Functional Magnetic Resonance Imaging Studies of Emotional Processing in Normal and Depressed Patients: Effects of Venlafaxine

Ned H. Kalin, M.D., Richard J. Davidson, Ph.D., William Irwin, M.S., Gemma Warner, Jennifer L. Orendi, Steve K. Sutton, Ph.D., Bryan J. Mock, M.S., James A. Sorenson, Ph.D., Mark Lowe, Ph.D., and Patrick A. Turski, M.D.

Background: Functional magnetic resonance imaging (fMRI) techniques were used to identify the neural circuitry underlying emotional processing in control and depressed subjects. Depressed subjects were studied before and after treatment with venlafaxine. This new technique provides a method to noninvasively image regional brain function with unprecedented spatial and temporal resolution. ***Method:*** Echo-planar imaging was used to acquire whole brain images while subjects viewed positively and negatively valenced visual stimuli. Two control subjects and two depressed subjects who met DSM-IV criteria for major depression were scanned at baseline and 2 weeks later. Depressed subjects were treated with venlafaxine after the baseline scan. ***Results:*** Preliminary results from this ongoing study revealed three interesting trends in the data. Both depressed patients demonstrated considerable symptomatic improvement at the time of the second scan. Across control and depressed subjects, the negative compared with the positive pictures elicited greater global activation. In both groups, activation induced by the negative pictures decreased from the baseline scan to the 2-week scan. This decrease in activation was also present in the control subjects when they were exposed to the positive pictures. In contrast, when the depressed subjects were presented with the positive pictures they showed no activation at baseline, whereas after 2 weeks of treatment an area of activation emerged in right secondary visual cortex. ***Conclusion:*** While preliminary, these results demonstrate the power of using fMRI to study emotional processes in normal and depressed subjects and to examine mechanisms of action of antidepressant drugs.
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Recent developments in functional brain imaging are allowing researchers, for the first time, to characterize the functional neuroanatomy of emotional responses and to investigate the detailed circuitry underlying different aspects of emotion. Studies using positron emission tomography (PET) with radiolabeled tracers, such as fluorodeoxyglucose and oxygen-15 labeled water, are demonstrating involvement of a variety of cortical and subcortical structures in the processing of emotional responses in normal subjects as well as in subjects with anxiety and depressive disorders.[1–4] Recently, functional magnetic resonance imaging (fMRI) techniques have become available. Compared with PET, fMRI provides significant advantages in studying a number of brain functions, including emotional processing.[5,6] Using this technique, our group previously demonstrated the feasibility of examining the neural substrates underlying emotional processing.[7] We have currently undertaken a series of fMRI studies to compare the processing of positive and negative emotional stimuli between normal and depressed subjects. In addition, we are using this technique to examine the effects of the novel combined norepinephrine and serotonin reuptake inhibitor antidepressant, venlafaxine, on brain functioning as depressed subjects respond to treatment. This report reviews relevant issues related to fMRI and summarizes preliminary data from this ongoing project.

From the Departments of Psychiatry (Drs. Kalin and Davidson and Ms. Warner), Psychology (Drs. Kalin, Davidson, and Sutton and Mr. Irwin and Ms. Orendi), Medical Physics (Drs. Sorenson and Lowe and Mr. Mock), and Radiology (Drs. Sorenson and Turski), University of Wisconsin, Madison.

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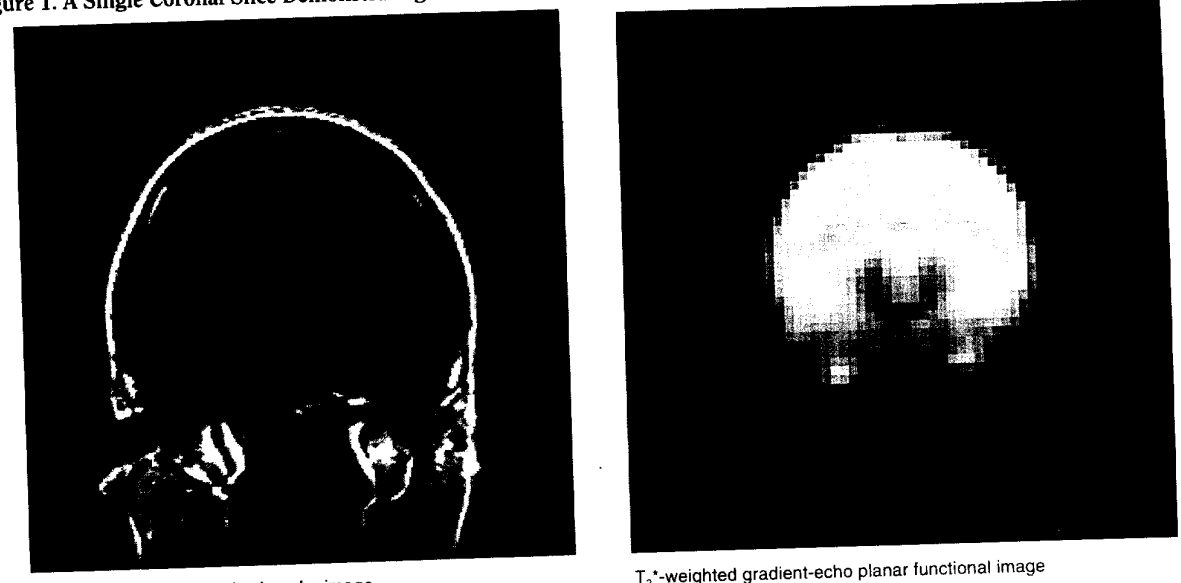
Figure 1. A Single Coronal Slice Demonstrating Conventional and High-Speed Imaging Techniques†



T_1-weighted conventional spin-echo image

T_2*-weighted gradient-echo planar functional image

†The high spatial resolution (~ 1 mm) of T_1-weighted conventional spin-echo techniques shown in the image on the left requires approximately 5 seconds to acquire. The reduced spatial resolution (~ 3.75 mm) of the echo-planar imaging technique, shown in the image on the right, can be acquired in approximately 100 milliseconds.

ADVANTAGES OF FUNCTIONAL MRI

fMRI capitalizes on the principles and techniques of traditional MRI in conjunction with a system that allows rapid and repeated imaging of the brain, thereby acquiring numerous images within a short time period.[5,6] Increased neuronal activity in a particular area is assumed to result in increased blood flow to that region. This change in blood flow is reflected in the difference between the magnetic properties of oxygenated and deoxygenated hemoglobin.[8] An important advantage of fMRI is that radioactive substances are not used. This allows greater safety in repeatedly scanning the same subject and also allows the method to be used in populations that may be more vulnerable to the effects of radiation, such as children. Compared with PET, fMRI results in much better spatial and particularly temporal resolution. The spatial resolution of fMRI can be within the 2- to 3-mm range, while the temporal resolution can be in the 1-second range.[9] Figure 1 compares a typical structural MRI image with a high-speed echo-planar image used to detect functional brain activity.

FUNCTIONAL MRI PRINCIPLES AND INSTRUMENTATION

The principles underlying traditional MRI techniques also apply to fMRI. In brief, when subjects are placed in the magnet, they are exposed to a static magnetic field. This field has the effect of aligning protons within the region of the body being scanned into one vector or direction. Next, a radio frequency pulse of a specific duration and frequency is applied. This pulse has the effect of knocking the protons out of alignment into another vector. Subsequently, the protons behave in different ways, including "relaxing" back to the fixed magnetic field and "dephasing" by losing some of their spin. Different types of images, such as T_1, T_2, and T_2*, can be generated, depending on which of these proton behaviors is examined.

fMRI is based on the assumption that a local increase in neuronal activity is associated with increased metabolic rate. This is rapidly followed by increased blood flow to the activated region. Since oxygenated and deoxygenated hemoglobin have different magnetic properties, the ratio of oxygenated to deoxygenated hemoglobin is important and is reflected by the intensity of the detected T_2* signal. Greater amounts of oxygenated hemoglobin result in more intense signals. It is as if oxygenated hemoglobin functions as an endogenous contrast agent. When a subject is engaged in a brain-activating task (i.e., sensory, motor, cognitive, or emotional), an increase in the metabolic rate occurs in involved brain regions. This increase in metabolism is thought to be accompanied by vasodilation and increased blood flow. It is believed that the increase in oxygenated hemoglobin exceeds the tissues' metabolic demands, resulting in an increase in the oxygenated/deoxygenated hemoglobin ratio found in the local capillary beds. This results in less susceptibility to dephasing, which is reflected by an increased signal strength (Figure 2).[9–13]

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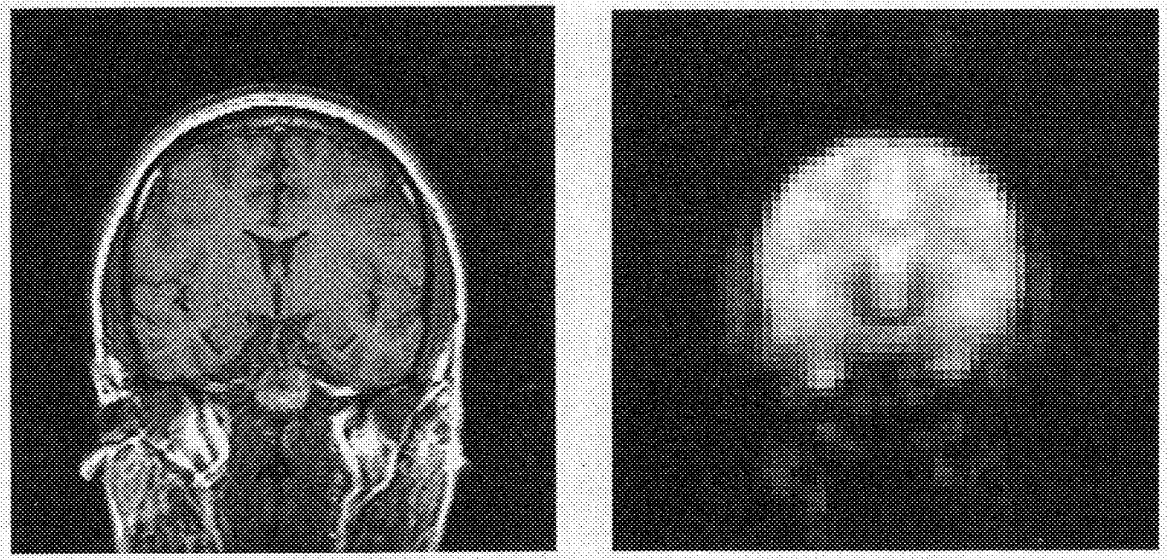

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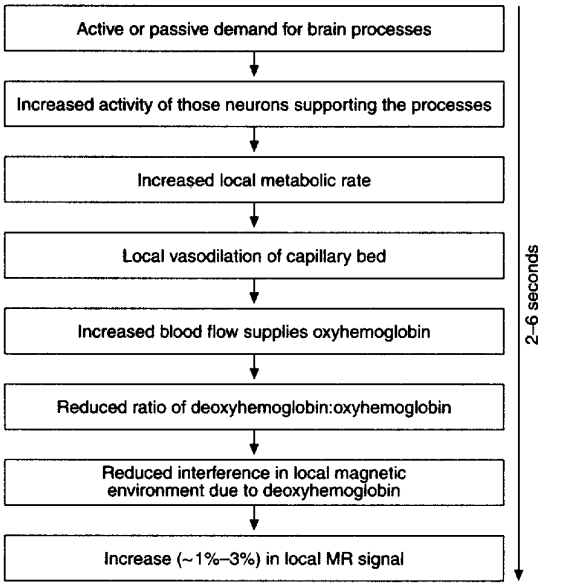
Figure 2. Schematic of the Blood Oxygenation Level–Dependent (BOLD) Contrast Method, Which Is Exploited Using Echo-Planar Imaging Techniques*



*Increased local neuronal activity is thought to cause a cascade of processes that result in an increase in the local MR signal. Note that when using conventional 1.5-T MR scanners, the maximum expected MR signal increase is approximately 1%–3%.

MRI scanners can be specially adapted to perform fMRI studies; these changes are relatively straightforward and can be readily accomplished on most existing magnets. One important component of our fMRI instrumentation is the use of a small, local head coil, which improves the ability to image the entire brain and allows a better signal-to-noise ratio. It is also essential that the magnet is equipped with a system that provides the capability to acquire numerous images rapidly. Our site uses an echo-planar system known as EchoSpeed, which is manufactured by General Electric (GE).

VALIDATION OF THE FUNCTIONAL MRI TECHNIQUE

fMRI is a relatively new technique, and research using fMRI to make inferences about the function of brain circuits subserving cognition and emotion is in its infancy. Before using fMRI to study emotional processes, we validated the technique by using well-defined motor tasks known to be mediated by specific brain regions. For example, subjects were instructed to engage in repeated cycles of brief periods of bilateral finger tapping followed by periods of inactivity in a typical "on-off paradigm." Figure 3 demonstrates the expected activation of motor cortex seen when subjects are engaged in this task and the temporally linked pattern of signal activation reflecting the subjects' repeated performance of the task in the on-off paradigm. Recently, we demonstrated that amygdala activation can be detected with fMRI in subjects that are exposed to negative emotionally laden visual images.[7] This was the first published report of amygdala activation in humans elicited by emotional stimuli and detected with fMRI.

EXPERIMENTAL DESIGN AND METHODS

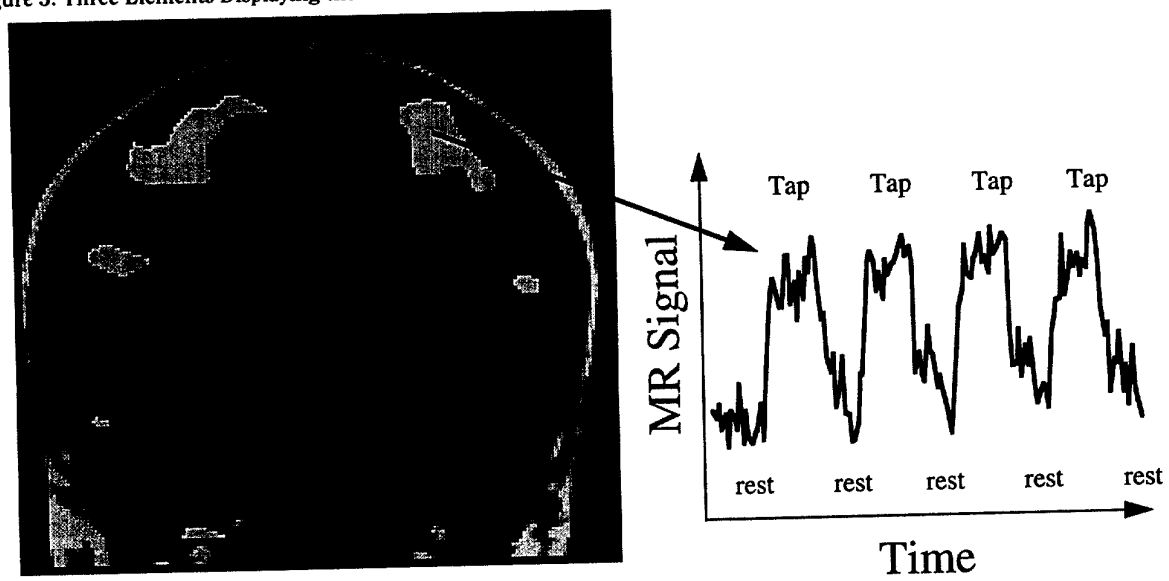
Experimental Design

Our ongoing study was designed to examine responses to positive and negative emotional stimuli in 20 depressed compared with 20 control subjects. After informed consent was obtained, each depressed subject received venlafaxine in an open-label design and underwent three scans: before treatment, 2 weeks after beginning venlafaxine treatment, and 8 weeks after beginning venlafaxine treatment. Control subjects were also scanned three times at the same intervals but were not administered the drug.

All subjects were right handed, between 18 and 70 years of age, and in good general health. Because of the high-strength magnetic field created by the MRI machine, individuals with metallic implants (e.g., prostheses, shrapnel, or aneurysm clips) or electronic implants (e.g., cardiac pacemakers) were excluded. Individuals who had sustained head injuries with lasting effects or brain damage were ineligible, and women who were pregnant were excluded. Additionally, all participants were required to be able to lay motionless on their backs for up to 120 minutes and to clearly see the pictures displayed through "goggles" (described below).

The depressed subjects met DSM-IV criteria for major depression and had scores of 20 or greater on the 21-item Hamilton Rating Scale for Depression (HAM-D).[14] Depressed subjects were free of psychotropic drugs for at least 2 weeks prior to their first scan; if they were taking fluoxetine, they were required to be drug free for a minimum of 4 weeks. Medical exclusion criteria included the use of medications known to affect central nervous system function, a history of seizures, insulin-dependent diabetes mellitus, significant cardiovascular disease and/or myocardial infarction within the preceding 3 months, participation in an investigational drug study within the preceding 30 days, and any significant medical illnesses. Psychiatric exclusion criteria included other current Axis I disorders, drug/alcohol abuse within the past 6 months, and a personal or family history of bipolar disorder. Eligible depressed women were practicing an accepted method of birth control or were at least 2 years postmenopausal. Depressed women who were pregnant or nursing were ineligible. The control subjects had no personal or immediate family history of mental illness, including major depressive disorder, dysthymic disorder, bipolar disorders, obsessive-compulsive disorder, panic disorder,

Figure 3. Three Elements Displaying the Detection of Brain Activation*



*On the left is a single coronal slice through the motor cortex in a single subject. While in the scanner, the subject performed a task that consisted of alternating between periods of bilaterally tapping each finger to the thumb and periods of rest. The cortical activation resulting from this task is superimposed upon the anatomic images (white). On the right, the changes in the MR signal accompanying the changes in the task are displayed. Note the increase in signal in the motor cortex when the subject is engaged in the finger tapping compared with when the subject is resting.

schizophrenia, other psychotic disorders, and/or alcohol abuse or dependence.

At the initial screening, all subjects were administered a Structured Clinical Interview for Axis I DSM-IV disorders (SCID),[15,16] a Beck Depression Inventory (BDI),[17] and a handedness inventory,[18] and were assessed for claustrophobia. In addition, complete psychiatric and medical histories were obtained from depressed subjects, as well as blood and urine samples for laboratory tests, pregnancy testing, and drug screening. Vital signs, including weight, were also recorded for depressed subjects.

Other Behavioral Tests

Prior to the first scan, all subjects were placed in an MRI simulator to habituate them to the environment, noise, anxiety, and other potential novel aspects related to MRI scanning. The simulation visit also included a preview of pictures similar to those shown during the actual scans. Exposure to the experimental setup prior to the actual scan is particularly important when using fMRI to study emotional processes because of the potential impact on brain activity of the anxiety generated by the procedure. Subjects were asked to remain motionless during the scan since any head movement could seriously compromise the quality of the data. To further minimize head movement, customized bite bars were prepared for each subject during the simulation visit and were reused during the actual scans. In addition, subjects wore ear plugs to attenuate the considerable ambient noise.

Prior to the simulation visit and each of the three scans, subjects completed a packet of questionnaires related to anxiety and depression. Each packet included PANAS–Past Week,[19] BIS/BAS scales,[20] the State-Trait Anxiety Inventory,[21] and a Menstrual Cycle Questionnaire (for females). Immediately before the scan, all subjects completed a PANAS–Now.[19] After each scan, subjects were asked to complete the PANAS–Now and a short questionnaire that inquired about their reaction to the pictures and the scan experience. In addition, depressed subjects were administered the HAM-D at each scan visit.

At the beginning of the medication phase of the study, depressed subjects were excluded if there had been a decrease of > 20% in their HAM-D score or if their absolute score had dropped below 20. After the first baseline scan, patients were treated with venlafaxine (by N.H.K.), using the following dose titration schedule as a guideline: Days 1–4, 18.75 mg b.i.d.; Days 5–14, 37.5 mg b.i.d.; Days 15–28, 75 mg b.i.d.; and Days 29–56, 112.5 mg b.i.d. Depressed subjects were assessed weekly for vital signs, clinical status, adverse events, medication adjustment, and HAM-D score.

Scanning Protocol

All image data were acquired with a GE EchoSpeed 1.5-T scanner (GE, Waukesha, Wis.). Data acquisition for each subject included whole-brain 3D spoiled grass (SPGR; for high-resolution anatomical images), 3D time-of-flight (for identifying vascular topography), dual-echo

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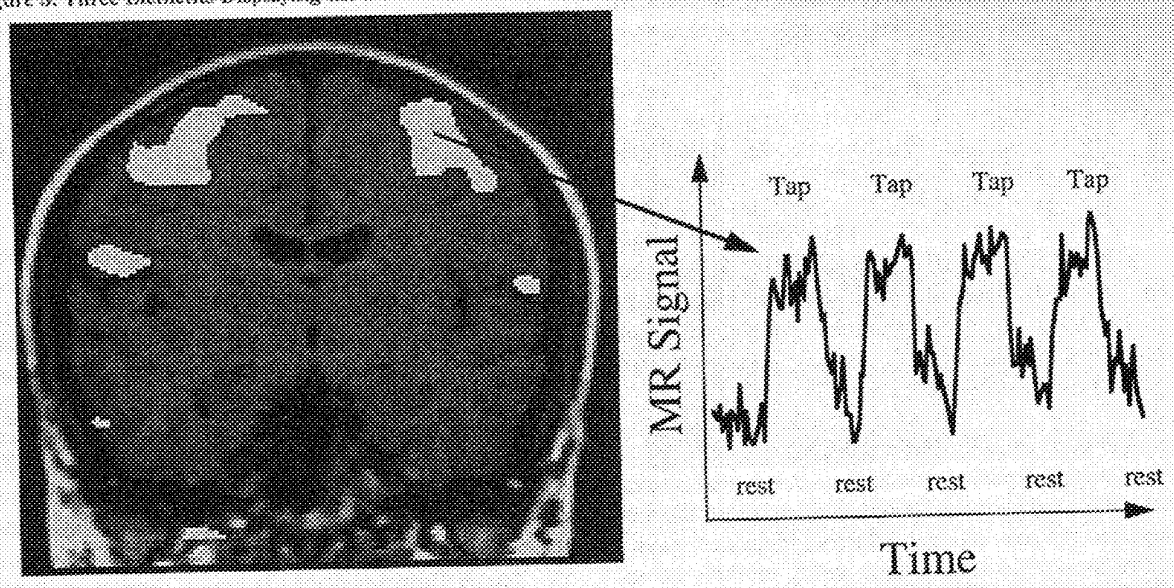

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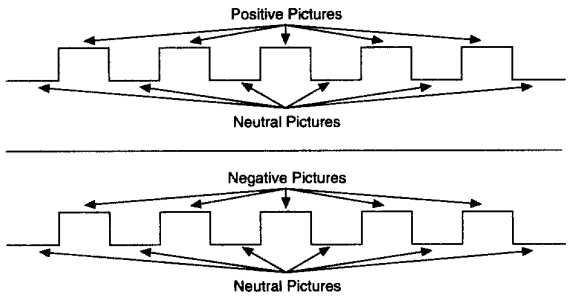
gradient echo (for identifying magnetic field inhomogeneities), T_1-weighted spin echo (for identifying the anatomical locations from which functional images would be acquired), and three T_2*-weighted gradient echo echo-planar imaging (EPI; for functional images) sequences. The results presented in the present report include only the use of the 3D SPGR (echo time [TE] = 8 ms, relaxation time [TR] = 35 ms, number of averages [NEX] = 1, flip angle = 30°, field of view [FOV] = 24 × 24, matrix = 256 × 256, 1.0- to 1.2-mm slices, 124 slices) and EPI (TE = 50 ms, TR = 3000 ms, NEX = 1, flip angle = 90°, FOV = 24 × 24, matrix = 64 × 64, 7-mm slices, 1-mm slice spacing, 23 slices, 191 shots per slice) image data. All EPI data were reconstructed off-line using an in-house code written by one of the investigators (B.J.M.).

Figure 4. Schematic of the Picture-Viewing Conditions*



*All subjects viewed three conditions: random-random, neutral-positive, and neutral-negative. The conditions consisted of alternating blocks of valence-constant pictures, always beginning and ending with a block of neutral pictures. The random-random trial (not diagrammed) was exactly the same in duration, but consisted of randomly ordered pictures not used in the other picture viewing trials.

Presentation of Emotional Stimuli

Photographs depicting positive, negative, and neutral scenes were used as the emotion elicitors. These pictures belonged to the International Affective Pictures System[22] and have been validated for their ability to elicit the expected emotional response. Previous work from our laboratory[23] and others[24] has demonstrated that these pictures modulate physiologic response in addition to their subjective response. For example, the amplitude of the eyeblink component of the startle reflex elicited by an acoustic probe is accentuated during the presentation of negative pictures and is attenuated during the presentation of positive pictures.[24] These findings represent a human analogue of the fear-potentiated startle in rodents, in which the neural circuitry has been well characterized and is known to involve the amygdala.[25]

Stimuli were presented through goggles mounted in the standard headcoil using a fiber-optic system designed by Avotec, Inc. (Jensen Beach, Fla.). The negative and positive pictures that were presented were matched for their ability to elicit the same intensity of emotional response.[22] During each scan, subjects were presented with three stimulus conditions: random-random, neutral-positive, and neutral-negative. Each condition was composed of alternating blocks of valence-constant pictures. For example, the neutral/positive condition consisted of alternating blocks of 12 neutral pictures followed by 12 positive pictures, each contiguously presented for 4 seconds. Each condition was composed of 11 blocks, always beginning and ending with a neutral block (Figure 4).

Data Analysis

Before statistical analyses were performed, the EPI image data were inspected for head movement. This included visual inspection of cineloops for signs of gross movement. There was no sign of this type of movement. To identify small amounts of head movement, all image data were subjected to a 3D image alignment procedure in which each image in the time course was aligned with the first image. The alignment procedure was performed using the Statistical Parametric Mapping software package (Wellcome Department of Cognitive Neurology, United Kingdom). This alignment procedure provided a metric of "head movement," which was < 0.5 mm for the data on which the results presented below are based. Given this small degree of possible head movement, the raw image data (i.e., not the realigned image data) were used for the statistical analyses described below.

Single-subject analyses. Time series analyses were conducted on the EPI data by computing a three-parameter (i.e., amplitude, slope, and mean) least-squares fit between a reference function and the MRI image pixel values. From this fitting procedure, a Student's t value can be derived and used to determine regions of significant MRI signal change.[26] The reference function was a boxcar corresponding to the presentation of alternating picture blocks. Each picture-viewing trial was preceded by 15 seconds (i.e., five images) of viewing the word "Begin," during which images were acquired to allow the MRI signal to achieve equilibrium (i.e., steady-state). The first picture block was 15 seconds (i.e., five images) longer than subsequent blocks to ensure an accurate measure of the baseline MRI signal. Since the hemodynamic delay between the change in picture blocks and the change in the MRI signal was 6 seconds (i.e., two images), a phase offset of seven functional images was used for all analyses. The Student's t threshold was set at 3.00 ($p < .0001$; df = 176 [191 images, 5 equilibrium images, 7 offset images, and 3 parameters]).

Anatomical coregistration and subject averaging. The least-squares analysis yielded a statistical parametric map (SPM) in which the pixel values reflected the Student's t. The Analysis of Functional Neuroimages (AFNI)[27] was used to coregister the SPMs with the 3D SPGR anatomical images. This allowed precise anatomical localization of areas of activation as well as transformation of each

Table 1. Effects of Venlafaxine on Depressive Symptoms After 2 Weeks of Treatment*

	Prior to Treatment		2 Weeks of Treatment		Venlafaxine
Patient	HAM-D	BDI	HAM-D	BDI	Dosage
Patient 1	22	27	12	9	75 mg/day
Patient 2	20	20	8	3	75 mg/day

*Abbreviations: BDI = Beck Depression Inventory, HAM-D = Hamilton Rating Scale for Depression.

subject's SPM into the Talairach[28] coordinate system, which then permitted comparisons across subjects. The Talairach-transformed SPMs were combined across subjects by summing the square of the Student's t for each pixel. The "summed t-square" distribution was equivalent to the chi-square distribution, with the degrees of freedom equal to the number of subjects.[29] A threshold was used such that only those pixels with significant paradigm-correlated signal changes ($\chi^2 = 18.25$, df = 2, $p < .0001$) were displayed.

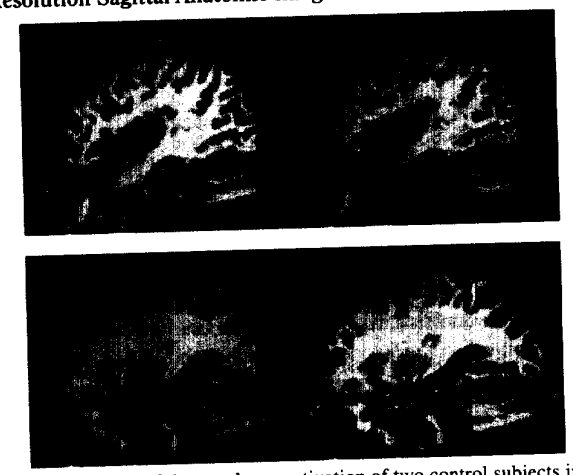
Results

The results presented in this report are preliminary and involve only the data from the first two scanning sessions (baseline and 2 weeks later) for two control and two depressed subjects. Because the results are based on such a small sample size, they must be interpreted with caution. Nevertheless, the data reveal three potentially important trends. The drug doses and HAM-D and BDI scores are presented in Table 1. As can be seen, both patients demonstrated clinically significant symptomatic improvement after 2 weeks of treatment.

For both the depressed and control subjects, the negative pictures induced a greater volume of activation than did the positive pictures in the baseline and 2-week scans. For example, analysis of the baseline data from the negative pictures in the control subjects revealed a volume of activation of approximately 203,646 mm^3 compared with a volume of 7342 mm^3 induced by exposure to the positive pictures. In both groups at both time points, the negative stimuli induced bilateral activation in regions of the prefrontal cortex (Brodmann's areas 10 and 46) and in parietal and occipital regions (Brodmann's areas 19 and 37). Exposure to the negative pictures resulted in greater brain activation at baseline compared with the 2-week scan in both the depressed and control subjects. The mean volumes of activation were approximately 128,048 mm^3 at baseline and 41,183 mm^3 at the second scan.

Responses to the positive pictures differed between the depressed and control subjects. Little activation of prefrontal regions was observed in either group. From the baseline to the 2-week scan, the control subjects showed an overall reduction in global activation, whereas the depressed patients displayed an increase in overall brain activity. This effect can be seen in Figure 5, which shows the significant areas of activation coregistered onto a sagittal slice. The probability of the areas of significant activation are reflected by the colorization, ranging from $p < .0001$ (red) to $p < .0000001$ (yellow). In the figure, scans from the control subjects are on the top row, with baseline on the left and the 2-week scan on the right. This activation is located in the middle occipital sulcus (part of Brodmann's area 19). In the baseline image, the focus of the area 19 activation is located at Talairach coordinates x = –39, y = –70, and z = –3. Also, a focus of activation is present in the cerebellum. In the 2-week image, the spatial extent of the area 19 activation shows an overall reduction, and the cerebellar activation has disappeared. In the depressed subjects (bottom row in Figure 5), a focus of activation located at Talairach coordinates x = –30, y = –76, and z = –11 is not apparent in the baseline scan but emerges in the 2-week scan. Although the activation foci displayed in Figure 5 are not in the same locations for the control and depressed subjects, the locations do reflect activation in the same functional region, namely area 19.

Figure 5. Significant Activation Registered on High-Resolution Sagittal Anatomic Images*



*On the top, the left image shows activation of two control subjects in the baseline scan elicited by viewing positive pictures. The focus of the activation is in the middle occipital sulcus (Brodmann's area 19), located at Talairach coordinates x = –39, y = –70, and z = –3. On the top, the right image shows activation of control subjects at the 2-week scan. Note the overall reduction in the magnitude and spatial extent of the area 19 activation as well as the disappearance of the focus of activation in the cerebellum. On the bottom, the left image shows the absence of activation in the depressed subjects in the baseline scan. On the bottom, the right image shows the emergence of a focus of activation at Talairach coordinates x = –30, y = –76, and z = –11 and in the functional zone of area 19. The probability of the areas of significant activation are reflected by the colorization, ranging from $p < .0001$ (red) to $p < .0000001$ (yellow) of the chi-square statistic (see text for details).

Consistent with our earlier report,[7] the negative pictures induced bilateral activation of the amygdala in the baseline scans of the control subjects. When scanned the second time, the controls did not display evidence of amygdala activation. In the depressed patients at baseline, exposure to the negative pictures resulted in a small focus

Table 1. Effects of Venlafaxine on Depressive Symptoms After 2 Weeks of Treatment*

	Prior to Treatment		2 Weeks of Treatment		Venlafaxine
Patient	HAM-D	BDI	HAM-D	BDI	Dosage
Patient 1	22	27	12	9	75 mg/day
Patient 2	20	20	8	3	75 mg/day

*Abbreviations: BDI = Beck Depression Inventory, HAM-D = Hamilton Rating Scale for Depression.

subject's SPM into the Talairach[28] coordinate system, which then permitted comparisons across subjects. The Talairach-transformed SPMs were combined across subjects by summing the square of the Student's t for each pixel. The "summed t-square" distribution was equivalent to the chi-square distribution, with the degrees of freedom equal to the number of subjects.[29] A threshold was used such that only those pixels with significant paradigm-correlated signal changes ($\chi^2 = 18.25$, df = 2, $p < .0001$) were displayed.

Results

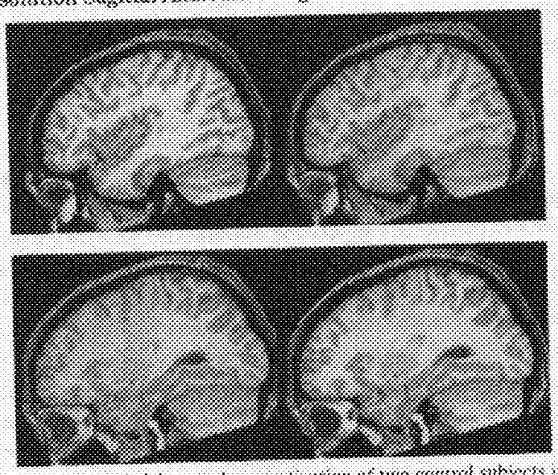
The results presented in this report are preliminary and involve only the data from the first two scanning sessions (baseline and 2 weeks later) for two control and two depressed subjects. Because the results are based on such a small sample size, they must be interpreted with caution. Nevertheless, the data reveal three potentially important trends. The drug doses and HAM-D and BDI scores are presented in Table 1. As can be seen, both patients demonstrated clinically significant symptomatic improvement after 2 weeks of treatment.

For both the depressed and control subjects, the negative pictures induced a greater volume of activation than did the positive pictures in the baseline and 2-week scans. For example, analysis of the baseline data from the negative pictures in the control subjects revealed a volume of activation of approximately 203,646 mm^3 compared with a volume of 7342 mm^3 induced by exposure to the positive pictures. In both groups at both time points, the negative stimuli induced bilateral activation in regions of the prefrontal cortex (Brodmann's areas 10 and 46) and in parietal and occipital regions (Brodmann's areas 19 and 37). Exposure to the negative pictures resulted in greater brain activation at baseline compared with the 2-week scan in both the depressed and control subjects. The mean volumes of activation were approximately 128,048 mm^3 at baseline and 41,183 mm^3 at the second scan.

Responses to the positive pictures differed between the depressed and control subjects. Little activation of prefrontal regions was observed in either group. From the baseline to the 2-week scan, the control subjects showed an overall reduction in global activation, whereas the depressed patients displayed an increase in overall brain activity. This effect can be seen in Figure 5, which shows the significant areas of activation coregistered onto a sagittal slice. The probability of the areas of significant activation are reflected by the colorization, ranging from $p < .0001$ (red) to $p < .0000001$ (yellow). In the figure, scans from the control subjects are on the top row, with baseline on the left and the 2-week scan on the right. This activation is located in the middle occipital sulcus (part of Brodmann's area 19). In the baseline image, the focus of the area 19 activation is located at Talairach coordinates x = –39, y = –70, and z = –3. Also, a focus of activation is present in the cerebellum. In the 2-week image, the spatial extent of the area 19 activation shows an overall reduction, and the cerebellar activation has disappeared. In the depressed subjects (bottom row in Figure 5), a focus of activation located at Talairach coordinates x = –30, y = –76, and z = –11 is not apparent in the baseline scan but emerges in the 2-week scan. Although the activation foci displayed in Figure 5 are not in the same locations for the control and depressed subjects, the locations do reflect activation in the same functional region, namely area 19.

Consistent with our earlier report,[7] the negative pictures induced bilateral activation of the amygdala in the baseline scans of the control subjects. When scanned the second time, the controls did not display evidence of amygdala activation. In the depressed patients at baseline, exposure to the negative pictures resulted in a small focus

Figure 5. Significant Activation Registered on High-Resolution Sagittal Anatomic Images*



*On the top, the left image shows activation of two control subjects in the baseline scan elicited by viewing positive pictures. The focus of the activation is in the middle occipital sulcus (Brodmann's area 19), located at Talairach coordinates x = –39, y = –70, and z = –3. On the top, the right image shows activation of control subjects at the 2-week scan. Note the overall reduction in the magnitude and spatial extent of the area 19 activation as well as the disappearance of the focus of activation in the cerebellum. On the bottom, the left image shows the absence of activation in the depressed subjects in the baseline scan. On the bottom, the right image shows the emergence of a focus of activation at Talairach coordinates x = –30, y = –76, and z = –11 and in the functional zone of area 19. The probability of the areas of significant activation are reflected by the colorization, ranging from $p < .0001$ (red) to $p < .0000001$ (yellow) of the chi-square statistic (see text for details).

of activation in the left amygdala. This area of activation was absent in the 2-week scan. Amygdala activation was never observed in response to the positive pictures in either the depressed or control subjects.

DISCUSSION

Studies involving patients with selective brain lesions[30] and those utilizing regional EEG measures[31] have provided evidence to support the hypothesis that left anterior cortical regions are importantly involved in the processing of positive emotional states and associated approach behaviors. In contrast, right frontal cortical regions appear to be involved in the processing of negative emotions, such as fear and disgust. In regard to depression, many[3,32] but not all[4] results from PET studies generally show that depressed patients have decreased metabolism, or blood flow, in left anterior regions. By using an image analytic strategy that examined relations between specific depressive symptoms and patterns of regional blood flow in a large group of depressed patients, individual differences in the reduction in cerebral blood flow in the left dorsolateral prefrontal cortex were associated with the symptoms of psychomotor retardation and depressed mood.[32] Decreased blood flow in the left anterior prefrontal cortical region was also correlated with increased cognitive impairment.[32] Increased amygdala activity has also been reported in depressed patients,[4] as have correlations between amygdala activity and the severity of depression.[33]

Studies that examine the circuitry underlying emotional processing in normal subjects generally use affective probes to assess the relation between emotional responses and the activation of specific brain regions. PET studies in normal subjects have recently been performed with affective probes, and these studies support the hypothesis regarding anterior cortical lateralization of the processing of positive and negative emotions.[34] However, other studies suggest that recalled negative emotional states may be associated with increased left frontal cortical activity,[1,2] although this regional pattern may be a function of the cognitive activity required to generate the recalled emotional state. Pharmacologic challenges have also been used as tools to examine affective processing, but these agents frequently induce multiple, complex effects, including affective, perceptual, and cognitive changes. Subjects reporting a strong dysphoric response to procaine showed an increase in right-sided blood flow in select limbic regions.[35] Procaine also induced amygdala activation.

On the basis of the results summarized above, we hypothesized that the negative stimuli would induce right frontal and amygdala activity in both depressed and control subjects. We anticipated that the positive stimuli would result in left prefrontal activation. With treatment, we expected that the depressed patients would show increased left frontal activity in response to presentation of the positive pictures. We also expected that a response to treatment would be associated with decreased amygdala activity induced by exposure to the negative stimuli.

It is important to underscore that the data presented are preliminary, representing findings from only a few subjects, and therefore should be interpreted with caution. In the subjects studied, the predicted anterior lateralized effects were not found, but in the control subjects amygdala activation was observed in response to presentation of the negative stimuli. In addition, increased brain activity in response to the positive pictures, albeit in posterior regions, occurred in the depressed subjects after 2 weeks of treatment.

In all subjects, the negative pictures elicited greater brain activity than did the positive pictures. Despite the similar subjective intensity ratings for the positive and negative pictures,[24] this finding suggests that the negative pictures had a greater physiologic impact compared with the positive pictures. In both the depressed and control subjects, the impact of the negative pictures was reduced in the 2-week scan compared with the baseline scan. Reduced brain activity in the 2-week scan was also observed in response to the positive stimuli in the control subjects. These effects could be due to habituation to the second presentation of the stimuli.

Interestingly, the depressed patients demonstrated an opposite response to the positive stimuli. An increased response to presentation of the positive stimuli was seen in the right occipital region at the 2-week scan, and this was associated with a clinically significant treatment response to venlafaxine.

Some investigators have proposed that arousal and alerting processes may be associated with selective activation of right posterior cortex, particularly right temporoparietal regions.[36] In addition, posterior activation has been reported in response to visual emotional stimuli.[37] In the present study, both control and depressed subjects displayed bilateral activation in posterior regions in response to the negative stimuli. This posterior activation was not seen in relation to the positive stimulus in the control subjects during both scans, nor was it observed in the depressed subjects at baseline. The fact that depressed subjects showed an increase in right posterior activation after 2 weeks of treatment may indicate that the positive stimuli were beginning to attract attention. The absence of associated prefrontal changes may signify that the positively valanced responses to these stimuli had not yet developed. It will be important to examine the changes that occur at the 8-week follow-up.

Amygdala activation was observed in the control subjects in response to the negative stimuli, which was consistent with our earlier work.[7] The initial amygdala activation appeared to attenuate, which was similar to the response of other brain regions to the repeated presentation of the negative stimuli. No amygdala activation was observed in

response to the positive stimuli, and minimal amygdala activation was seen in the depressed patients at baseline. This was somewhat unexpected but could have been due to the nature of fMRI. One possible explanation for our inability to detect more robust negative stimuli-induced amygdala activity in the depressed patients could be that, in fMRI studies, activation is determined by the difference in activity detected between the negative and neutral stimuli. If in the depressed patients amygdala activity in response to the neutral stimuli is already high, the likelihood of observing further increases might be reduced. Clearly, no definitive conclusions can be drawn until more depressed subjects are studied.

fMRI is a method ideally suited to characterize circuitry that is activated in emotion and to determine how the function of this circuitry changes in response to antidepressants. fMRI has excellent spatial and temporal resolution and is noninvasive. Therefore, fMRI studies of the functional neuroanatomy of emotional activation in depression and of changes with antidepressant treatment hold considerable promise in identifying the nature of the dysfunction in affective processing in patients with affective disorders, as well as mechanisms of action of antidepressant drugs.

Drug names: fluoxetine (Prozac), procaine (Novocain), venlafaxine (Effexor).

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