of significant rCBF changes. Instead, the MNI atlas, a spatially normalized composite of 152 MRIs of a healthy brain, was used for localization purposes. Concerns regarding anatomic localization were further mitigated by the fact that we had concise, evidence-based, a priori hypotheses for the present study involving the ventral PFC and amygdala.

Patients with MDD+A experience a remission of anger attacks in concert with remission of their depressive symptoms after successful treatment, whereas other patient populations that frequently exhibit impulsive aggression typically exhibit a more chronic, treatment-refractory clinical course. For these reasons, future studies that include assessments of MDD+A patients before and after treatment may provide valu-

able insight into the brain mechanisms underlying the resolution of these symptoms.

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Correspondence: Darin D. Dougherty, MD, MSc, Massachusetts General Hospital–East, CNY-2612, Bldg 149, 13th Street, Charlestown, MA 02129 (ddougherty@partners.org).

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