Different Effects of Mirtazapine and Venlafaxine on Brain Activation: An Open Randomized Controlled fMRI Study

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Objective: Antidepressants with different mechanisms of action might have different effects on brain functions. The aim of the study was therefore to investigate effects of 2 antidepressants on brain activation and to identify predictors for therapy response.

Method: Twenty-four untreated patients with major depressive disorder (according to Structured Clinical Interview for *DSM-IV*) were enrolled in a prospective, randomized, 4-week trial with mirtazapine and venlafaxine. Functional magnetic resonance imaging (fMRI) was performed at baseline and after 4 weeks in the patients and in 15 healthy controls. The primary outcome measure was fMRI blood-oxygen-level dependence (BOLD) activation. The patients were recruited in 2007 and 2008.

Results: Comparison between patients and controls revealed that emotional face matching elicited enhanced activation in the anterior cingulate cortex (ACC), dorsomedial prefrontal cortex, dorsolateral prefrontal cortex, and basal ganglia in patients. During treatment, a significant decrease of BOLD responses was seen in the hippocampus, basal ganglia, thalamus, and cerebellum of venlafaxine-treated patients, and a significant increase in BOLD responses was seen in the middle cingulate gyrus and supplementary motor area of mirtazapine-treated patients ($P < .05$, family wise error [FWE] cluster-level corrected). Larger BOLD responses in the left fusiform gyrus at baseline predicted a better response to venlafaxine, and smaller BOLD responses in the right rolandic operculum at baseline predicted a better response to mirtazapine ($P < .05$, FWE cluster-level corrected).

Conclusions: These fMRI results indicate that antidepressants with different mechanisms of action have different effects on brain function. It therefore seems that fMRI can be used for therapy evaluation and response prediction and can facilitate the development of new pharmaceuticals.

J Clin Psychiatry 2011;72(4):448–457

Submitted: *May 27, 2009; accepted September 30, 2009.*
Online ahead of print: *September 21, 2010 (doi:10.4088/JCP.09m05393blu).*
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The World Health Organization has found that major depression is one of the most important human diseases, with a prevalence of about 10%.[1] Although effective antidepressants are available, up to 20% of patients develop chronic, treatment-resistant depression. Different antidepressants with different mechanisms of action are available,[2] but the exact effects on the brain and, in particular, the effects on the brain's network of mood regulation remain unclear. Moreover, no markers for therapy evaluation and response prediction are available at present; such markers would facilitate drug development and treatment. Functional magnetic resonance imaging (fMRI) is becoming established as a method of visualizing the action of drugs on animal and human brain; in this context it is called *pharmacoMRI* or *phMRI*. Longitudinal functional imaging studies (without a comparison treatment arm) that investigated changes in the brains of patients with major depression after treatment with an antidepressant medication found different results: Exaggerated left amygdala activation in 11 patients during a face-matching paradigm decreased to a normal activation level following treatment with the selective serotonin reuptake inhibitor (SSRI) sertraline.[3] In a face-affect matching task, 12 patients with major depression showed significantly increased activation in the left insular cortex after 2 weeks of treatment with venlafaxine and in the left anterior cingulate cortex (ACC) after 8 weeks of treatment.[4] During an 8-week course of fluoxetine, 19 depressed patients showed a decrease of overactivity in the left amygdala, ventral striatum, and frontoparietal cortex in an emotional fMRI task. Moreover, changes in ACC function, which are associated with symptomatic improvement, indicate that fMRI may become a useful marker of antidepressant treatment response.[5]

We used innovative and state-of-the-art functional neuroimaging modalities to prospectively study and characterize changes in the brain—related to depression and recovery from depression—under different antidepressant treatments. Mirtazapine is a noradrenergic and specific serotonergic antidepressant with a profile of α_2-, serotonin (5-hydroxytryptamine [5-HT]) 2A-, 5-HT_{2B}-, 5-HT_3-, and histamine 1 (H_1)- receptor antagonism.[6–9] Studies indicate that the radiotracer [^{11}C]mirtazapine binds to a greater extent to cortical brain regions like the prefrontal cortex, insula cortex, and occipital cortex and, to a lesser extent, to subcortical regions.[10] The primary effect of serotonin-norepinephrine reuptake inhibitors (SNRIs) like venlafaxine is to elevate extracellular serotonin (5-HT) and norepinephrine levels by

inhibiting their reuptake to presynaptic sites. Venlafaxine blocks 5-HT transporters (5-HTT), and the blockade seems to be greatest in subcortical regions like the basal ganglia and thalamus, and in the frontal cortex and ACC.[11] We therefore hypothesized that mirtazapine and venlafaxine may have different, region-specific effects. In particular, our primary new hypotheses were the following: (1) the antidepressant mirtazapine primarily normalizes cortical regions, whereas the antidepressant venlafaxine normalizes a wider area of the brain, including subcortical regions like the basal ganglia and thalamus, and (2) patients with greater ACC activity are more likely to remit during antidepressant treatment. The secondary hypotheses were (1) patients with major depressive disorder will show a higher blood-oxygen-level dependence (BOLD) response than healthy controls in the ACC, prefrontal cortex, and amygdala, and (2) antidepressant therapy will normalize these altered brain activities.

On the basis of the results of earlier fMRI studies, we estimated that a sample size of 12 participants per treatment arm would be large enough to show differences between the 2 groups.

METHOD

Study Participants

Twenty-four patients with major depressive disorder were recruited at the Department of Psychiatry of the Ludwig-Maximilian University, Munich, in 2007 and 2008 (Table 1). Psychiatric diagnoses were based on *DSM-IV* criteria and the Structured Clinical Interview for *DSM-IV*[12] and were determined by a consensus of at least 2 psychiatrists. All patients were medication free at the time of enrollment: 15 patients had never received antidepressant medication and 9 had received antidepressant medications for a previous episode but not within the year before the fMRI investigation. Patients were randomly assigned to 4 weeks' treatment with mirtazapine or venlafaxine. The clinical team chose daily doses within the range of 30 to 45 mg for mirtazapine and 150 to 300 mg for venlafaxine on the basis of each patient's symptoms. Comedication with benzodiazepine lorazepam and the hypnotic zopiclone to treat insomnia was allowed, but no other comedication was permitted. Neuroimaging was performed at baseline (before treatment was started) and after 4 weeks. No side effects that resulted in a patient dropping out were reported. Clinical variables were documented using the Hamilton Depression Rating Scale (HDRS)[13] and determined at baseline (on the day of the scan) and then after 7, 14, 21, and 28 days. Response was defined as a reduction in the HDRS score by more than 50% after 28 days. Change in depression severity was calculated by dividing the percentage change during the trial by the baseline HDRS score.

For comparison, 15 healthy control participants—matched for age, sex, education level, and handedness—were recruited. A structured interview was used to assess medical history, trauma, and other exclusion criteria. Neither the healthy controls nor their first-degree relatives had a history of neurologic or mental illness.

Exclusion criteria for patients and controls were previous head injury with loss of consciousness, cortisol treatment in the medical history, previous alcohol or substance abuse or neurologic diseases, age under 18 or over 65 years, and pregnancy. For patients, comorbidity with other mental or neurologic illnesses or personality disorders and previous electroconvulsive therapy were additional exclusion criteria.

Handedness of all participants was determined by the Edinburgh Inventory (Oldfield[14]). The study was explained in detail to all participants, and written informed consent was obtained. The study protocol was approved by the local ethics committee of the Ludwig-Maximilian University and prepared in accordance with the ethical standards laid down in the Declaration of Helsinki.

Emotional Paradigm

Stimuli consisted of faces drawn from a well-established emotional face database.[15] The facial recognition task was adapted from Hariri et al[16]; we made changes with respect to the kind of emotion and used both explicit and implicit conditions. Instead of sad and anxious faces, as used by Hariri et al,[16] we used sad and angry ones because we wanted to focus on clear major depressive disorder without comorbid anxiety. In the explicit task, study participants were shown triplets of either 3 female or 3 male faces; 1 face was at the top of the screen (in the middle) and 2 faces were at the bottom (on the left and right). There were 48 of these triplets of emotional faces (sad or angry); the triplets were arranged in a block design—8 blocks of 6 triplets each—and interspersed with 9 control blocks of 6 triplets each. Control blocks consisted of simple black geometrical figures (squares, triangles, circles, ellipses). Participants were instructed to choose which face at the bottom (left or right) had the same emotional expression as the face at the top. Responses were given with an fMRI-compatible LUMItouch system (Photon Control Inc, Burnaby, British Columbia, Canada) by pressing 1 of 2 keys to choose the right or left face. In the implicit task, each triplet consisted of 1 male or female face as the target at the top (in the middle) and 1 male and 1 female face at the bottom (on the left and right). Participants were asked to determine which face at the bottom (left or right) matched the sex of the target face at the top. The target faces alternately showed angry and sad emotions. Again, participants had to respond with the LUMItouch system. Each triplet was presented for 5.3 seconds; thus, each task (consisting of 8 blocks with 6 triplets of emotional faces and 9 control blocks with 6 triplets of geometrical figures) lasted about 9 minutes. The order of tasks (explicit, implicit) and of target stimuli was randomized.

Image Acquisition

Functional images were acquired on a 3T MRT scanner (Signa HDx, GE Healthcare, Milwaukee, Wisconsin) using a T2*-weighted gradient echo-planar imaging sequence (TR 2100 ms, TE 35 ms, flip angle of 90°, matrix 64 × 64, FOV 256 × 256 mm). Two functional runs of 265 contiguous

volumes were acquired. Volumes comprised 37 axial slices of 4 mm thickness and covered the whole brain. Slices were positioned to the connecting line between the anterior and posterior commissure.

Structural T1-weighted MRI images were acquired within the same session using a 3-dimensional fast spoiled gradient echo (3D-FSPGR) sequence (TR 6.9 ms, TE 3.2 ms, flip angle of 15°, matrix 256 × 256, FOV 220 mm, slice thickness 1.4 mm, number of slices 248).

Behavioral Data Analysis

Behavioral performance differences between healthy controls and patients were calculated separately for the implicit and explicit trials by using 2-sample *t* tests for reaction time and errors.

fMRI Data Analysis

Statistical Parametric Mapping, version 5 (SPM5), was used to analyze data after the following preprocessing steps: realigning of all volumes to the sixth scan to correct for subject motion (exclusion criteria: more than 3 mm); coregistration of the functional and structural data sets; spatial normalizing into a standard stereotactic space, using a template of the Montreal Neurologic Institute; and smoothing of the data with an 8 mm Gaussian Kernel. Statistical parametric maps were calculated by using a general linear model based on a voxel-by-voxel method.[17] Based on results of previous studies using fMRI, sample size calculations found that 12 participants in each treatment arm would be sufficient to show differences in longitudinal changes.

First-Level Analysis

The statistical design matrix of the first-level analysis, which involves analysis of individual subjects, included 2 sessions (implicit and explicit), each with 2 regressors and 1 constant. Motion parameters were not used as covariates. Each regressor consisted of a box-car function convolved with an estimated hemodynamic response function. Thus, the expected hemodynamic response to the experimental stimulus was modeled using the relative contributions of a delayed box-car reference wave function and confounding variables (whole-brain activity and low-frequency variations).

After parameter estimation, contrast images were constructed for explicit triplets > control stimuli and implicit triplets > control stimuli.

Second-Level Analysis

The contrast images for the implicit and the explicit tasks were entered into the second-level analysis, with age and sex as cofactors, as follows:

1. Differences between baseline and follow-up in the patient group.
2. Differential effects of medication: 2 × 2 factorial design matrix with medication group (venlafaxine versus mirtazapine) and time (baseline versus 4-week follow-up).
3. Functional differences at baseline: healthy controls versus patients.
4. Response prediction: responder versus nonresponder.

The primary outcome measures were fMRI BOLD responses. Baseline differences and differences in therapeutic effects between patients treated with mirtazapine and those treated with venlafaxine were assessed; a statistical threshold of $P < .05$ was used at the cluster level, family wise error (FWE) corrected (primary threshold of $P < .001$ at the voxel level). Multiple regression analysis was used to find linear associations between changes in depression severity during the trial and BOLD responses ($P < .05$, FWE corrected on cluster level). Additionally, exclusive masking—an analysis method implemented in SPM5—was only used to compare patients with healthy controls at baseline. These group comparisons are performed using exclusive masking to reveal voxels showing significant activation for the contrast (emotion > neutral) in 1 population but no such effect in the other population for the exact same contrast.[18] The threshold for SPM-exclusive masks was $P < .05$ (uncorrected), whereas for the contrasts it was $P < .05$ at the cluster level, FWE corrected (primary threshold of $P < .001$ at the voxel level). It should be noted that the more liberal the threshold of an exclusive mask, the more conservative is the masking procedure.

The anatomic localization of significant clusters was identified using the SPM toolbox automated anatomical labeling, which is described by Tzourio-Mazoyer et al.[19]

RESULTS

There were no significant differences between patients and controls with respect to age, sex, and weight (Table 1) or between patients receiving mirtazapine and those receiving venlafaxine with respect to age, sex, illness duration, number of episodes, or depression severity. Lorazepam daily doses did not differ between the mirtazapine and venlafaxine groups (first fMRI: $t = 0.55$, $P = .59$; second fMRI: $t = -0.67$, $P = .51$; cumulative dose during the 4-week trial: $t = -0.33$, $P = .77$). Doses of zopiclone also did not differ between the medication groups (first fMRI: $t = -1.5$, $P = .14$; second fMRI: $t = -1.4$, $P = .19$; cumulative dose during the 4-week trial: $t = -1.0$, $P = .34$). Moreover, responders differed from nonresponders only with respect to the cumulative dose of zopiclone, which was higher for nonresponders ($t = 2.2$, $P = .042$). Depression severity decreased significantly from baseline to the 4-week follow-up in both the venlafaxine ($t = 7.0$, $P < .001$) and the mirtazapine groups ($t = 11.0$, $P < .001$).

Behavioral Data

The number of correct responses and the reaction time in the explicit, implicit, and comparison conditions were similar in patients and controls. No significant change between baseline and the follow-up investigation was observed in the behavioral data, except that patients chose the emotional face faster after treatment than before ($t = 2.4$,

Table 1. Demographic Characteristics of Healthy Controls and Patients (whole group) and of Patients Receiving Mirtazapine and Those Receiving Venlafaxine[a]

	Comparison of Healthy Controls and Patients			Comparison of Patient Groups		
Characteristic	Healthy Controls (n = 15)	Patients (n = 24)	*P* Value	Mirtazapine (n = 11)	Venlafaxine (n = 13)	*P* Value
Age, y	35.5 (10.8)	38.9 (10.4)	.32	36.9 (8.5)	40.7 (11.8)	.39
Women/men[b]	5/10	8/16	> .99	4/7	4/9	.77
Weight, kg	70.0 (10.5)	74.4 (12.5)	.20	69.1 (8.9)	78.9 (13.7)	.05
HDRS score at baseline	…	20.9 (5.2)	…	21.1 (5.9)	20.7 (4.8)	.86
HDRS score at 4-week follow-up	…	10.4 (5.4)	…	8.6 (4.6)	11.8 (5.7)	.15
Illness duration, mo	…	56.0 (63.4)	…	68.3 (72.1)	45.5 (55.8)	.39
No. of episodes	…	1.6 (0.7)	…	1.6 (0.7)	1.6 (0.7)	.96
Medication dose, mg/d	…	…	…	36.8 (7.2)	202.0 (47.3)	< .001

[a]Values are shown as mean (SD).
[b]χ^2 test.
Abbreviation: HDRS = Hamilton Depression Rating Scale.

P = .027); however, this result was no longer significant after Bonferroni correction.

Functional Differences at Baseline

BOLD responses—analyzed using FWE cluster corrections—did not differ between patients and healthy controls. Using the exclusive masking procedure, in explicit processing, we found that patients showed significantly BOLD responses in a cluster within the right and left ACC and middle cingulate gyrus (MCG) (ACC, Brodmann area 32 and MCG, Brodmann area 24, respectively) and in the right and left superior frontal medial cortex extending to the supplementary motor area (SMA), in the right middle frontal gyrus (dorsolateral prefrontal cortex [DLPFC]) and in a cluster in the left parietal cortex and angular gyrus (*P* < .05, FWE corrected at the cluster level), whereas healthy controls did not show any significant emotion-related responses in these areas. In the implicit condition, healthy controls showed BOLD responses within the left superior parietal, precuneus and superior occipital cortex that were absent in the patients. The contrast images for explicit and implicit processing showed significant (*P* < .05, FWE corrected at the cluster level) BOLD responses in patients in the ACC (Brodmann area 32), MCG (Brodmann area 24), and superior dorsomedial prefrontal cortex (DMPFC) in both hemispheres and in the right basal ganglia, whereas healthy participants did not show responses in these regions.

Response Prediction

In the analysis at the FWE-corrected cluster level, responders to either treatment did not show significantly more or less BOLD responses than nonresponders. Multiple regression analysis for the whole group of patients found no significant associations between BOLD responses at baseline and the change of depression severity during the trial. However, in the implicit task, patients responding better to mirtazapine during the study showed less BOLD activation at baseline in the right rolandic operculum (Brodmann area 43) of the parietal cortex (*P* = .027, FWE cluster corrected, k = 22, *t* = 7.17, x = 48, y = −24, z = 20; k = number of voxels). Those patients who responded better to venlafaxine showed larger BOLD responses in the left fusiform gyrus (*P* = .010, FWE cluster corrected, k = 171, *t* = 6.91, x = −42, y = −52, z = −16) (Figure 1).

Effect of Time (pretreatment versus posttreatment)

In the explicit condition, patients' BOLD responses decreased significantly from baseline to follow-up in a cluster in the left orbitofrontal cortex, with extensions to the left insular cortex, and in the left and right thalamus and basal ganglia regions (*P* < .05, FWE corrected at the cluster level, Figure 2). In implicit processing, no significant differences were detected between baseline and follow-up. These results were detected in the standard analysis. Results from exclusive masking procedures are not reported for the time effects.

Differential Effects of Response and Time

There was no significant interaction between the effects of responders versus nonresponder and the possible alterations due to pharmacologic treatment. Changes in depression scores did not correlate with the change of the BOLD responses during the trial in the whole group of patients.

Differential Effects of Medication and Time

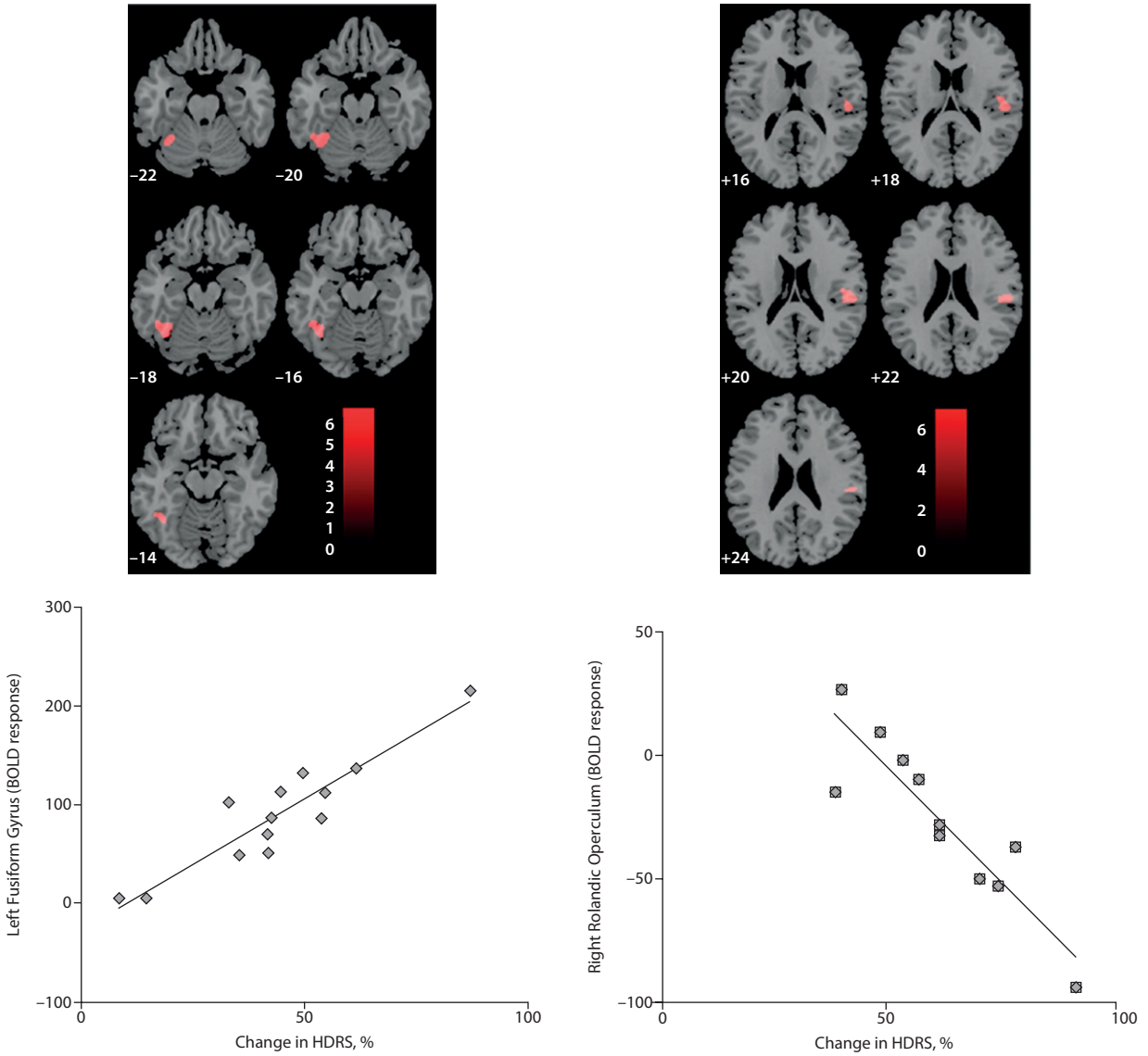
In the baseline (pretreatment) measurement of the explicit condition, patients randomly assigned to venlafaxine differed significantly from patients randomly assigned to mirtazapine in the cerebellum only (*P* < .05, FWE corrected at the cluster level); in the implicit condition, no significant differences were found between the patient groups at baseline.

With respect to longitudinal changes (Table 2), in the explicit condition, patients receiving venlafaxine showed a significant decrease in activation from baseline to week 4 in the left hippocampus, left thalamus, left fusiform gyrus, left precuneus, and left and right cerebellum (*P* < .05, FWE corrected at the cluster level). In the implicit condition, patients receiving mirtazapine showed increased activation in the left and right MCG and left and right SMA (*P* < .05, FWE corrected at the cluster level). These effects remained significant when the effects of the venlafaxine treatment were compared with those of mirtazapine and vice versa (Figure 3).

Interaction of Medication, Response, and Time

The result of the interaction analysis of effects of medication group, response or nonresponse, and time was not significant. However, when the severity of depression—measured with the HDRS scale—was included as a covariate in the analysis of covariance, we obtained the following

Figure 1. Multiple Regression of Effect of Change in Depression Severity (percent change from baseline HDRS score) on fMRI BOLD Response[a,b]



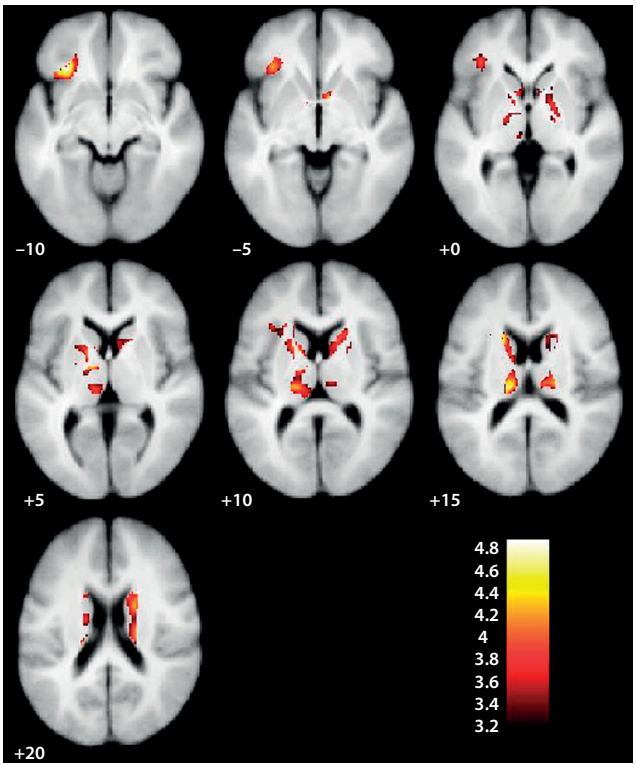
[a]The upper images show significant regression in the left fusiform gyrus (left) and significant association between HDRS change and BOLD response in the right rolandic operculum (Brodmann area 43) (right) ($P < .05$, FWE corrected at the cluster level). The lower scattergrams show BOLD responses of the left fusiform gyrus and changes in HDRS scores (%) (left) and BOLD responses and right rolandic operculum (right).
[b]Numbers in lower-left corner of each image indicate the z coordinate; numbers in the color bar indicate *t* values.
Abbreviations: BOLD = blood-oxygen-level dependence, fMRI = functional magnetic resonance imaging, HDRS = Hamilton Depression Rating Scale.

results for changes from baseline to the 4-week follow-up (Figure 4): Patients receiving mirtazapine still showed an increase in activation in the left and right SMA and in the MCG (Brodmann area 24, cluster k = 249, $P = .035$, x = 12, y = −0, z = 48; right SMA 86.8% of the cluster; left SMA, 1.2%; right MCG, 12.0%) and also a significant increase in BOLD responses in the right precentral and right superior frontal regions (cluster k = 214, $P = .05$, x = 30, y = −10, z = 62; right precentral 18.3% of the cluster; right superior frontal, 81.7%). Patients receiving venlafaxine still showed a significant decrease in a cluster comprising the left and right cerebellum, left and right lingual cortex, left hippocampus, and left precuneus (cluster k = 485, $P = .008$, x = 6, y = −52, z = −2; left lingual cortex 26.6% of the cluster; right lingual cortex, 4.8%; left precuneus, 8.5%; left hippocampus, 3.1%; left calcarine, 16.7%; left cerebellum, 25.9%; right cerebellum, 14.0%). Additionally, we saw a significant decrease in BOLD response in a cluster in prefrontal areas (cluster k = 465, $P = .009$, x = 8, y = 52, z = 38; right DMPFC 59.4% of the cluster; right superior frontal, 33.6%; right DLPFC frontal, 7%).

DISCUSSION

This is the first open, randomized study accepted for publication to use functional MRI to compare 2 antidepressants. We expected to find changes primarily in ACC, DMPFC, DLPFC, and basal ganglia regions that showed different BOLD responses in patients and controls at baseline and

Figure 2. Significant Decreases in BOLD Responses of Patients in the Left Orbitofrontal Cortex and in Regions of the Left and Right Thalamus and Basal Ganglia During the Trial[a,b]



[a]$P < .05$, FWE corrected at the cluster level.
[b]Numbers in lower-left corner of each image indicate the z coordinate; numbers in the color bar indicate *t* values.
Abbreviations: BOLD = blood-oxygen-level dependence, FWE = family wise error.

Table 2. Changes in fMRI BOLD Responses During the Trial in Patients Taking Mirtazapine and in Patients Taking Venlafaxine

Anatomic Region	% of cluster	k	x, y, z Coordinates	*P*
Mirtazapine group (n = 12)				
Activation smaller at baseline than at follow-up (implicit task)[a]				
Cluster 1		366	4, −10, 50	.014
SMA R	46.99			
MCG R	36.34			
MCG L	9.29			
SMA L	7.38			
Venlafaxine group (n = 12)				
Activation larger at baseline than at follow-up (explicit task)[b]				
Cluster 1		1,839	−4, −54, 6	.000
Thalamus L	31.21			
Sulcus calcarinus L	15.12			
Precuneus L	11.26			
Lingual gyrus L	7.50			
Precuneus R	6.04			
Vermis	8.86			
Cluster 2		596	−8, −44, −24	.003
Hippocampus L	34.40			
Cerebellum L	27.02			
Parahippocampus L	13.59			
Fusiform gyrus L	9.06			
Vermis	8.56			

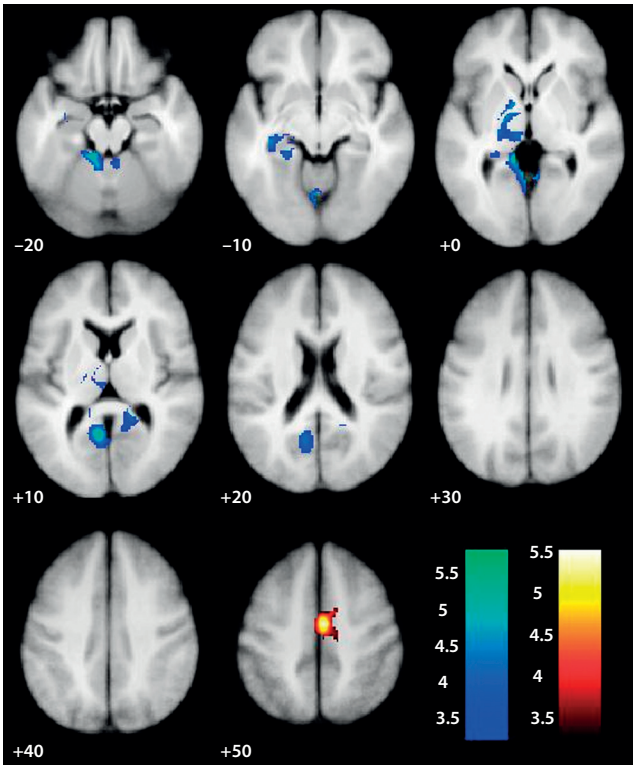
[a]Patients in the mirtazapine group showed a significant increase in activation in a cluster in the middle cingulum.
[b]Patients in the venlafaxine group showed a significant decrease in activity in a cluster including the left thalamus and occipital cortex and in another cluster including the left hippocampus and left cerebellum ($P < .05$, family wise error corrected at the cluster level).
Abbreviations: BOLD = blood-oxygen-level dependence, fMRI = functional magnetic resonance imaging, k = number of voxels, L = left, MCG = middle cingulate gyrus, R = right, SMA = supplementary motor area.

found these changes in DMPFC and DLPFC after considering the depression severity at baseline and follow-up as covariate in patients receiving venlafaxine and in the MCG in the mirtazapine group. Since patients were treated for 4 weeks, we expected to see not only direct effects of the antidepressants—caused by changes in the neurotransmission of serotonin and norepinephrine and in brain function—but also effects associated with the recovery from major depressive disorder and, in turn, with the normalization of altered brain function in the neural networks activated during the face-matching task.

The novel finding of the study is that 2 antidepressants (venlafaxine and mirtazapine) were found to have significantly different effects in untreated patients with major depressive disorder. In the explicit task, venlafaxine resulted in a significant decrease of activation from baseline to follow-up, predominantly in the left thalamus, left hippocampus, left fusiform gyrus, right and left precuneus, and left and right cerebellum. This pattern of changes is in line with the distribution of the 5-HTT binding of venlafaxine, which is mainly in the basal ganglia, thalamus, and prefrontal cortex in studies in humans,[11] but also in the hippocampus in animal studies.[20] When we included depression severity as a covariate in the statistical analysis, to account for the effect of symptom change during response, we found a decrease of the BOLD signal also in the right DMPFC and DLPFC areas. This effect seems to be specific to venlafaxine because it is independent of response or nonresponse. Therefore, the decrease of BOLD signals seen under venlafaxine treatment is in line with the binding pattern of venlafaxine shown in the above-mentioned studies and also with the exaggerated responses that were seen at baseline in the present study and seems to be more specific to the medication and its mechanism of action than to the change in the severity of depression in general.

Our findings are in line with those of a recent fMRI study in 19 patients with major depressive disorder treated with fluoxetine for 8 weeks; in this study, BOLD responses decreased significantly not only in the basal ganglia and thalamus regions but also in the amygdala, ACC, insula, precentral and postcentral gyrus, and inferior parietal lobule.[5] Moreover, in this sample, treatment with fluoxetine was associated with a significant increase in functional coupling between the amygdala and subgenual ACC.[21] Effects on amygdala activation were also found in other studies; for example, exaggerated left amygdala activation in 11 patients with major depression during a face-matching paradigm decreased to a normal activation level following treatment with the SSRI sertraline.[3] This effect may have been a direct effect of the antidepressant: after 21 days of treatment with escitalopram, 13 healthy volunteers without depression showed

Figure 3. Differences in Activation Between Venlafaxine and Mirtazapine[a,b]



[a]Significant differences in activation existed between the 2 treatment groups: in the explicit condition, the venlafaxine group showed less activation than the mirtazapine group (blue) in both hemispheres of the hippocampus, thalamus, basal ganglia, and cerebellum; in the implicit condition, the mirtazapine group showed more activation than the venlafaxine group (red) in both hemispheres of the middle cingulate gyrus and supplementary motor area ($P < .05$, FWE corrected at the cluster level).
[b]Numbers in lower-left corner of each image indicate the z coordinate; numbers in the color bar indicate *t* values.
Abbreviation: FWE = family wise error.

less activation in the amygdala when shown fearful faces than when shown control shapes.[22] Only 1 earlier study in 12 patients with major depression found significantly increased activation in the left insular cortex after 2 weeks of treatment with venlafaxine and in the left anterior cingulate cortex after 8 weeks of treatment.[4] Thus, the majority of studies of SSRIs found decreased BOLD responses in cortical and subcortical brain regions. The sample size in our study was similar to those of previous studies, which supports our assumption that our study had sufficient power to identify significant differences between the groups.

Interestingly, patients receiving mirtazapine showed a significantly different pattern of changes: during implicit processing, these patients showed more BOLD responses after 4 weeks' treatment than before in the left and right MCG and the left and right SMA, which indicates that mirtazapine had some stimulating effects in these brain areas. This is in line with the observations that mirtazapine is sedating at low doses (eg, 15 mg), whereas at higher doses (eg, 30 mg and above), as in this study, it is more activating. A recent pharmacologic MRI study in 45 healthy male volunteers who were randomly allocated to receive mirtazapine or placebo in a double-blind fashion[23] supports our findings: it found increased activation in the right orbitofrontal cortex after a single oral dose of mirtazapine.

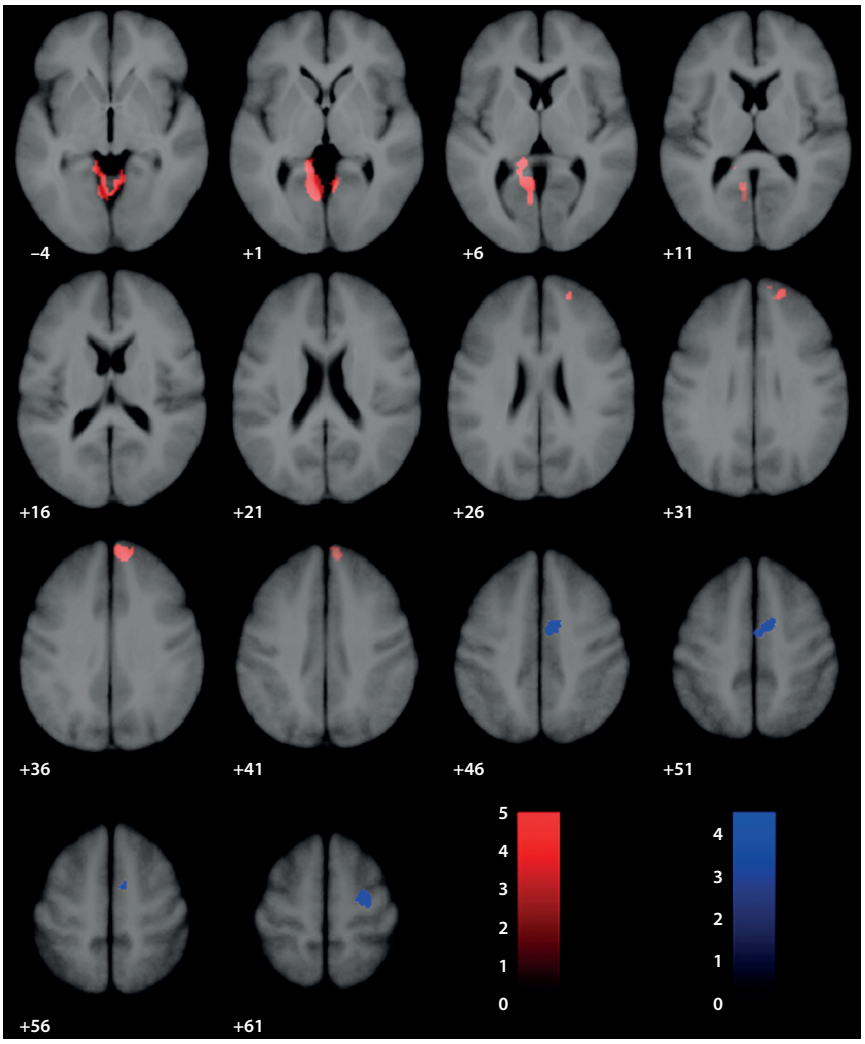
When depression severity was included as a covariate in our analysis, the effects in the SMA remained stable, and increases in BOLD responses also were seen in the precentral and superior frontal area; the effect in the MCG, however, was smaller. Therefore, the increase in BOLD response seen in the MCG seems to be related to both the medication and the improvement in depressive symptomatology: mirtazapine seems to change function in the MCG and this functional change seems also to be associated with recovery from depression. These findings indicate that the function of the cingulate cortex is highly interesting as a potential marker for treatment effects and recovery, as previously hypothesized.[24]

The association of the MCG with the motor areas is not surprising when one considers the dense projections from the cingulate cortex to the motor cortex. Our finding may also support that the cingulate gyrus plays an important role in the willed control of actions.[25] The change in activation in the MCG, SMA, and superior frontal cortex is in line with the observation that mirtazapine has a high binding potential in cortical regions but only relatively low binding levels in the basal ganglia and thalamus.[10]

Whether this effect is triggered by the α_2-receptor antagonism of mirtazapine or the effect on 5-HT_{1A} receptors remains unclear. Studies have shown that the density of α_2 receptors is highest in the primary sensory cortical regions[26]; however, these were not activated in our tasks, so it is not surprising that we did not see changes in BOLD responses in the visual fields. On the basis of findings from recent studies on post mortem receptor mapping in the cingulate cortex one can speculate whether the area of increased activation in the MCG has a particularly high density of these receptors.[27] The density of α_2 receptors is higher in the anterior part of the cingulate area 24 than in the posterior part, which includes most parts of the ACC and MCG, and the same has been reported for the 5-HT_{1A} receptors. However, the MCG still has an average density of α_2 and 5-HT_{1A} receptors.[27] The effects seen in our study could therefore be related α_2 and 5-HT_{1A} receptors; however, the postmortem findings of Palomero-Gallagher et al[27] cannot necessarily be transferred to major depression: in postmortem studies of depressed patients, α_{2A} receptors were up-regulated,[28] and in animal models of chronic psychosocial stress α_2 receptors were up-regulated.[29] Receptor distributions, therefore, seem not to answer the question why increased activation is observed in the MCG during therapy with mirtazapine. Another possibility might be that neural activity in the cingulate cortex is modulated by the arousal state of the organism.[25] However, because of the specific activation of the motor areas and part of the MCG during therapy, such a general effect seems to be rather unlikely.

Of interest is that the BOLD response changes were seen in the mirtazapine group in the implicit condition but in the venlafaxine group in the explicit condition. In a previous study

Figure 4. Changes in fMRI BOLD Responses During the Trial[a,b]



[a]Significant decreases in activation were seen for the venlafaxine group (red) in the right dorsomedial prefrontal cortex and right dorsolateral prefrontal cortex as well as the left and right cerebellum, left and right lingual cortex, left hippocampus, and left precuneus. Significant increases in activation were found for the mirtazapine group (blue) in the supplementary motor area and middle cingulate gyrus as well as the right superior frontal and precentral region ($P < .05$, FWE corrected at the cluster level).

[b]Numbers in lower-left corner of each image indicate the z coordinate; numbers in the color bar indicate *t* values.

Abbreviations: BOLD = blood-oxygen-level dependence, fMRI = functional magnetic resonance imaging, FWE = family wise error.

in healthy controls, we demonstrated that in the implicit task the motor area and areas in the parietal and frontal lobes and the thalamus and hippocampus are activated, whereas in the explicit task the ACC, dorsomedial and dorsolateral prefrontal cortices, basal ganglia, thalamus, and cerebellum show more activation.[30] These differences in activated areas in explicit and implicit processing may explain why in the present study we saw an increase of BOLD response in the thalamus, dorsomedial and dorsolateral prefrontal cortices, and cerebellum in the explicit task and the change of BOLD response in the motor area in the implicit task. Therefore, if one wants to study the effects of a drug in a particular region of the brain it is important to choose a task that is known to involve that region.

We could not confirm our second primary hypothesis that patients with higher BOLD activity in the ACC are more likely to remit during antidepressant treatment. Instead, we found that patients who had fewer BOLD responses in the right rolandic operculum before treatment responded better to mirtazapine. The rolandic operculum is part of the motor areas and is known to be relevant for speech processes.[31] The observation that patients with reduced BOLD response in the rolandic area at baseline responded better to mirtazapine fits well to the increase in BOLD response in motor areas during treatment with mirtazapine. In turn, this may be related to psychomotor symptoms and, indeed, there are some studies that show that patients with depression and agitation respond relatively well to mirtazapine.[32] We also found that those patients who exhibited more BOLD responses in the left fusiform gyrus before treatment responded better to venlafaxine. The physiologic plausibility of this finding is underlined by the fact that the fusiform gyrus is specialized in face perception and was involved functionally in our tasks.[33] Moreover, we saw a decrease of BOLD responses in the fusiform gyrus during treatment with venlafaxine. The above findings also underline the differential effects that mirtazapine and venlafaxine seem to have on brain activation: mirtazapine seems to work better when patients have underactivated brain areas, whereas venlafaxine seems to be more effective when patients have areas with more activation.

Previous studies have shown that patients who respond well to antidepressant treatment have increased activity in the ACC,[5] whereas patients who respond well to cognitive-behavioral therapy show a low reactivity to emotional stimuli in the subgenual cingulate cortex and a high reactivity in the amygdala.[34] Moreover, positron emission tomography investigations have found a pattern of hypermetabolism in the cingulate cortex in responders and hypometabolism in nonresponders, both in medication-treated patients[24] and in patients treated with sleep deprivation.[35] Improvement in depressive symptoms was best correlated with decreases in subgenual cingulate activity.[24] These studies support the suggestion that fMRI can help to predict antidepressant treatment response. We have shown that hyperactivity and

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hypoactivity can potentially predict response, depending on the mechanism of the antidepressant being used.

Since we did not find any significant differences between patients and healthy controls using the standard analysis, we used the exclusive masking method to examine whether some brain regions are involved only in patients but not in controls. Our sample of untreated patients with major depressive disorder showed significantly BOLD responses in the ACC, DLPFC, and DMPFC during explicit emotion processing, whereas the healthy controls did not show emotion-related responses in these regions, indicating that only patients involve some brain regions or that they involve them in a greater or larger extend than the controls. These findings are in line with those of our previous study in medication-treated patients with major depression[36] and are consistent with the greater responses to sad faces found in the ACC in 2 earlier fMRI investigations.[5,37] One of these studies also found increased activity in the medial prefrontal cortex.[37] In the contrast between explicit and implicit processing, patients also had BOLD responses in the basal ganglia that were not seen in healthy controls, which is in line with studies that found increased BOLD responses in the ventral striatum,[5] the pallidostriatum,[37] and the putamen.[38] A possible explanation may be that, in order to complete the tasks, depressive patients have to activate certain brain regions to a greater extent than healthy controls or that depressive patients pay more attention to sad stimuli.[39] In contrast to findings in other studies, in our study, BOLD responses in the amygdala were not larger in patients than in controls. Increased responses in the amygdala to masked fearful faces,[3] to sad faces,[5] and to sad pictures[37] have been reported. In our tasks, the participants probably used more visual and cognitive strategies to solve the task so that amygdala activation may have been inhibited by the ACC and prefrontal cortices.

The aim of this study was not a critical comparison of the drugs with respect to the clinical outcome, and the sample size would have been too small to answer such a question. However, the sample size was relatively large for an fMRI study and of adequate size to show differences in BOLD responses. One limitation is the unbalanced number of female (8) and male (16) patients; we therefore used sex and age as cofactors in the analysis to account for possible differences. Another limitation is the fact that the treatments were not administered in a blinded manner. This first study comparing effects of different antidepressants was open for reasons of practicability associated with recruiting patients. A placebo-controlled double-blind trial would be desirable but would require a larger patient sample to also account for dropouts.

In conclusion, we showed different effects of mirtazapine (an α_2-receptor antagonist), which increased BOLD responses in the MCG and motor areas, and venlafaxine (an SNRI), which decreased exaggerated BOLD responses in the thalamus, dorsomedial prefrontal cortex, fusiform gyrus, and hippocampus. The effect in the MCG is especially interesting because it shows medication effects that seem also to be associated with response. This finding is in line with our other finding that pretreatment hypo-activation in motor areas like the rolandic operculum and hyperactivation in the fusiform gyrus predict treatment response. Although mirtazapine and venlafaxine have different regional effects in the brain, they both have potential antidepressive effects; a combination of an SNRI or SSRI with a noradrenergic and specific serotonergic antidepressant is a potent strategy for treating patients who do not respond to monotherapy with 1 of these substances.[2,40] Therefore, our findings provide the neurobiological basis for an individual and differential antidepressant therapy and support the combination of different substances in treatment-resistant depression. We hope that these results will stimulate further research into differential treatment effects and facilitate the use of phMRI in patients to investigate the acute effects of pharmacologic challenge on the functional correlates of the brain.

Drug names: fluoxetine (Prozac and others), lorazepam (Ativan and others), mirtazapine (Remeron and others), sertraline (Zoloft and others), venlafaxine (Effexor and others), zopiclone (Lunesta).

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Potential conflicts of interest: None reported.

Funding/support: The authors thank the Eli Lilly International Foundation for supporting this study with a grant to Drs Frodl, Meisenzahl, and Möller. Further funding was obtained through the Science Foundation Ireland (SFI) Stokes Programme (Drs Bokde and Frodl) and the SFI investigator neuroimaging programme grant 08/IN.1/B1846 to Dr Hampel. Dr Hampel is further supported by the Alzheimer Association (Chicago, Illinois) and the Health Service Executive and Health Research Board of Ireland.

Acknowledgment: The authors thank Jacquie Klesing, BMedSci (Hons), for editing the manuscript. Ms Klesing reports no financial or other potential conflicts of interest related to the subject of this article.

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