ORIGINAL ARTICLE

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, psychophysiologic 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 psychophysiologic 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.

Arch Gen Psychiatry. 2004;61:795-804

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).

MAJOR DEPRESSIVE DISORder (MDD) is a clinical syndrome characterized by affect dysregulation, neurovegetative symptoms, autonomic disturbances, and endocrine abnormalities. Freud[1] theorized that depression resulted from anger turned inward. In fact, numerous studies[2-8] have demonstrated that depressed patients have higher rates of anger and aggression than controls. One study[9] 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[10] in 1990. These anger attacks 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).[11] The prevalence of anger attacks in depressed patients is approximately 30% to 40%,[4,5,11-14] and the attacks resolve after successful treatment of the depressive episode.[5,11,12]

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

©2004 American Medical Association. All rights reserved.
Downloaded From: http://archpsyc.jamanetwork.com/ on 05/02/2016

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,[16-18] myocardial infarction,[19-22] and abnormal glucose metabolism.[23-27] Given that depression itself is a significant risk factor for heart disease[28-30] and diabetes mellitus,[31,32] 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.[33] 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.[34-38] 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.[39-41] Although a variety of functional neuroimaging studies[42-46] 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 subjects. 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.[47-52] In contrast, numerous studies[36,53,54] 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[44] and others,[42,43,45,46] 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[55]) 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*,[56] the Anger Attacks Questionnaire,[4] and the 17-item Hamilton Depression Rating Scale.[57] 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,[4] 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

©2004 American Medical Association. All rights reserved.
Downloaded From: http://archpsyc.jamanetwork.com/ on 05/02/2016

of the *Structured Clinical Interview for* DSM-IV *Disorders*,[56] 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.[44,58-61] 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 ^{15}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, psychophysiologic 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,[44,59-61] 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

Psychophysiologic assessment was performed during the PET study using equipment from ADInstruments (Sydney, Australia). Measured parameters included heart rate and galvanic skin response (GSR). Psychophysiologic 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 periods (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 psychophysiologic 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.[62] 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 ^{15}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.[63,64] 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.

©2004 American Medical Association. All rights reserved.
Downloaded From: http://archpsyc.jamanetwork.com/ on 05/02/2016

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

We report regions containing foci of activation with z scores ≥ 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 ± 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 ± 1.85 (t_{17} = 16.18) for patients with MDD + A, 7.11 ± 2.32 (t_{19} = 13.70) for patients with MDD − A, and 6.91 ± 2.57 (t_{19} = 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 ± 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 ± 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 ± 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 ± 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 ± 7.57 bpm, which was a significant increase (t_{19} = 3.44; P = .003). These subjects also experienced an increase in GSR AUC of 81.80 ± 96.99 microsiemens during the anger condition, which was significant (t_{19} = 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

©2004 American Medical Association. All rights reserved.
Downloaded From: http://archpsyc.jamanetwork.com/ on 05/02/2016

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

Brain Region (BA)	Maximum Voxel *z* Score	MNI Coordinates
Control Subjects		
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
Patients With MDD + A		
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	. . .	. . .
Patients With MDD – A		
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.

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

Brain Region (BA)	Maximum Voxel *z* Score	MNI Coordinates
MDD + A vs Controls		
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
MDD – A vs Controls		
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
MDD + A vs MDD – A		
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.

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 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

©2004 American Medical Association. All rights reserved.
Downloaded From: http://archpsyc.jamanetwork.com/ on 05/02/2016

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 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 ($P=.38$).

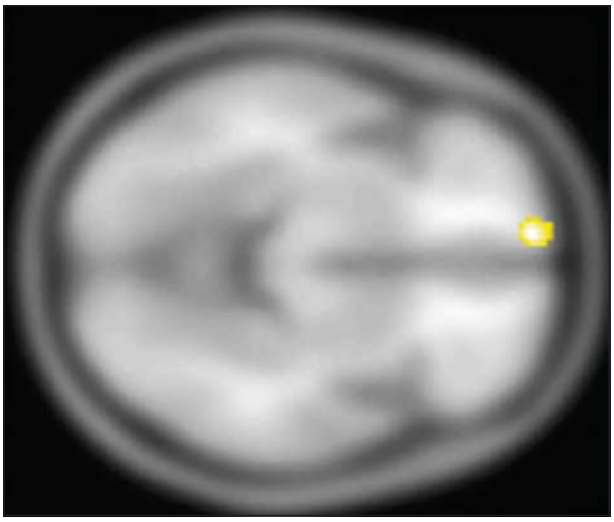

Figure 1. A statistical parametric map of positron emission tomography data corresponding to a between-group comparison of the anger vs neutral conditions is superimposed over a nominally normal magnetic resonance image in Montreal Neurological Institute space for gross anatomic reference. Voxels exceeding 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.

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[44] and others[42,43,45,46] 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
			Negative Correlation					
Amygdala	**3.29**	**–22, 2, –12**	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						
			Positive Correlation					
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		3.25	–58, –32, 6
			Amygdala	**3.59**	**–22, –12, –22**	Ventromedial prefrontal cortex	3.41	12, 54, –16
			Anterior cingulate cortex (24/32)	3.54	4, 12, 38	Occipital cortex	3.38	–24, –98, 12
			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.

©2004 American Medical Association. All rights reserved.
Downloaded From: http://archpsyc.jamanetwork.com/ on 05/02/2016

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[66,67] and functional neuroimaging[42-46] 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.[40] 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[68-81] 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[82] 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[83] 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[84-93] 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.[94-96] In addition, recent [^{18}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[49,50] or metachlorophenylpiperazine.[51] 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 antisocial behavior.[47] Patients with APD show reduced potentiation of the startle reflex following exposure to threatening visual stimuli[97] and impaired aversive conditioning.[98,99] These impairments are also found in patients with amygdala lesions.[100-102] Patients with amygdala lesions and those with APD also exhibit impairments in the processing of fearful (and possibly sad) facial expressions.[103-107] Neuropsychologic studies[108] have shown similar deficits in decision making in patients with amygdala and VMPFC lesions. In addition, one structural MRI study[109] 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[110] 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.[42,105,111] A functional MRI study[112] using a memory task demonstrated that participants who scored higher on a scale of antisocial behavior demonstrated reduced amygdala activation while pro-

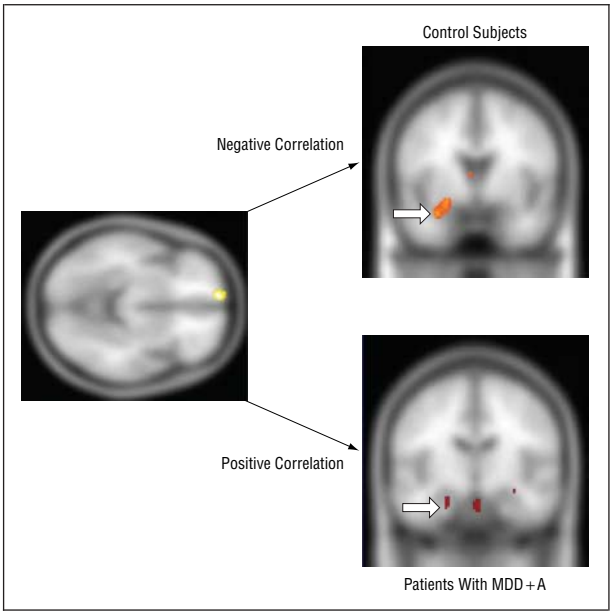

Figure 2. The image on the left corresponds to the within-group comparison of the anger vs neutral conditions in the control subjects; it demonstrates increased regional cerebral blood flow (rCBF) in the left ventromedial prefrontal cortex during anger induction. On the right are statistical parametric 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.

©2004 American Medical Association. All rights reserved.
Downloaded From: http://archpsyc.jamanetwork.com/ on 05/02/2016

cessing negatively valenced words compared with individuals who scored lower on the scale. Another recent functional MRI study[113] 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 arousal states and those in the PFC result in dyscontrol states.[114] There are known bidirectional connections between the PFC (especially the medial PFC) and the amygdala,[115-120] and there is evidence[121,122] 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 valuable insight into the brain mechanisms underlying the resolution of these symptoms.

Submitted for publication July 7, 2003; final revision received January 9, 2004; accepted February 17, 2004.

This study was supported by Mentored Patient-Oriented Research Career Development Award MH01735 from the National Institute of Mental Health, Bethesda, Md (Dr Dougherty).

We thank the individuals who served as research participants and Sandra Barrow, BS, and Steve Weise, BS, for technical assistance.

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

REFERENCES

1. Freud S. *Mourning and Melancholia*. Vol 4. London, England: Hogarth Press; 1917.
2. Bland RC, Orn J. Family violence and psychiatric disorder. *Can J Psychiatry*. 1986;31:129-137.
3. Eronen M, Hakola P, Tiihonen J. Mental disorders and homicidal behavior in Finland. *Arch Gen Psychiatry*. 1996;53:497-501.
4. Fava M, Rosenbaum JF, McCarthy MK, Pava JA, Steingard RJ, Bless E. Anger attacks in depressed outpatients and their response to fluoxetine. *Psychopharmacol Bull*. 1991;27:275-279.
5. Fava M, Nierenberg AA, Quitkin FM, Zisook S, Pearlstein T, Stone A, Rosenbaum JF. A preliminary study on the efficacy of sertraline and imipramine on anger attacks in atypical depression and dysthymia. *Psychopharmacol Bull*. 1997; 33:101-103.
6. Koh KB, Kim CH, Park JK. Predominance of anger in depressive disorders compared with anxiety disorders and somatoform disorders. *J Clin Psychiatry*. 2002; 63:486-492.
7. Swanson JW, Holzer CE, Ganju VK, Jono RT. Violence and psychiatric disorder in the community: evidence from the Epidemiological Catchment Area surveys. *Hosp Community Psychiatry*. 1990;41:761-770.
8. Weissman M, Klerman GL, Paykel ES. Clinical evaluation of hostility in depression. *Am J Psychiatry*. 1971;128:41-46.
9. Schless AP, Mendels J, Kipperman A, Cochrane C. Depression and hostility. *J Nerv Ment Dis*. 1974;159:91-100.
10. Fava M, Anderson K, Rosenbaum JF. "Anger attacks": possible variants of panic and major depressive disorders. *Am J Psychiatry*. 1990;147:867-870.
11. Fava M, Rosenbaum JF, Pava JA, McCarthy MK, Steingard RJ, Bouffides E. Anger attacks in unipolar depression, part 1: clinical correlates and response to fluoxetine treatment. *Am J Psychiatry*. 1993;150:1158-1163.
12. Fava M, Alpert J, Nierenberg AA, Ghaemi N, O'Sullivan R, Tedlow J, Worthington J, Rosenbaum JF. Fluoxetine treatment of anger attacks: a replication study. *Ann Clin Psychiatry*. 1996;8:7-10.
13. Morand P, Thomas G, Bungener C, Ferreri M, Jouvent R. Fava's Anger Attacks Questionnaire: the evaluation of the French version in depressed patients. *Eur Psychiatry*. 1998;13:41-45.
14. Sayar K, Guzelhan Y, Solmaz M, Ozer OA, Ozturk M, Acar B, Arikan M. Anger attacks in depressed Turkish outpatients. *Ann Clin Psychiatry*. 2000;12:213-218.
15. Posternak MA, Zimmerman M. Anger and aggression in psychiatric outpatients. *J Clin Psychiatry*. 2002;63:665-672.
16. Iribarren C, Sidney S, Bild DE, Liu K, Markovitz JH, Roseman JM, Matthews K. Association of hostility with coronary artery calcification in young adults: the CARDIA study: Coronary Artery Risk Development in Young Adults. *JAMA*. 2000; 283:2546-2551.
17. Julkunen J, Salonen R, Kaplan GA, Chesney MA, Salonen JT. Hostility and the progression of carotid atherosclerosis. *Psychosom Med*. 1994;56:519-525.
18. Matthews KA, Owens JF, Kuller LH, Sutton-Tyrell K, Jansen-McWilliams L. Are hostility and anxiety associated with carotid atherosclerosis in healthy postmenopausal women? *Psychosom Med*. 1998;60:633-638.
19. Barefoot JC, Dahlstrom WG, Williams RB. Hostility, CHD incidence, and total mortality: a 25-year follow-up study of 255 physicians. *Psychosom Med*. 1983; 45:59-63.
20. Barefoot JC, Larsen S, von der Leith L, Schroll M. Hostility, incidence of myocardial infarction, and mortality in a sample of older Danish men and women. *Am J Epidemiol*. 1995;142:477-484.

©2004 American Medical Association. All rights reserved.
Downloaded From: http://archpsyc.jamanetwork.com/ on 05/02/2016

21. Hecker M, Chesney MA, Black GW, Frautschi N. Coronary-prone behaviors in the Western Collaborative Group Study. *Psychosom Med*. 1988;50:153-164.
22. Shekelle RB, Gale M, Ostfeld AM, Paul O. Hostility, risk of coronary heart disease, and mortality. *Psychosom Med*. 1983;45:109-114.
23. Kawakami N, Akari S, Ohtsu H, Hayashi T, Masumoto T, Yokohama K. Effects of mood states, smoking, and urinary catecholamine excretion on hemoglobin A1C in male Japanese workers. *Ind Health*. 1995;33:153-162.
24. Niaura R, Banks SM, Ward KD, Stoney CM, Spiro A, Aldwin CM, Landsberg L, Weiss ST. Hostility and the metabolic syndrome in older males: the Normative Aging Study. *Psychosom Med*. 2000;62:7-16.
25. Raikkonen K, Keltikangas-Jarvinen L, Hautanen A. The role of psychological coronary risk factors in insulin and glucose metabolism. *J Psychosom Res*. 1994; 38:705-713.
26. Raikkonen K, Matthews KA, Kuller LH, Reiber C, Bunker CH. Anger, hostility, and visceral adipose tissue in healthy postmenopausal women. *Metabolism*. 1999;48:1146-1151.
27. Surwit RS, Williams RB, Siegler IC, Lane JD, Helms M, Applegate KL, Zucker N, Feinglos MN, McCaskill CM, Barefoot JC. Hostility, race, and glucose metabolism in nondiabetic individuals. *Diabetes Care*. 2002;25:835-839.
28. Ariyo A, Haan M, Tangen C, Rutledge JC, Cushman M, Dobs A, Furberg CD. Depressive symptoms and risks of coronary artery disease and mortality in elderly Americans. *Circulation*. 2000;102:1773-1779.
29. Frasure-Smith N, Lesperance F, Talajic M. Depression and 18-month prognosis after myocardial infarction. *Circulation*. 1995;91:999-1005.
30. Pratt LA, Ford DE, Crum RM, Armenian HK, Gallo JJ, Eaton WW. Depression, psychotropic medication, and risk of myocardial infarction: prospective data from the Baltimore ECA follow-up. *Circulation*. 1996;94:3123-3129.
31. Hamilton J, Daneman D. Deteriorating diabetes control during adolescence: physiological or psychosocial? *J Pediatr Endocrinol Metab*. 2002;15:115-126.
32. Lernmark B, Persson B, Fisher L, Rydelius P-A. Symptoms of depression are important to psychological adaptation and metabolic control in children with diabetes mellitus. *Diabet Med*. 1999;16:14-22.
33. World Health Organization. *The World Health Report: Mental Health: New Understanding, New Hope*. Geneva, Switzerland: World Health Organization; 2001.
34. Davidson RJ, Pizzagalli D, Nitschke JB, Putnam K. Depression: perspectives from affective neuroscience. *Annu Rev Psychol*. 2002;53:545-574.
35. Dougherty DD, Rauch SL. Neuroimaging and neurobiological models of depression. *Harv Rev Psychiatry*. 1997;5:138-159.
36. Drevets WC. Neuroimaging studies of mood disorders. *Biol Psychiatry*. 2000; 48:813-829.
37. Drevets WC. Neuroimaging and neuropathological studies of depression: implications for the cognitive-emotional features of mood disorders. *Curr Opin Neurobiol*. 2001;11:240-249.
38. Mayberg HS. Limbic-cortical dysregulation: a proposed model of depression. *J Neuropsychiatry Clin Neurosci*. 1997;9:471-481.
39. Brower MC, Price BH. Neuropsychiatry of frontal lobe dysfunction in violent and criminal behavior: a critical review. *J Neurol Neurosurg Psychiatry*. 2001; 71:720-726.
40. Davidson RJ, Putnam KM, Larson CL. Dysfunction in the neural circuitry of emotion regulation: a possible prelude to violence. *Science*. 2000;289:591-594.
41. Kavoussi R, Armstead P, Coccaro E. The neurobiology of impulsive aggression. *Psychiatr Clin North Am*. 1997;20:395-403.
42. Blair RJR, Morris JS, Frith CD, Perrett DI, Dolan RJ. Dissociable neural responses to facial expressions of sadness and anger. *Brain*. 1999;122:883-893.
43. Damasio AR, Grabowski TJ, Bechara A, Damasio H, Ponto LLB, Parvizi J, Hichwa RD. Subcortical and cortical brain activity during the feelings of self-generated emotions. *Nat Neurosci*. 2000;3:1049-1056.
44. Dougherty DD, Shin LM, Alpert NM, Pitman RK, Orr SP, Lasko M, Macklin ML, Fischman AJ, Rauch SL. Anger in healthy men: a PET study using script-driven imagery. *Biol Psychiatry*. 1999;46:466-472.
45. Kimbrell TA, George MS, Parekh PI, Ketter TA, Podell DM, Danielson AL, Repella JD, Benson BE, Willis MW, Herscovitch P, Post RM. Regional brain activity during transiently self-induced anxiety and anger in healthy adults. *Biol Psychiatry*. 1999;46:454-465.
46. Pietrini P, Guazzelli M, Basso G, Jaffe K, Grafman J. Neural correlates of imaginal aggressive behavior assessed by positron emission tomography in healthy subjects. *Am J Psychiatry*. 2000;157:1772-1781.
47. Blair RJR. Neurobiological basis of psychopathy. *Br J Psychiatry*. 2003;182:5-7.
48. McKay KE, Halperin JM. ADHD, aggression, and antisocial behavior across the lifespan: interactions with neurochemical and cognitive function. *Ann N Y Acad Sci*. 2001;931:84-96.
49. Siever LJ, Buchsbaum MS, New AS, Spiegel-Cohen J, Wei T, Hazlett EA, Sevin E, Nunn M, Mitropoulou V. d,l-Fenfluramine response in impulsive personality disorder assessed with [^{18}F]fluorodeoxyglucose positron emission tomography. *Neuropsychopharmacology*. 1999;20:413-423.
50. Soloff PH, Meltzer CC, Greer PJ, Constantine D, Kelly TM. A fenfluramine-activated FDG-PET study of borderline personality disorder. *Biol Psychiatry*. 2000; 47:540-547.
51. New AS, Hazlett EA, Buchsbaum MS, Goodman M, Reynolds D, Mitropoulou V, Sprung L, Shaw RB, Koenigsberg H, Platholi J, Silverman J, Siever LJ. Blunted prefrontal cortical ^{18}fluorodeoxyglucose positron emission tomography response to meta-chlorophenylpiperazine in impulsive aggression. *Arch Gen Psychiatry*. 2002;59:621-629.
52. Tebartz van Elst L, Hesslinger B, Thiel T, Geiger E, Haegele K, Lemieux L, Lieb K, Bohus M, Hennig J, Ebert D. Frontolimbic brain abnormalities in patients with borderline personality disorder: a volumetric magnetic resonance imaging study. *Biol Psychiatry*. 2003;54:163-171.
53. Drevets WC, Price JL, Bardgett ME, Reich T, Todd RD, Raichle ME. Glucose metabolism in the amygdala in depression: relationship to diagnostic subtype and plasma cortisol levels. *Pharmacol Biochem Behav*. 2002;71:431-447.
54. Whalen PJ, Shin LM, Somerville LH, McLean AA, Kim H. Functional neuroimaging studies of the amygdala in depression. *Semin Clin Neuropsychiatry*. 2002; 7:234-242.
55. Oldfield RC. The assessment and analysis of handedness: the Edinburgh Inventory. *Neuropsychologia*. 1971;9:97-113.
56. First MB, Spitzer RL, Gibbon M, Williams JBW. *Structured Clinical Interview for Axis I DSM-IV Disorders–Patient Edition (With Psychotic Screen), Version 2.0*. New York: Biometrics Research Department, New York State Psychiatric Institute; 1995.
57. Hamilton M. A rating scale for depression. *J Neurol Neurosurg Psychiatry*. 1960; 23:56-62.
58. Pitman RK, Orr SP, Forgue DF, de Jong JB, Claiborn JM. Psychophysiologic assessment of posttraumatic stress disorder imagery in Vietnam combat veterans. *Arch Gen Psychiatry*. 1987;44:970-975.
59. Pitman RK, Orr SP, Forgue DF, Altman B, de Jong JB. Psychophysiologic responses to combat imagery of Vietnam veterans with posttraumatic stress disorder versus other anxiety disorders. *J Abnorm Psychol*. 1990;99:49-54.
60. Orr SP, Pitman RK, Lasko NB, Herz LR. Psychophysiological assessment of posttraumatic stress disorder imagery in World War II and Korean combat veterans. *J Abnorm Psychol*. 1993;102:152-159.
61. Rauch SL, van der Kolk BA, Fisler RE, Alpert NM, Orr SP, Savage CR, Fischman AJ, Jenike MA, Pitman RK. A symptom provocation study of posttraumatic stress disorder using positron emission tomography and script-driven imagery. *Arch Gen Psychiatry*. 1996;53:380-387.
62. Kops ER, Herzog H, Schmid A, Holte S, Feinendegen LE. Performance characteristics of an eight-ring whole body PET scanner. *J Comput Assist Tomogr*. 1990;14:437-445.
63. Friston KJ, Frith CD, Liddle PF, Frackowiak RSJ. Comparing functional (PET) images: the assessment of significant change. *J Cereb Blood Flow Metab*. 1991; 11:690-699.
64. Friston KJ, Holmes AP, Worsley KJ, Poline JP, Frith CD, Frackowiak RSJ. Statistical parametric maps in functional imaging: a general approach. *Hum Brain Mapp*. 1995;2:189-210.
65. Brett M, Anton J-L, Valabregue R, Poline J-B. Region of interest analysis using an SPM toolbox. Abstract presented at: 8th International Conference of Functional Mapping of the Human Brain; June 2-6, 2002; Sendai, Japan.
66. Harmon-Jones E, Sigelman J. State anger and prefrontal brain activity: evidence that insult-related relative left-prefrontal activation is associated with experienced anger and aggression. *J Pers Soc Psychol*. 2001;80:797-803.
67. Harmon-Jones E, Allen JJ. Anger and frontal brain activity: EEG asymmetry consistent with approach motivation despite negative affective valence. *J Pers Soc Psychol*. 1998;74:1310-1316.
68. Best M, Williams JM, Coccaro EF. Evidence for a dysfunctional prefrontal circuit in patients with an impulsive aggressive disorder. *Proc Natl Acad Sci U S A*. 2002;99:8448-8453.
69. Bergvall AH, Wessely H, Forsman A, Hansen S. A deficit in attentional set-shifting of violent offenders. *Psychol Med*. 2001;31:1095-1105.
70. Blair RJR, Colledge E, Mitchell DGV. Somatic markers and response reversal: is there orbitofrontal cortex dysfunction in boys with psychopathic tendencies? *J Abnorm Child Psychol*. 2001;29:499-511.
71. Deckel AW, Hesselbrock V, Bauer L. Antisocial personality disorder, childhood delinquency, and frontal brain functioning: EEG and neuropsychological findings. *J Clin Psychol*. 1996;52:639-650.
72. Dinn WM, Harris CL. Neurocognitive function in antisocial personality disorder. *Psychiatry Res*. 2000;97:173-190.
73. Dolan M, Park I. The neuropsychology of antisocial personality disorder. *Psychol Med*. 2002;32:417-427.
74. Foster HG, Hillbrand M, Silverstein M. Neuropsychological deficit and aggressive behavior: a prospective study. *Prog Neuropsychopharmacol Biol Psychiatry*. 1993;17:939-946.

©2004 American Medical Association. All rights reserved.
Downloaded From: http://archpsyc.jamanetwork.com/ on 05/02/2016

75. Giancola PR, Zeichner A. Neuropsychological performance on tests of frontal-lobe functioning and aggressive behavior in men. *J Abnorm Psychol*. 1994; 103:832-835.
76. Giancola PR, Moss HB, Martin CS, Kirisci L, Tarter RE. Executive cognitive functioning predicts reactive aggression in boys at high risk for substance abuse: a prospective study. *Alcohol Clin Exp Res*. 1996;20:740-744.
77. Giancola PR, Mezzich AC, Tarter RE. Executive cognitive functioning, temperment, and antisocial behavior in conduct-disordered adolescent females. *J Abnorm Psychol*. 1998;107:629-641.
78. LaPierre D, Braun CMJ, Hodgins S. Ventral frontal deficits in psychopathy: neuropsychological test findings. *Neuropsychologia*. 1995;33:139-151.
79. Lau MA, Pihl RO, Peterson JB. Provocation, acute alcohol intoxication, cognitive performance, and aggression. *J Abnorm Psychol*. 1995;104:150-155.
80. Mitchell DGV, Colledge E, Leonard A, Blair RJR. Risky decisions and response reversal: is there evidence of orbitofrontal cortex dysfunction in psychopathic individuals? *Neuropsychologia*. 2002;40:2013-2022.
81. Rosse RB, Miller MW, Deutsch SI. Violent antisocial behavior and Wisconsin Card Sorting Test performance in cocaine addicts [letter]. *Am J Psychol*. 1993; 150:170-171.
82. Raine A, Lencz T, Bihrle S, LaCasse L, Colletti P. Reduced prefrontal gray matter volume and reduced autonomic activity in antisocial personality disorder. *Arch Gen Psychiatry*. 2000;57:119-127.
83. Woermann FG, Tebartz van Elst L, Koepp MJ, Free SL, Thompson PJ, Trimble MR, Duncan JS. Reduction of frontal neocortical grey matter associated with affective aggression in patients with temporal lobe epilepsy: an objective voxel by voxel analysis of automatically segmented MRI. *J Neurol Neurosurg Psychiatry*. 2000;68:162-169.
84. Amen DG, Stubblefield M, Carmichael B, Thisted R. Brain SPECT findings and aggressiveness. *Ann Clin Psychiatry*. 1996;8:129-137.
85. Goyer PF, Andreason PJ, Semple WE, Clayton AH, King AC, Compton-Toth BA, Schulz SC, Cohen RM. Positron-emission tomography and personality disorders. *Neuropsychopharmacology*. 1994;10:21-28.
86. Kuruoglu AC, Arikan Z, Vural G, Karatas M, Arac M, Isik E. Single photon emission computerised tomography in chronic alcoholism: antisocial personality disorder may be associated with decreased frontal perfusion. *Br J Psychiatry*. 1996; 169:348-354.
87. Raine A, Buchsbaum M, LaCasse L. Brain abnormalities in murderers indicated by positron emission tomography. *Biol Psychiatry*. 1997;42:495-508.
88. Raine A, Meloy JR, Bihrle S, Stoddard J, LaCasse L, Buchsbaum MS. Reduced prefrontal and increased subcortical brain functioning assessed using positron emission tomography in predatory and affective murderers. *Behav Sci Law*. 1998;16:319-332.
89. Raine A, Phil D, Stoddard J, Bihrle S, Buchsbaum M. Prefrontal glucose deficits in murderers lacking psychosocial deprivation. *Neuropsychiatry Neuropsychol Behav Neurol*. 1998;11:1-7.
90. Soderstrom H, Tullberg M, Wikkelso C, Ekholm S, Forsman A. Reduced regional cerebral blood flow in non-psychotic violent offenders. *Psychiatry Res*. 2000;98:29-41.
91. Soderstrom H, Hultin L, Tullberg M, Wikkelso C, Ekholm S, Forsman A. Reduced frontotemporal perfusion in psychopathic personality. *Psychiatry Res*. 2002;114:81-94.
92. Volkow ND, Tancredi L. Neural substrates of violent behavior: a preliminary study with positron emission tomography. *Br J Psychiatry*. 1987;151:668-673.
93. Volkow ND, Tancredi LR, Grant C, Gillespie H, Valentine A, Mullani N, Wang GJ, Hollister L. Brain glucose metabolism in violent psychiatric patients: a preliminary study. *Psychiatry Res*. 1995;61:243-253.
94. Arango V, Underwood MD, Gubbi AV, Mann JJ. Localized alterations in pre- and postsynaptic serotonin binding sites in the ventrolateral prefrontal cortex of suicide victims. *Brain Res*. 1995;688:121-133.
95. Mann JJ, Huang YY, Underwood MD, Kassir SA, Oppenheim S, Kelly TM, Dwork AJ, Arango V. A serotonin transporter gene promoter polymorphism (5-HTTLPR) and prefrontal cortical binding in major depression and suicide. *Arch Gen Psychiatry*. 2000;57:729-738.
96. Pandey GN, Dwivedi Y, Rizavi HS, Ren X, Pandey SC, Pesold C, Roberts RC, Conley RR, Taminga CA. Higher expression of serotonin 5-HT(2A) receptors in the postmortem brains of teenage suicide victims. *Am J Psychiatry*. 2002;159: 419-429.
97. Patrick CJ, Bradley MM, Lang PJ. Emotion in the criminal psychopath: startle reflex modulation. *J Abnorm Psychol*. 1993;102:82-92.
98. Hare RD. Psychopathy, affect and behavior. In: Van Dusen KT, Mednick SA, eds. *Prospective Studies of Crime and Delinquency*. Boston, Mass: Kluwer-Nijhoff; 1998:225-236.
99. Lykken DT. *The Antisocial Personalities*. Hillsdale, NJ: Lawrence Erlbaum Associates Inc; 1995.
100. Angrilli A, Mauri A, Palomba D, Flor H, Birhaumer N, Sartori G, di Paola F. Startle reflex and emotion modulation impairment after a right amygdala lesion. *Brain*. 1996;119:1991-2000.
101. Bechara A, Tranel D, Damasio H, Adolphs R, Rockland C, Damasio AR. Double dissociation of conditioning and declarative knowledge relative to the amygdala and hippocampus in humans. *Science*. 1995;269:1115-1118.
102. LaBar KS, LeDoux JE, Spencer DD, Phelps EA. Impaired fear conditioned behavior following unilateral temporal lobectomy in humans. *J Neurosci*. 1995; 15:6846-6855.
103. Adolphs R, Tranel D, Young AW, Calder AJ, Phelps EA, Anderson AK, Lee GP, Damasio AR. Recognition of facial emotion in nine individuals with bilateral amygdala damage. *Neuropsychologia*. 1999;37:1111-1117.
104. Blair RJR, Coles M. Expression recognition and behavioural problems in early adolescence. *Cogn Dev*. 2000;15:421-434.
105. Blair RJR, Colledge E, Murray L, Mitchell DGV. A selective impairment in the processing of sad and fearful expressions in children with psychopathic tendencies. *J Abnorm Child Psychol*. 2001;29:491-498.
106. Fine C, Blair RJR. The cognitive and emotional effects of amygdala damage. *Neurocase*. 2000;6:435-450.
107. Stevens D, Charman T, Blair RJR. Recognition of emotion in expression and vocal tones in children with psychopathic tendencies. *J Genet Psychol*. 2001; 162:201-211.
108. Bechara A, Damasio H, Damasio AR. Role of the amygdala in decision-making. *Ann N Y Acad Sci*. 2003;985:356-369.
109. Tebartz van Elst L, Woermann F, Lemieux L, Thompson PJ, Trimble MR. Affective aggression in patients with temporal lobe epilepsy: a quantitative magnetic resonance study of the amygdala. *Brain*. 2000;123:234-243.
110. Tiihonen J, Hodgins S, Vaurio O, Laakso M, Repo E, Soininen H, Aronen HJ, Nieminen P, Savolainen L. Amygdaloid volume loss in psychopathy. In: *Abstracts: Society for Neuroscience*. Vol 26. Washington, DC: Society for Neuroscience; 2000:2017.
111. Blair RJR, Frith U. Neuro-cognitive explanations of the antisocial personality disorders. *Crim Behav Ment Health*. 2000;10(suppl):S66-S82.
112. Kiehl KA, Smith AM, Hare RD, Mendrek A, Forster BB, Brink J, Liddle PF. Limbic abnormalities in affective processing by criminal psychopaths revealed by functional magnetic imaging. *Biol Psychiatry*. 2001;50:677-684.
113. Veit R, Flor H, Erb M, Hermann C, Lotze M, Grodd W, Birbaumer N. Brain circuits involved in emotional learning in antisocial behavior and social phobia in humans. *Neurosci Lett*. 2002;328:233-236.
114. Tebartz van Elst L, Trimble MR, Ebert D. Dual brain pathology in patients with affective aggressive episodes [letter]. *Arch Gen Psychiatry*. 2001;58:1187-1188.
115. Amaral DG, Price JL. Amygdalo-cortical projections in the monkey (*Macaca fascicularis*). *J Comp Neurol*. 1984;230:465-496.
116. Amaral DG, Insuasti R. Retrograde transport of D-[H]-aspartate injected into the monkey amygdaloid complex. *Exp Brain Res*. 1992;88:375-388.
117. Chiba T, Kayahara T, Nakano K. Efferent projections of infralimbic and prelimbic areas of the medial prefrontal cortex in the Japanese monkey, *Macaca fuscata*. *Brain Res*. 2001;888:83-101.
118. Stefanacci L, Amaral DG. Some observations on cortical inputs to the macaque monkey amygdala: an anterograde tracing study. *J Comp Neurol*. 2002;451:301-323.
119. Price JL. Comparative aspects of amygdala connectivity. *Ann N Y Acad Sci*. 2003; 985:50-58.
120. Carmichael ST, Price JL. Limbic connections of the orbital and medial prefrontal cortex in macaque monkeys. *J Comp Neurol*. 1995;363:615-641.
121. Milad MR, Quirk GJ. Neurons in medial prefrontal cortex signal memory for fear extinction. *Nature*. 2002;420:70-74.
122. Hariri AR, Bookheimer SY, Mazziotta JC. Modulating emotional responses: effects of a neocortical network on the limbic system. *Neuroreport*. 2000;11:43-48.

©2004 American Medical Association. All rights reserved.
Downloaded From: http://archpsyc.jamanetwork.com/ on 05/02/2016