Effect of Bupropion Extended Release on Negative Emotion Processing in Major Depressive Disorder: A Pilot Functional Magnetic Resonance Imaging Study

Brigitte Robertson, M.D.; Lihong Wang, Ph.D.; Michele T. Diaz, Ph.D.; Marilyn Aiello, B.A.; Kenneth Gersing, M.D.; John Beyer, M.D.; Srinivasan Mukundan, Jr., M.D., Ph.D.; Gregory McCarthy, Ph.D.; and P. Murali Doraiswamy, M.D.

Background: Prior imaging studies suggest that patients with major depressive disorder have abnormalities in frontal and limbic neural circuitry including the amygdala, which is relatively more activated at rest and in response to negative emotional stimuli (sadness, fear, etc.) in depressed patients than in controls. Concurrently, patients with depression may have decreased activation of attentional executive regions in response to attentional stimuli. This study examined the effect of bupropion XL, an extended release formulation of the nonserotonergic antidepressant agent bupropion, using a paradigm that investigated both negative emotional response and attentional processing.

Method: Functional magnetic resonance imaging (fMRI) scans and clinical ratings were obtained for 10 patients with DSM-IV-TR–defined major depressive disorder (mean [SD] age = 41 [± 7] years, mean [SD] Hamilton Rating Scale for Depression [HAM-D] score = 21 [± 4]) before and after 8 weeks of treatment with bupropion XL. The fMRI sessions were conducted during administration of the Emotional Oddball Task; scans were obtained while subjects viewed emotional distracters and performed an attentional executive function task. The primary outcome was fMRI activations evoked by the emotional distracters. The first baseline fMRI scan was performed in December 2004, and the last posttreatment scan was in March 2005.

Results: Treatment with bupropion XL was associated with improvements in HAM-D and Clinical Global Impressions scale ratings ($p < .05$). Treatment reduced fMRI activation during emotional distracters in several regions including right orbital frontal cortex, left dorsomedial prefrontal cortex, right ventromedial prefrontal cortex, right anterior cingulate cortex, right inferior frontal cortex, right amygdala/parahippocampal area, right caudate, right fusiform gyrus, and left posterior cingulate. In addition, changes in fMRI activation in the amygdala correlated with improvements on the HAM-D ($p < .05$). Treatment increased activation to attentional targets in the following regions: right middle and inferior frontal gyri, right caudate, and bilateral precuneus.

Conclusion: Despite the limitations of a small sample size and the lack of a placebo control group, this study demonstrated that bupropion XL therapy for 8 weeks may attenuate emotion-induced, blood-oxygen-level-dependent (BOLD) activation responses in the amygdala and related brain regions. Such attenuation may be associated with a positive clinical response in depression. Bupropion XL also improved activation in the executive-function neural network. These fMRI surrogate markers offer promise for studying antidepressant and neurocognitive effects of existing and novel therapies.

(J Clin Psychiatry 2007;68:261–267)

Received Feb. 7, 2006; accepted Aug. 14, 2006. *From Clinical Pharmacology and Discovery Medicine, GlaxoSmithKline, Research Triangle Park (Dr. Robertson); and the Department of Psychiatry and the Duke-UNC Brain Imaging and Analysis Center, Duke University Medical Center, Durham (Drs. Wang, Diaz, Gersing, Beyer, Mukundan, McCarthy, and Doraiswamy and Ms. Aiello), N.C.*

The study was supported by an investigator-initiated grant from GlaxoSmithKline.

Financial disclosure appears at the end of the article.

Corresponding author and reprints: Brigitte Robertson, M.D., DUMC Box 3018, Durham, NC 27710 (e-mail: bigsnos@aol.com).

Functional magnetic resonance imaging (fMRI) allows for the mapping of neural networks underlying normal and potential pathologic responses to emotional and cognitive stimuli. These patterns of activation are evidenced by associated changes in the blood-oxygen-level-dependent (BOLD) response and may underlie the symptoms observed in psychiatric disorders such as depression. Patients with depression demonstrate a fundamental impairment in processing emotional affect.[1–8] These impairments are manifest as a mood-congruent processing bias such that ambiguous or positive events tend to be perceived as negative.[9–12] In particular, depressed patients have limited ability to discriminate ranges of affect in faces (e.g., happy and sad facial expressions).[13–15] This impairment contributes significantly to the psychosocial and interpersonal difficulties

© COPYRIGHT 2007 PHYSICIANS POSTGRADUATE PRESS, INC

commonly experienced during an acute depressive episode, and its persistence during remission of clinical symptoms is associated with a vulnerability for future episodes.[16–19]

In addition, during processing of emotional cues, patients tested during a major depressive episode showed different patterns of activation in the amygdala and frontal regions. Specifically, they have excessive activation of the amygdala when exposed to negative emotional stimuli, such as those depicting sadness or fear,[1,20,21] and relatively less activation in frontal regions mediating responses to attentional stimuli.[21] This finding not only is consistent with preclinical and clinical evidence of a key role of the amygdala in mediating evaluations and responses to stress,[22] but also denotes the potentially negative effects that demanding emotional states may have on the capacity of the brain to mediate everyday tasks requiring attentiveness. The exaggerated activation of the amygdala may play a role in the abnormal processing of negative emotions and is reflected in the core symptoms of a depressive episode. Importantly, recent pharmaco-fMRI studies showed that antidepressant therapy (6–8 weeks) with selective serotonin reuptake inhibitors and venlafaxine in patients with a major depressive episode produced an attenuation of emotion-induced increases in the amygdala and related brain structures.[2,23,24] Bupropion differs from these agents in that it does not possess any direct serotonergic activity, but rather exerts its effects through noradrenergic and/or dopaminergic systems. Recently, an extended release formulation of bupropion, bupropion XL, has been made commercially available. To our knowledge, bupropion effects have never been studied using fMRI in patients with major depressive disorder (MDD).

The current study is based on a model of the neural basis of executive function and emotional processing that posits that a dorsal system, including dorsolateral prefrontal cortex (PFC), dorsal anterior cingulate, and inferior parietal cortex, supports executive function, while a ventral system, including ventral medial PFC, orbital frontal cortex (OFC), ventral cingulate, and amygdala, participates in emotion-related processing.[21,24] Interaction and coordination among these regions are necessary for the normal regulation of mood and associated cognitive processing and vegetative function. Depression may result if the synchronized communication between these regions is compromised. Specifically, Mayberg and colleagues[6,21] have suggested that limbic and fronto-cortical structures interact in a reciprocal inhibitory fashion in healthy adults and that this reciprocal inhibition may be impaired in depressed individuals.

The primary objective of this open-label, pilot study was to measure neural activation differences in the emotional and attentional-executive function systems using an Emotional Oddball Task,[25] a modification of the standard visual oddball task. In this event-related fMRI paradigm, "standards" were squares of varying size and color, while infrequent attentional "targets" were circles of varying size and color. In addition, there were 2 kinds of task-irrelevant distracters: emotional distracters, pictures of emotionally unpleasant themes of warfare and violence taken from the International Affective Picture System, and neutral distracters, pictures that were neutral in arousal and valence, that were matched in terms of the number of individuals in the scenes. All measurements were performed in outpatients with MDD before and after 8 weeks of treatment with bupropion XL.

METHOD

The protocol was approved by the Duke University Medical Center Institutional Review Board, and written informed consent was obtained from each subject prior to enrollment. This was an 8-week, open-label, outpatient, single-center study of 10 subjects (7 women; mean [SD] age = 41.4 [± 7] years) with MDD (mean duration of depression = 43.3 [± 37] weeks) (Table 1). The mean score on the Hamilton Rating Scale for Depression (HAM-D)[26] total at baseline was 21 (± 4), and all subjects had a rating of 4 (moderate severity) on the Clinical Global Impressions-Severity of Illness scale (CGI-S).[27] The anatomic MRI studies demonstrated that all subjects were within normal limits.

The study included subjects who were in good health with no unstable medical conditions and taking no or few concomitant medications at stable doses. Inclusion criteria were as follows: men and women between the ages of 18 and 51 years who met criteria for MDD as defined by DSM-IV-TR, had a HAM-D score > 14, and, in women of childbearing potential, were willing to commit to consistent and correct use of approved birth control. Subjects with serious suicidal or homicidal risk, psychosis, substance abuse, or any contraindications to prescribing bupropion XL were excluded from participation. Before subjects were accepted into the study, no other unstable illness or MRI contraindication such as pacemaker or metallic implants was permitted. Exclusion criteria also included uncontrolled hypertension, seizure disorder, eating disorder, a history of treatment-resistant depression, and prior nonresponse to or an intolerance of bupropion. Subjects who were taking any other psychoactive drugs that could confound the brain scans were excluded from participation. Subjects were allowed to continue taking concomitant medications as appropriate.

Participants attended 4 sessions across a 10-week period. The first baseline fMRI scan was performed in December 2004, and the last posttreatment scan was in March 2005. Demographic information and medical and psychiatric histories were collected at the first visit. Psychiatric assessments that measure depression (i.e.,

Table 1. Clinical Variables in Individual Participants[a]

Age (y)	Sex	Medical Conditions and History	Concomitant Medications	HAM-D Score		Days Between fMRI Scans[b]	Days on Treatment With Bupropion XL[c]
				Baseline	Posttreatment		
34	F	Migraines	None	20	18	77	77
36	F	Allergies	Cetirizine/pseudoephedrine	25	7	55	55
32	F	Asthma, borderline hyperglycemia, allergies, polycystic ovaries	Albuterol prn, rosiglitazone, fluticasone, loratadine/ pseudoephedrine	22	6	64	49[d]
44	M	Possible Crohn's disease	Vitamins	27	10	57	57
46	F	Hypothyroidism	Levothyroxine	24	2	44	44
47	M		None	15	7	54	54
50[e]	F		Vitamins, melatonin	23	18	29	27
50[e]	F	Perimenopausal	Ethinyl estradiol/norethindrone	17	10	30	30
37[f]	F	Herpes, headaches	Acyclovir, vitamins, ibuprofen pm	23	NA	NA	NA
38[f]	M	Acid reflux	Famotidine	19	NA	NA	NA

[a]Only major medical problems are noted. Minor or cosmetic surgeries or resolved problems are not described.
[b]Mean ± SD = 51 ± 17 days.
[c]Mean ± SD = 50 ± 16 days.
[d]This subject's use of bupropion XL was interrupted in the middle of the study while she recovered from an allergic reaction to an antibiotic.
[e]Developed side effects; for details, see Adverse Events in Results.
[f]Did not complete the study, and NA is used to specify that a second datapoint is nonapplicable.
Abbreviations: F = female, fMRI = functional magnetic resonance imaging, HAM-D = Hamilton Rating Scale for Depression, M = male, XL = extended release.

HAM-D and CGI-S) were given at each visit. The Clinical Global Impressions-Improvement scale (CGI-I) was performed at visits 3 and 4. Blood pressure and heart rate were recorded at each visit. During the first visit, subjects spent approximately 15 minutes in an MRI scanner simulator to determine if they could comply with the environment during the actual MRI experiment. In addition, they completed a computerized practice neurocognitive testing session measuring memory and reaction time during their first visit. The neurocognitive test battery had 3 subsets: the immediate visual memory task, 1- and 3-item memory scan task, and the delayed visual memory task.

For subjects meeting entry criteria, anatomic and functional MRI data were collected at visit 2 for baseline measurements. Neurocognitive assessments were repeated at visits 2 and 4. Bupropion XL was started the morning after visit 2 and was dosed at 150 mg for 7 days and then increased to the target dose of 300 mg daily. In the event that subjects were unable to tolerate the 300-mg daily dose, they were allowed to remain at the 150-mg dose. The protocol allowed the dose to be increased to 450 mg daily based on clinical response. These doses are in the labeled range for bupropion XL. A second set of anatomic and functional MRI data was collected at visit 4, approximately 8 weeks after the start of bupropion XL treatment. In the event that a subject discontinued use of bupropion XL early and if the subject was amenable, it was decided on a case-by-case basis by the principal investigator whether the subject would have the second follow-up scan.

Participants were asked to refrain from eating and drinking in the 3 hours prior to the collection of MRI data. Subjects were also asked to refrain from alcohol, tobacco, caffeine, and any prescription or nonprescription drugs for 12 hours prior to their procedure as an attempt to reduce factors that could confound brain blood flow. MRI scanning was completed on a General Electric 1.5-Tesla LX Nvi MRI scanner equipped with a 41-mT/m gradient coil and using a birdcage radio frequency (RF) head coil for transmission and receiving of RF signal (General Electric; Milwaukee, Wis.). Sagittal T-1 weighted localizer images were acquired and used to define an imaging volume. The anterior and posterior commissures were identified for slice selection. High resolution structural images were acquired using a spin echo proton-density T2 pulse sequence (field of view [FOV] = 24 cm^2; voxel size = 0.9375 × 0.9375 × 2.9 mm, 48 slices), and 2 series of T1-weighted images were collected: 3D high resolution (FOV = 24 cm^2; voxel size = 0.9375 × 0.9375 × 1.5 mm, 124 slices) and coplanar (FOV = 24 cm^2; voxel size = 0.9375 × 0.9375 × 1.9 mm, 68 slices). Functional images sensitive to BOLD contrast were acquired using an inverse spiral pulse sequence (repeat time [TR] = 2 s; time of echo [TE] = 10 ms; FOV = 24 cm^2; voxel size = 3.75 × 3.75 × 3.8 mm; 36 contiguous axial slices). Four initial RF excitations were performed at the beginning of each functional run to achieve steady state equilibrium.

During the fMRI sessions, subjects performed the Emotional Oddball Task (8 functional runs), which lasted approximately 45 minutes. This was an event-related fMRI paradigm in which 90% of the stimuli were "standards," or squares of varying color and size. The remaining stimuli were either attentional targets (i.e., circles of varying size and color) or task-irrelevant distracters. Distracters were 1 of 2 types: emotional distracters were

pictures of emotionally unpleasant themes of warfare and violence taken from the International Affective Picture System, and neutral distracters were pictures, neutral in arousal and valence, that were matched in terms of the number of individuals in the scenes. Distracters and targets were randomly interspersed within the standards and occurred with the same frequency. Subjects responded with a designated button press for "targets" and an alternate button press for all other stimulus types.

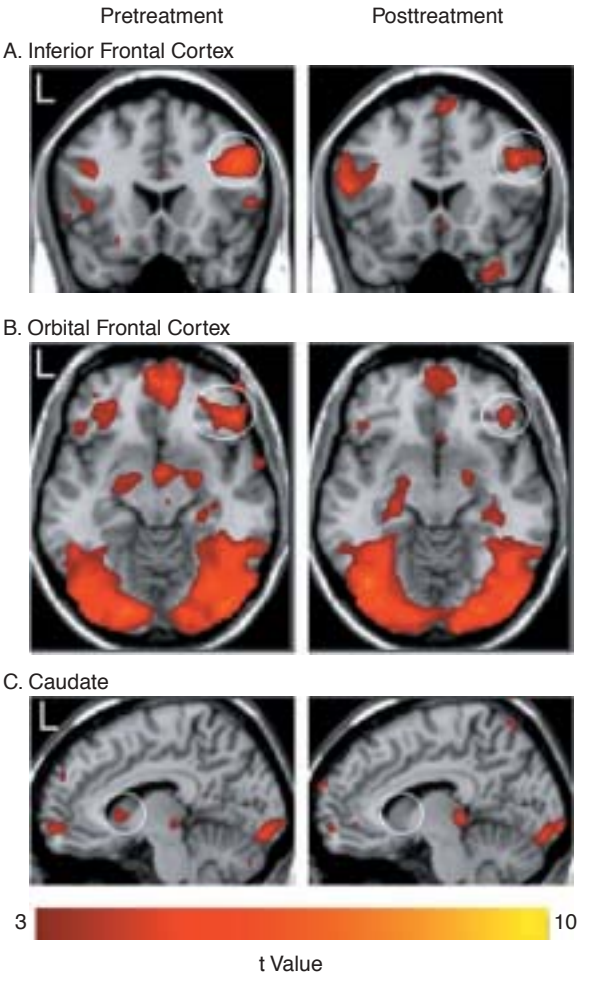
Each functional run was approximately 4 minutes long. During the Emotional Oddball Task, the subjects viewed 3 types of stimuli: standards, targets, and distracters presented in random order. During this task, the subjects were asked to press a button using their right index finger whenever a target appeared and their right middle finger for all other stimuli. Activations evoked by emotional distracters, which indexed negative emotional processing, were the primary outcome. Before proceeding to this endpoint analysis, the values of BOLD signal changes produced by emotional distracters were compared with those produced by neutral distracters. Only those with statistically different values were considered for final analysis. Activations evoked by the target stimuli, which probed the attentional-executive function network, were the secondary outcome. Again, before proceeding to this endpoint analysis, the values of BOLD signal changes produced by the targets' presentation were compared with those produced by the standard stimuli. Only those with statistically different values were considered for final analysis.

Functional MRI data analysis was performed using Statistical Parametric Mapping (SPM99; Wellcome Department of Cognitive Neurology, London, United Kingdom) and custom Matlab (Mathworks, Natick, Mass.) scripts. No subject had a movement greater than 3 mm in the X, Y, or Z dimension. Images were corrected for time of acquisition and head motion, normalized to a standard stereotaxic space (Montreal Neurological Institute; Montreal, Quebec, Canada), and smoothed with an 8-mm Gaussian kernel. The normalized and smoothed data were used in the analyses reported below. Epochs time-locked to the critical stimuli were extracted from the continuous time series and averaged according to trial type (emotional and neutral distracters, targets). Each epoch consisted of a total of 10 images (at onset and 2 preceding and 7 following event onset, capturing –4 s to 14 s). Voxel-wise fixed-effects analyses were conducted for each subject by regressing an empirically derived hemodynamic template with the epochs for each trial type, which produced t-statistic activation maps for each condition in each subject.

Statistical Analyses

All comparisons were within-subject between baseline and posttreatment endpoint observations. Primary outcomes were percent signal changes from baseline for the fMRI task. For the emotional distracters, only responses that were significantly different from neutral distracters were considered significant. p Values less than .05 were significant for primary outcomes in the paired t test. We also tested the correlation between clinical and fMRI BOLD signal changes using the Pearson correlation coefficient, where $r > 0.5$, $p < .05$ were considered significant. Of the 10 subjects, only 8 subjects completed a posttreatment fMRI scan (Table 1), and only their data were analyzed.

Figure 1. Average t Statistic Maps Showing the Results of a Fixed-Effects Analysis of the Responses Evoked by Emotional Distracters at Pretreatment and Posttreatment[a]



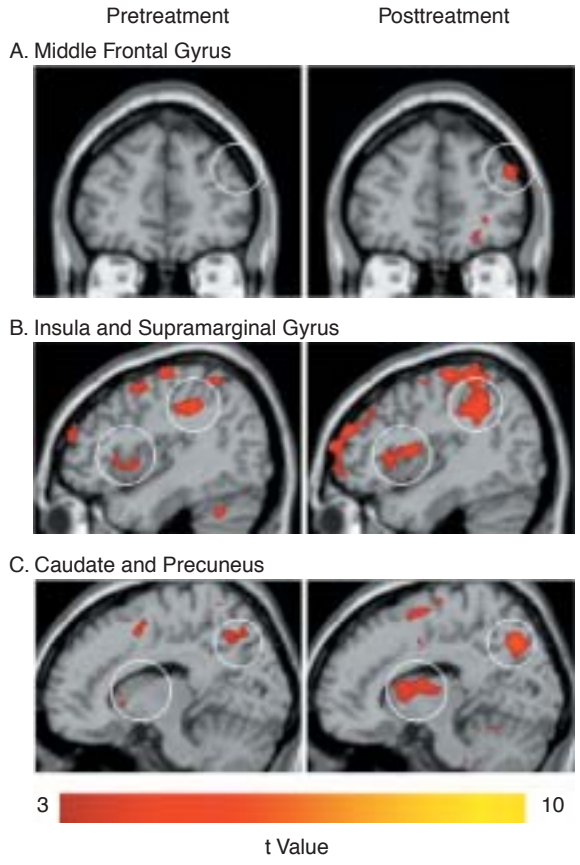
[a]Threshold $t > 3$, $p < .01$. Circles indicate the regions that showed significant differences between pretreatment and posttreatment.

RESULTS

Effect of Treatment on Depression

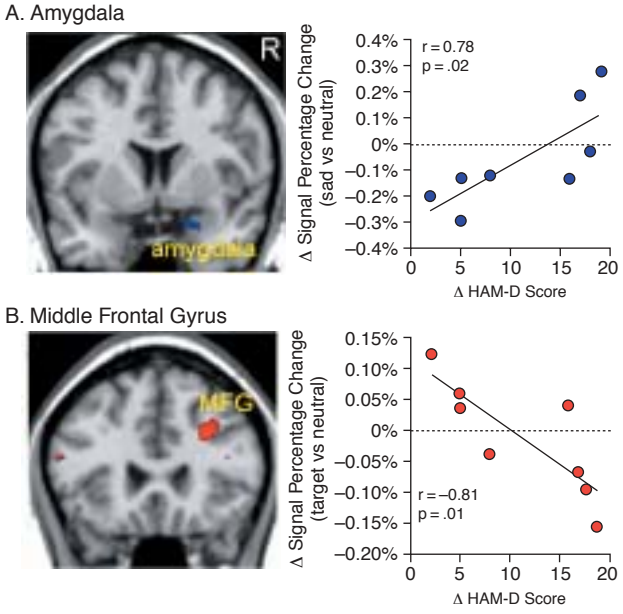
Statistically significant improvements in HAM-D ($p < .005$), CGI-S ($p < .01$), and CGI-I ($p < .05$) scores

Figure 2. Average t Statistic Maps Showing the Results of a Fixed-Effects Analysis of the Responses Evoked by Attentional Targets at Pretreatment and Posttreatment[a]



[a]Threshold t > 3, p < .01. Circles indicate the regions that showed significant differences between pretreatment and posttreatment.

Figure 3. Voxel-Based Paired t Test Analysis Showing Decreased Peak Activation in the Amygdala and Increased Peak Activation in Middle Frontal Gyrus Posttreatment[a,b]



[a]t > 1.9, p < .05.
[b]As demonstrated in the graphs, decreased activation in the left amygdala and increased activation in the right middle frontal gyrus showed significant regional correlation with decreased HAM-D score posttreatment.
Abbreviation: HAM-D = Hamilton Rating Scale for Depression.

were noted from week 4 through endpoint at week 8. At endpoint on the CGI-S, 25% (N = 2) of the subjects remained with moderate depression and 75% (N = 6) had improved. Of the patients who improved, half (N = 3) were rated as having mild symptoms and the other half as having normalized or only borderline symptoms. At endpoint, both mean HAM-D score (9.8 ± 6) and mean CGI-S score (2.6 ± 4) were indicative of the degree of improvement. The secondary neurocognitive indices of memory did not show any significant effects of treatment. There were no significant reaction time differences or performance differences during the Emotional Oddball Task.

Effects of Treatment on fMRI Activation Patterns

Figures 1–3 and Table 2 show fMRI results. Treatment with bupropion XL reduced activation seen in the right OFC, right ventromedial PFC, right anterior cingulate cortex, right inferior frontal cortex (IFC), right amygdala/parahippocampal area (PHipp), right caudate, right fusiform gyrus (FFG), and left dorsomedial PFC and posterior cingulate cortex during passive viewing of emotional distracters. In 2 regions (left IFC and left FFG), bupropion XL increased the activation evoked by emotional distracters. The decrease in fMRI activation to emotional distracters in the right OFC, IFC, PHipp, and FFG and left amygdala was highly correlated with the improvement in the HAM-D score during bupropion XL therapy (r = 0.78, p < .05, in some regions). Treatment with bupropion XL increased activation to attentional targets in the right middle frontal gyrus, IFC, and caudate and bilateral precuneus. The increased activation in the middle frontal gyrus was strongly correlated with the improvement in the HAM-D score (r = –0.95, p < .01). Because of the sample size and statistical threshold used, our results should be viewed as pilot rather than definitive.

Adverse Events

Of the 10 subjects, 4 stopped study medication prematurely. One subject developed a mild allergic reaction, a second subject developed tremors, and a third subject felt that the drug was ineffective. The fourth subject had a panic attack and was hospitalized briefly to rule out a cardiac event. This was felt to be drug related. In addition to this subject, 2 other subjects had serious adverse events.

© COPYRIGHT 2007 PHYSICIANS POSTGRADUATE PRESS, INC

Table 2. Regions Showing Significant Peak Activation Changes Posttreatment Compared With Baseline (paired t test, p < .05)

Stimuli	Side	x_{tal}	y_{tal}	z_{tal}	t Value	r Value[a]
Decreased activation posttreatment						
Sad vs neutral contrast						
OFC	R	31	37	–11	3.32	
DmPFC	L	–3	52	26	3.04	
VmPFC	R	7	33	–6	4.02	
ACC	R	3	35	11	3.44	0.92
IFC	R	42	24	5	4.41	0.93
Amygdala/parahippocampal	R	24	–39	0	2.64	0.84
Caudate	R	14	17	9	3.94	
PCC	L	–7	–47	–22	4.24	
FFG	R	28	–58	–3	3.06	
Attentional targets						
Ventral putamen	R	28	–10	7	2.62	
SMG	L	–55	–49	21	4.02	
FEF	L	31	–58	0	4.54	
Increased activation posttreatment						
Sad vs neutral contrast						
IFC	L	–49	28	15	6.32	
FFG	L	–31	–58	0	4.21	
Attentional targets						
MFG	R	35	52	14	2.26	–0.95
IFC	R	55	11	25	2.98	
Caudate	R	17	–2	23	2.97	
Precuneus	R	10	–73	46	3.52	
	L	–3	–73	46	3.73	

[a]Only regions that showed significant blood-oxygen-level-dependent (BOLD) signal changes posttreatment and the changes significantly correlated with decreased HAM-D score posttreatment are shown here. The r value is the correlation coefficient value at the voxel that showed peak signal change.

Abbreviations: ACC = anterior cingulate cortex, DmPFC = dorsomedial prefrontal cortex, FEF = frontal eye field, FFG = fusiform gyrus, HAM-D = Hamilton Rating Scale for Depression, IFC = inferior frontal cortex, L = left, MFG = middle frontal gyrus, OFC = orbital frontal cortex, PCC = posterior cingulate cortex, R = right, SMG = supramarginal gyrus, tal = Talairach coordinate, VmPFC = ventromedial prefrontal cortex.

One subject developed worsening bronchitis/asthma that required steroids and antibiotics. This was considered unrelated to the study drug. The subject resumed bupropion XL treatment after her medical stabilization and found it to be beneficial. Another subject developed worsening suicidal ideation from multiple concurrent life crises that required brief hospitalization. Overall, the most common adverse events reported were dry mouth (N = 5), constipation (N = 3), reduced appetite (N = 1), weight loss (N = 1), tremors (N = 1), panic attack (N = 1), rash (N = 1), and intermittent palpitation (N = 1).

DISCUSSION

Patients with MDD may show abnormal processing of negative emotions associated with an excessive increase in activation through the amygdala and a series of related limbic structures when exposed to negative emotional stimuli (sadness, fear, etc.). Consistent with previous reports, we found increased activation to emotional stimuli relative to neutral stimuli in the amygdala at baseline. Our study demonstrates that bupropion XL therapy for 8 weeks may attenuate this abnormally increased emotion-induced activation in the OFC and amygdala. This is consistent with other pharmaco-fMRI studies that have demonstrated decreases in activation in the amygdala and OFC after treatment.[2,23,28] Further, the data suggest that such attenuation may be closely linked to improvement in clinical ratings of depression. These findings extend prior fMRI studies of mood neural network functionality in depressed and nondepressed individuals as well as prior pilot studies of serotonergic antidepressants.

The main limitations of this study are the small sample size and lack of nondepressed and untreated depressed control groups. As such, this was a pilot study, and hence our findings should be interpreted with caution. The main strengths are the careful clinical and fMRI data collection that used a reliable task. In addition, this is the first fMRI study of a nonserotonergic antidepressant. Our study supports a role for norepinephrine in modulating the response of the depressed brain to negative emotions. Given that treatment with bupropion increased activation to attentional targets[25,29,30] in the middle frontal and inferior frontal cortex, the data suggest that bupropion improved activation in the executive-function system. Controlled studies are suggested to confirm these findings and test the promise of fMRI surrogate markers for studying antidepressant efficacy, mechanisms of action, and response patterns.

Drug names: acyclovir (Zovirax and others), albuterol (Ventolin, Proventil, and others), bupropion (Wellbutrin and others), cetirizine (Zyrtec), famotidine (Pepcid and others), fluticasone (Flovent and others), ibuprofen (Motrin and others), levothyroxine (Synthroid, Levo-T, and others), loratadine (Clarinex), rosiglitazone (Avandia), venlafaxine (Effexor and others).

Financial disclosure: Dr. Robertson was an employee of GlaxoSmithKline at the time the research was conducted. Ms. Aiello received salary support from industry research grants. Drs. Gersing and McCarthy have received research funding from several pharmaceutical companies. Dr. Beyer has served as a consultant for or received research grants from several antidepressant manufacturers. Dr. Mukundan has received grant/research support from the American Society of Neuroradiology and the American Roentgen Ray Society and has received honoraria from GE Healthcare. Dr. Doraiswamy has been a consultant to, received grant/research support and honoraria from, and been on the speakers/advisory boards of GlaxoSmithKline, Pfizer, Eisai, Eli Lilly, Forest, Bristol-Myers Squibb, Sanofi, Organon, and GE. Drs. Wang and Diaz report no additional financial or other relationship relevant to the subject of the article.

REFERENCES

1. Drevets WC. Neuroimaging studies of mood disorders. Biol Psychiatry 2000;48:813–829
2. Sheline YI, Barch DM, Donnelly JM, et al. Increased amygdala response to masked emotional faces in depressed subjects resolves with antidepressant treatment: an fMRI study. Biol Psychiatry 2001;50:651–658
3. Siegle GJ, Steinhauser SR, Thase ME, et al. Can't shake that feeling: event-related fMRI assessment of sustained amygdala activity in response to emotional information in depressed individuals.

Biol Psychiatry 2002;51:693–707
4. Yurgelun-Todd DA, Gruber SA, et al. fMRI during affect discrimination in bipolar affective disorder. Bipolar Disord 2000;2:237–248
5. Ketter TA. Functional brain imaging, limbic function, and affective disorders. Neuroscientist 1996;2:55–65
6. Mayberg HS. Limbic-cortical dysregulation: a proposed model of depression. J Neuropsychiatry Clin Neurosci 1997;9:471–481
7. Drevets WC, Price JL, Simpson JR, et al. Subgenual prefrontal cortex abnormalities in mood disorders. Nature 1997;386:824–827
8. Elliott R, Rubinsztein JS, Sahakian BJ, et al. The neural basis of mood-congruent processing biases in depression. Arch Gen Psychiatry 2002;59:597–604
9. Amado-Boccara I, Gougoulis N, Poirier Littre MF, et al. Effects of antidepressants on cognitive functions: a review. Neurosci Biobehav Rev 1995;19:479–493
10. Brand N, Jolles J. Information processing in depression and anxiety. Psychol Med 1987;17:145–153
11. Brand N, Jolles J, Gispen de Wied C. Recall and recognition memory deficits in depression. J Affect Disord 1992;25:77–86
12. Klassen T, Riedel WJ, Deutz NEP, et al. Mood congruent memory bias induced by tryptophan depletion. Psychol Med 2002;32:167–172
13. Baird AA, Gruber SA, Fein DA, et al. Functional magnetic resonance imaging of facial affect recognition in children and adolescents. J Am Acad Child Adolesc Psychiatry 1999;38:195–199
14. McClure EB, Pope K, Hoberman AJ, et al. Facial expression recognition in adolescents with mood and anxiety disorders. Am J Psychiatry 2003; 160:1172–1174
15. Morris JS, Frith CD, Perrett DI, et al. A differential neural response in the human amygdala to fearful and happy facial expressions. Nature 1996;383:812–815
16. Deldin PJ, Keller J, Gergen JA, et al. Cognitive bias and emotion in neuropsychological models of depression. Cogn Emot 2001;15:787–802
17. Nitschke JB, Heller W, Imig JC, et al. Distinguishing dimensions of anxiety and depression. Cogn Ther Res 2001;25:1–22
18. Sloan DM, Strauss ME, Quirk SW, et al. Subjective and expressive emotional responses in depression. J Affect Disord 1997;46:135–141
19. Taylor SE, Brown JD. Illusions and well-being: a social psychological perspective on mental health. Psychol Bull 1988;103:193–210
20. Abercrombie HC, Schaefer SM, Larson CL, et al. Metabolic rate in the right amygdala predicts negative affect in depressed patients. Neuroreport 1998;9:3301–3307
21. Mayberg HS, Liotti M, Brannan SK, et al. Reciprocal limbic-cortical function and negative mood: converging PET findings in depression and normal sadness. Am J Psychiatry 1999;156:675–682
22. Rogan MT, Staubli UV, Ledoux J. Fear conditioning induces associative long-term potentiation in the amygdala. Nature 1997;390:604–607
23. Davidson RJ, Irwin W, Anderle WJ, et al. The neural substrates of affective processing in depressed patients treated with venlafaxine. Am J Psychiatry 2003;160:64–75
24. Mayberg HS, Brannan SK, Tekell JL, et al. Regional metabolic effects of fluoxetine in major depression: serial changes and relationship to clinical response. Biol Psychiatry 2000;48:830–843
25. Yamasaki H, Labar KS, McCarthy G. Dissociable prefrontal brain systems for attention and emotion. PNAS 2002;99:11447–11451
26. Hamilton M. A rating scale for depression. J Neurol Neurosurg Psychiatry 1960;23:56–62
27. Guy W. ECDEU Assessment Manual for Psychopharmacology. US Dept Health, Education, and Welfare publication (ADM) 76-338. Rockville, Md: National Institute of Mental Health; 1976:218–222
28. Sheline YI. Neuroimaging studies of mood disorder effects on the brain. Biol Psychiatry 2003;54:338–352
29. Kirino E, Belger A, Goldman-Rakic P, et al. Prefrontal activation evoked by infrequent target and novel stimuli in a visual target detection task: an event-related functional magnetic resonance imaging study. J Neurosci 2000;20:6612–6618
30. Wang L, McCarthy G, Song AW, et al. Amygdala activation to sad pictures during high-field (4 tesla) functional magnetic resonance imaging. Emotion 2005;5:12–22