

# Brain Blood Flow Changes in Depressed Patients Treated With Interpersonal Psychotherapy or Venlafaxine Hydrochloride

## Preliminary Findings

Stephen D. Martin, MBBS, MRCPsych; Elizabeth Martin, RMN, BSc; Santoch S. Rai, MBChB, MRCPsych; Mark A. Richardson, BSc; Robert Royall, BSc, C. Eng, IEE, MIPEM

**Background:** Functional brain imaging studies in major depression have suggested abnormalities of areas, including the frontal cortex, cingulate gyrus, basal ganglia, and temporal cortex. We hypothesized that venlafaxine hydrochloride and interpersonal psychotherapy (IPT) might each alter brain blood flow in some or all of these areas on sequential single photon emission computed tomography (SPECT) scans.

**Methods:** Twenty-eight men and women aged 30 to 53 years with a DSM-IV major depressive episode, a 17-item Hamilton Rating Scale for Depression (HAM-D) rating of 18 or higher, and antidepressant-naïve for at least 6 months were studied. After baseline <sup>99m</sup>technetium-hexa-methyl-propylene-amine-oxime scan, 1-T magnetic resonance imaging, and psychometric ratings, patients were assigned to different treatments. Thirteen patients had 1-hour weekly sessions of IPT from the same supervised therapist (E.M.). Fifteen patients took 37.5 mg twice-daily of venlafaxine hydrochloride. Single-photon emission computed tomogra-

phy scans and ratings were repeated at 6 weeks.

**Results:** Both treatment groups improved substantially, more so with venlafaxine (mean [SD] HAM-D scores at pretreatment: IPT, 22.7 [2.7], and venlafaxine, 22.4 [3.1]; and posttreatment: IPT, 16.2 [7.1], and venlafaxine, 10.9 [8.6]). No patients had structural brain abnormalities. On analysis with statistical parametric mapping 96, the venlafaxine group showed right posterior temporal and right basal ganglia activation ( $P=.01$ ), while the IPT group had limbic right posterior cingulate and right basal ganglia activation ( $P=.01$ ).

**Conclusions:** This preliminary investigation has shown limbic blood flow increase with IPT yet not venlafaxine, while both treatments demonstrated increased basal ganglia blood flow. This was, however, a short trial with a small sample, no control group, and different symptom reduction in the 2 groups.

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**I**N MAJOR DEPRESSION, studies are showing consistent findings, aiding in the understanding of focal and circuit brain function changes. Abnormalities in the cingulate and temporal cortices and basal ganglia have been shown repeatedly in depressed patients compared with controls.<sup>1-9</sup> Another replicated result is the association between psychomotor retardation and reduced function in the left dorsolateral prefrontal cortex.<sup>10,11</sup>

There is very little single-photon emission computed tomography (SPECT) antidepressant psychotherapy. One group reported basal ganglia abnormalities with subsequent temporal and cingulate perfusion increase in patients treated with cognitive therapy or antidepressant medication but, because of small sample size, significant brain changes were only reported with patients from both treatments pooled.<sup>1</sup>

Several studies have found brain changes with different antidepressant medicines, electroconvulsive therapy, and sleep deprivation, with variable increase or decrease in frontal or cingulate function.<sup>12-14</sup> Cingulate changes have been mainly anterior.

*See also pages 631, 649, and 651*

There is more work on functional brain changes with antidepressants, which implicates consistent brain regions between studies, yet has conflicting results in respect of activation or deactivation. Venlafaxine hydrochloride responders were reported to have baseline prefrontal and paralimbic hypometabolism compared with controls,<sup>15</sup> and venlafaxine has been shown to reduce anterior paralimbic blood flow.<sup>16</sup> A decrease of prefrontal

From the Research Unit, Cherry Knowle Hospital, Sunderland (Dr Martin and Ms Martin); the Hutton Centre, St Lukes Hospital, Middlesbrough (Dr Rai); and the Northern Regional Medical Physics Department, South Cleveland Hospital, Middlesbrough (Messrs Richardson and Royall, England).

## PATIENTS AND METHODS

### PATIENTS

Twenty-eight patients with DSM-IV<sup>21</sup>-defined major depressive episode and having a 17-item Hamilton Rating Scale for Depression<sup>22</sup> (HAM-D) score of 18 or higher were included from general practitioner referrals, after approval from the Local Research Ethics Committee and the United Kingdom Administration of Radioactive Substances Advisory Committee. Patients read an information sheet and signed witnessed informed consent. Four males and 9 females were assigned to IPT. Four males and 11 females were assigned to venlafaxine (**Table 1**). All patients were right-handed on the Annett Scale,<sup>23</sup> apart from 1 given IPT and 1 given venlafaxine.

Patients' conditions were diagnosed by the pharmacotherapist (S.S.R.) checking against DSM-IV criteria. The Structured Clinical Interview for the DSM-IV was not used, as patients faced heavy demands on their time with other tests. All DSM-IV diagnoses other than major depressive disorder constituted exclusion criteria, although comorbid anxiety disorders or dysthymic disorder with major depression were included. No patients were bipolar. As well as drug or alcohol dependence being excluded, no patients who had used amphetamine, cocaine, hallucinogens, inhalants, opioids, or phencyclidine even once in the previous 6 months were admitted to the study. One patient with occasional cannabis use 3 months before recruitment, but never having been dependent, was included.

All patients had case note reviews, physical examinations, and biochemical and hematological screening. Other exclusion criteria were documented disease of the central nervous system, any physical illness that might affect clinical ratings, or significant test abnormalities.

All female patients were actively using contraception and not breastfeeding. The age range was small to minimize any confounding diagnoses, overt or undetected, associated with adolescence or old age. The lower age limit was also determined by United Kingdom radiation ethics requirements, as was the absence of normal controls. Patients currently taking any psychotropic medicine or with any magnetic resonance imaging abnormalities on visual reporting by 2 neuroradiologists were excluded.

To avoid antecedent psychotropic medicines confounding scan patterns, it was intended to recruit only drug-naïve subjects in their first episode of depression, but it was not possible to obtain large enough samples for the 2 treatment cells. The protocol was modified in the course of the study to recruit drug-free subjects at the start of a new, recurrent depressive episode. Ten IPT patients and 9 venlafaxine patients were completely drug-naïve. Three IPT patients and 4 venlafaxine patients had previously received antidepressants, but not in the last 6 months. Of the recurrent episode patients, 1 had received diazepam from the general practitioner and was given a 4-week washout before baseline scan. A second patient had a single dose of zopiclone and had a 2-week washout before baseline scan. All patients were

antipsychotic naïve. Use of sumatriptan succinate and hormone replacement therapy constituted exclusion criteria.

### PROCEDURE

Patients were randomized to IPT<sup>24,25</sup> or 37.5-mg, twice-daily doses of venlafaxine as an antidepressant medicine, both being of proven efficacy in large trials for major depression.

Venlafaxine studies<sup>26-29</sup> support the efficacy of this low dosage, chosen for these patients who were not treatment-resistant. This dose was not altered in any patients. While a twice-daily dosage had the potential to diminish compliance compared with once-daily slow-release venlafaxine, the latter was not licensed when this study commenced.

In premodern observations, the natural course of a depressive episode was commonly observed to remit after 3 months without treatment<sup>30</sup> and only one third of patients have episodes longer than 2 years.<sup>31</sup> A 6-week follow-up interval was chosen to minimize bias by spontaneous remission and match the interval for many studies of antidepressant medication. We were aware that 6 weeks was early to expect a psychotherapy response. At the time the study commenced, there were no substantial scientific data on rapidity of IPT response.

There was some selection to minimize bias against psychotherapy for patients who were not psychologically minded and preferred medication. Twenty-three patients were randomized to 1 of the 2 treatment cells using the sealed-envelope technique. Four patients were allowed nonrandomized venlafaxine and 1 patient, who expressed a strong view, was allowed nonrandomized IPT. There was no formal instrument used to measure subject preference.

The IPT therapist (E.M.) was a psychiatric nurse, with 14 years' clinical experience, trained in various psychotherapies, including IPT, before the study. Interpersonal psychotherapy patients had up to 16 one-hour, weekly sessions talking through IPT problem areas. The second scan was conducted after the sixth IPT session (ie, after 6 weeks). Three patients' complete IPT sessions were tape recorded in the course of the study for external assessment, to validate therapeutic technique, and to certify fully the IPT therapist for research. All patients had 6 weekly IPT sessions in between scans. The IPT therapist did not do pharmacotherapy or clinical ratings.

Of the 56 sets of ratings carried out, 53 were done by 1 clinically experienced psychiatrist (S.S.R.), who was not blind to treatment and also did the pharmacotherapy. Three of the 56 sets of ratings were done by a covering experienced psychiatrist. Both of these psychiatrists had satisfied interrater training with the HAM-D in another depression study with ratings matching expert tapes and had 4 years of clinical experience in psychiatry. No IPT sessions were done by the pharmacotherapists. They were prohibited from doing any sort of formal psychotherapy, yet saw patients every 2 weeks for 15 minutes to review progress, compliance with medication, and adverse effects as well as to make supportive comments. The clinical raters were blind to scan data.

metabolism has been reported with paroxetine.<sup>17</sup> Sertraline hydrochloride, however, increased dorsolateral prefrontal cortex metabolism.<sup>18</sup>

With functional abnormalities of temporal, limbic, frontal, and basal ganglia brain structures being impli-

cated in depression, it was hypothesized that any of these areas might be changing during recovery. Brain function was investigated in small areas throughout the whole brain, using the established technique of statistical parametric mapping 96 (SPM96).

Symptom rating scales with the HAM-D, the Hamilton Rating Scale for Anxiety (HAM-A)<sup>32</sup> as well as the Beck Depression Inventory (BDI),<sup>33</sup> and SPECT scans were performed at baseline before any treatment and at 6-week follow-up.

Single-photon emission computed tomography scans were carried out as near as possible to rating scales. Of the 56 SPECT scans carried out, 38 were within 24 hours of clinical ratings, 12 within 48 hours, and 6 within 72 hours.

#### SPECT METHOD AND IMAGE ANALYSIS

Cerebral blood flow (reflecting brain metabolism) imaging was done by SPECT,<sup>34</sup> using <sup>99m</sup>technetium-labelled hexa-methyl-propylene-amine-oxime (HMPAO).<sup>35</sup> All scans were done on the same single-headed camera, a Camstar XRT (GE Medical Systems, Milwaukee, Wis), fitted with a low-energy, general purpose collimator. Data were acquired in a 128 × 128-pixel matrix at each of 64 positions over a 360° rotation around the subject's head. Imaging commenced 2 minutes after injection of HMPAO and took 32 minutes.

Patient comfort and stillness were encouraged in a quiet environment. There were no activation paradigms given. The patients' eyes were open and their ears were not plugged. Tomographic reconstruction was performed on a HERMES workstation (Nuclear Diagnostics, Kent, England) using a method of filter backprojection with attenuation correction, the data having been prefiltered by a fourth-order Wiener filter. Acquisition and reconstruction was carried out by 1 physicist (M.A.R.) blind to clinical data, assisted by medical technologists.

The resolution of this technique is within the sizes of the major structures of interest (ie, cingulate, basal ganglia, prefrontal cortex, and temporal lobe). The transaxial slices, orientated to standard brain anatomy, were transferred to a SUN Classic workstation for processing using SPM-based software (Wellcome Department of Cognitive Neurology, London, England).

Statistical parametric mapping<sup>36-39</sup> performs an automated coregistration of all brain images to a standard stereotactic space, followed by a voxelwise statistical analysis based on the theory of gaussian fields.

It locates areas of significant change in the mean voxel intensity between groups of scans of different brain states and/or from different groups of subjects. This powerful analysis method removes the constraints imposed by determination of regions of interest, which assumes a priori knowledge of the functional anatomy of the diseased mind.

Using the positron emission tomography cerebral blood flow (CBF) template in SPM96 with a 12-parameter linear transformation to Talairach coordinate space, we performed scaling and shearing to account for differences in individual brain shape (ie, stereotactic anatomic standardization).<sup>40</sup> All spatially normalized scans were smoothed using a 12-mm full-width at half-maximum isotropic gaussian spatial filter before the voxelwise statistical analysis. Global voxel intensity normalization was achieved using

proportional scaling, so that any differences in global CBF (gCBF) were removed by scaling all voxels within a scan to the mean gCBF of that scan.

All scans were statistically analyzed using the appropriate statistical paradigm within SPM. This type of voxelwise analysis is documented elsewhere for neuroactivation studies.<sup>37</sup> It is based on the theory of gaussian fields and using global mean blood flow to normalize voxel activity. The resulting SPMs (SPM[t]) represent a map of change significance based on peak effect size (Z) within a contiguous volume with voxel values greater than  $Z = 2.33$ , the size (V) of this volume, the smoothness of the data set, and the overall size of the search volume (data available from the authors upon request).

The within-treatment group differences were analyzed using the statistics option "multisubject: different conditions" to investigate significant changes in regional CBF between SPECT scans before and after treatment. The differences between the treatment groups were investigated by using the statistics option, "multistudy: different conditions" using an interaction<sup>41</sup> paradigm to investigate the differences in the significant areas of regional CBF change between the 2 treatment groups.

While SPM96 shows surface magnetic resonance imaging normal template projections, it does not show deep projections except on a 3-dimensional black-and-white grid (Z map). Color representations of blood flow activation patterns on SPM96 were also superimposed on comparably sited normal magnetic resonance imaging templates with proportionate measurements on all axes being transferred from glass brain Z maps to the templates to show the sequentially different data for each treatment cell, pixel by pixel. Although this technique allows SPECT resolution within the main regions of interest on magnetic resonance imaging, the distortion of pooled magnetic resonance imaging scans to represent group data remains technically difficult and was not attempted.

This analysis was undertaken by one of the author (R.A.R.) with peer supervision in SPM96, both physicists being blinded to clinical data.

#### DATA ANALYSIS

Statistical analyses were performed using SPSS for Windows version 10.1 and MINITAB for Windows version 12.1.

Before the main analyses, all data distributions were checked using 2 separate normality tests, the Anderson-Darling and Shapiro-Wilks tests. Homogeneity of variances was confirmed using Levene test.

Within-group tests were performed via the matched *t* test, which is equivalent to a 2-group repeated-measures analysis of variance procedure in the case of time-separated variables.

Between-group tests were carried out via analysis of covariance, using base measurements as covariates. This method seeks to compensate for between-group inequalities in pretreatment scoring profiles.

The level of significance used was 5% ( $\alpha = .05$ ).

Recruiting a large sample was a major aim of this study. Whether the 2 approaches separately would show different biological changes was investigated as a preliminary test.

Interpersonal psychotherapy (IPT) was chosen as it is a well-researched, time-limited psychotherapy of

proven efficacy.<sup>19</sup> The simplicity of IPT technique gave a standardized psychotherapy model for a biological study. Interpersonal psychotherapy actively helps the depressed patient to understand his or her low mood in terms of complicated bereavement, role transition,

role dispute, or interpersonal deficit. The patient is then helped to learn strategies to change such interpersonal problems. Biological research on IPT is limited, although it has been shown that abnormal sleep electroencephalograms predicted negative IPT outcome but positive pharmacotherapy outcome.<sup>20</sup>

The recruitment of homogeneous yet potentially generalizable samples in neuroimaging studies is difficult and time-consuming. This project ran more than 2 years in an attempt to maximize the sample size, with patients being assessed and recruited in their general practitioners' surgical practices to allow drug-naïve and new-episode subjects to be screened.

## RESULTS

The within-group analyses (pretreatment scores vs 6 weeks scores) are described first. For each instrument, reduced scores indicate an improvement in symptoms. Overall, patients showed significant improvements over the 6-week study period on each instrument ( $P < .001$ ) (**Table 2**). For the BDI, the IPT group had a mean (SD) decrease of 9.92 (11.9) ( $P = .01$ ). Mean (SD) reduction for the venlafaxine group was 14.27 (7.47) ( $P < .001$ ). For the HAM-D, the IPT group showed a mean (SD) decrease of 6.54 (6.94) ( $P = .005$ ), while the mean (SD) difference for the venlafaxine group was 11.47 (6.67) ( $P < .001$ ).

For the HAM-A, mean (SD) difference for the IPT group was 4.54 (6.32) ( $P = .02$ ); for the venlafaxine group,

the difference was 6.93 (5.22) ( $P < .001$ ). **Table 3** shows the results in greater detail.

For the between-group analysis, at the base time-point, mean differences were 1.7 for the BDI, 0.29 for the HAM-D, and 2.03 for the HAM-A. Before each procedure, regression slope equivalence and homogeneity of variances were confirmed.

For the BDI, the adjusted 6-week mean difference was 5.32 ( $P = .13$ ). For the HAM-D, the adjusted difference was 4.8 ( $P = .07$ ). The adjusted mean difference for the HAM-A was 2.27 ( $P = .33$ ) (**Table 4**).

There is a consistent trend on all 3 instruments toward a better outcome for the venlafaxine group. However, the observed differences between means are not significant. The small numbers of subjects involved in the study coupled with the within-group variances preclude these differences from attaining significance. Based on the results obtained from this study, the sample sizes required to achieve 80% power at the 5% level are as follows: HAM-D, 44 per group; BDI, 70 per group; and HAM-A, 170 per group.

The groups' pretreatment scoring profiles were quite similar to each other; therefore, the use of base measures as covariates resulted in relatively small changes from the initial values, and in none of the cases did this affect the general tenor of the results.

No individual SPECT scans had gross abnormalities on visual reporting with respect to defects below 65% mean CBF. Statistical parametric mapping 96 yielded significant results. There was a significant difference between the scans of patients in the 2 treatment groups having IPT or venlafaxine throughout the study in that the IPT group had greater left striatal perfusion than the venlafaxine group at baseline and at 6 weeks. This finding does not diminish the significance of the following sequential SPECT data, which appeared in different areas for each treatment group.

The significance thresholds were set at  $P < .01$  (uncorrected height threshold) and  $P_k < .03$  (uncorrected extent threshold), where height is the voxel intensity within the SPM(t), and extent is the number of voxels above this height threshold corrected for multiple statistical testing.<sup>39</sup>

The 6-week scan showed significant patterns of regional cerebral perfusion activation when compared with the baseline scan ( $P = .01$ ). The total scan data are shown on glass brain diagrams in the 3-dimensional "Z maps" (**Figure 1**). The venlafaxine patients (**Figure 2**) showed right posterior temporal and right basal ganglia activation of function over the treatment period ( $P = .01$ ). Interpersonal therapy patients (**Figure 3**) had right basal

**Table 1. Patient Details**

	Venlafaxine Hydrochloride (n = 15)	Interpersonal Psychotherapy (n = 13)
Age, mean (SD) [range]	39.4 (8.3) [31-53]	38.4 (4.9) [30-46]
Sex		
Male	4	4
Female	11	9
Race		
White	14	13
Asian	1	0
First episode	7	5
Recurrent episode	8	8
No. of previous episodes, mean (range)	1.7 (1-3)	1.1 (1-4)
Duration of current episode, mo, mean (range)	6.3 (1-12)	5.6 (1-18)
Major depression	12	9
Double depression	3	4
Generalized anxiety disorder	3	4

**Table 2. Clinical Rating Scales Results of Within-Group Analyses for Combined Groups\***

Rating Scale	Pretreatment (n = 28), Mean (SD) [Range]	Posttreatment (n = 28), Mean (SD) [Range]	Difference	t Score†
HAM-D	22.5 (2.8) [19-29]	13.4 (8.2) [0-29]	9.2	6.8
BDI	27.0 (7.4) [16-43]	14.8 (9.6) [0-36]	12.3	6.6
HAM-A	18.1 (4.5) [11-28]	12.3 (7.7) [0-28]	5.8	5.3

\*HAM-D indicates Hamilton Rating Scale for Depression; BDI, Beck Depression Inventory; and HAM-A, Hamilton Rating Scale for Anxiety.

† $P < .001$ .



**Table 3. Clinical Rating Scales Results of Within-Group Analyses for Individual Groups\***

Rating Scale	Group†	Pretreatment, Mean (SD)	Posttreatment, Mean (SD)	Difference	t Score	P
HAM-D	IPT	22.7 (2.7)	16.2 (7.01)	6.5	3.4	.005
	Venlafaxine	22.4 (3.1)	10.9 (8.6)	11.5	6.7	<.001
BDI	IPT	27.9 (8.9)	18.0 (10.8)	9.9	3.0	.01
	Venlafaxine	26.3 (6.2)	12.0 (7.7)	14.3	7.4	<.001
HAM-A	IPT	19.2 (4.6)	14.7 (6.9)	4.5	2.6	.02
	Venlafaxine	17.2 (4.4)	10.3 (7.9)	6.9	4.2	<.001

\*HAM-D indicates Hamilton Rating Scale for Depression; IPT, interpersonal therapy; BDI, Beck Depression Inventory; and HAM-A, Hamilton Rating Scale for Anxiety.

†There were 13 patients in the IPT group and 15 in the venlafaxine group.

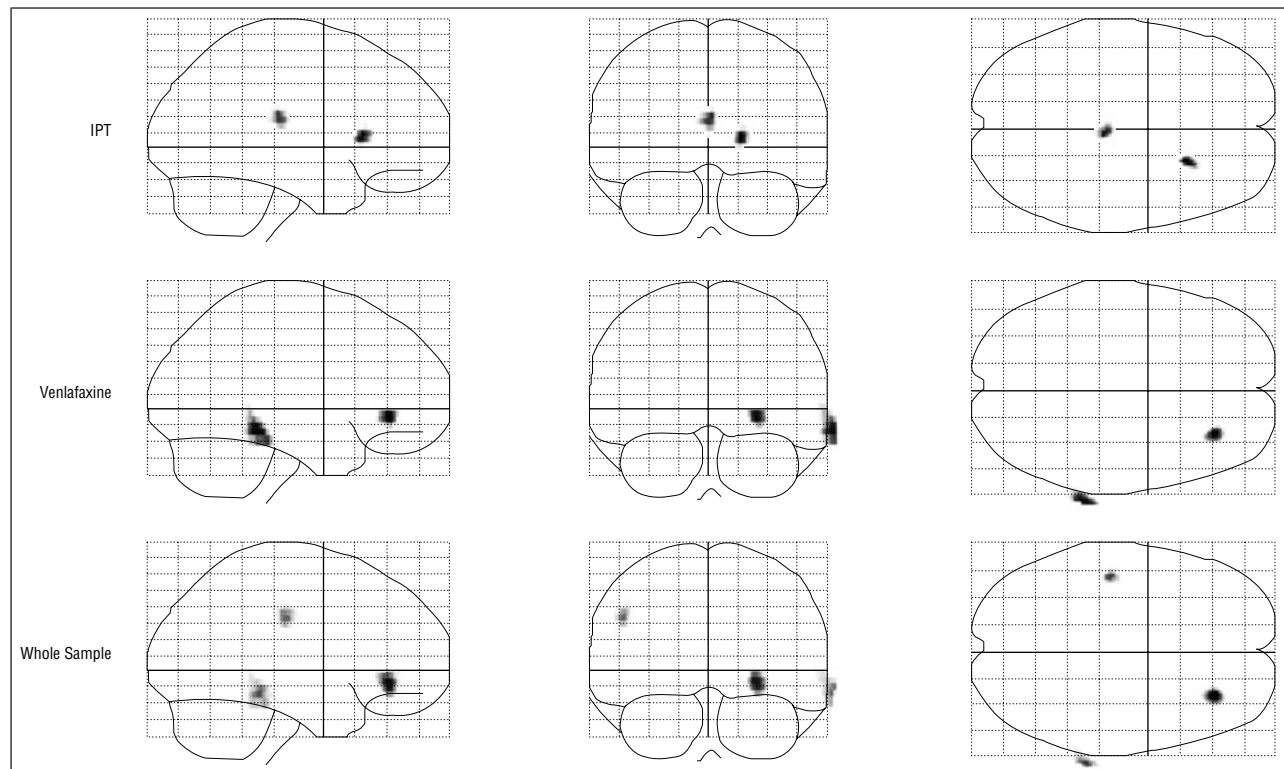
**Table 4. Clinical Rating Scales Results of Between-Group Differences (Adjusted 6-Week Means)\***

Rating Scale	IPT at 6 Weeks†	Venlafaxine at 6 Weeks‡	Difference Between Groups	F Score	P
HAM-D	15.9	11.1	4.8	3.5	.07
BDI	17.6	12.3	5.3	2.5	.13
HAM-A	13.6	11.3	2.3	0.99	.33

\*IPT indicates interpersonal psychotherapy; HAM-D, Hamilton Rating Scale for Depression; BDI, Beck Depression Inventory; and HAM-A, Hamilton Rating Scale for Anxiety.

†There were 13 patients in the IPT group.

‡There were 15 patients in the venlafaxine group.



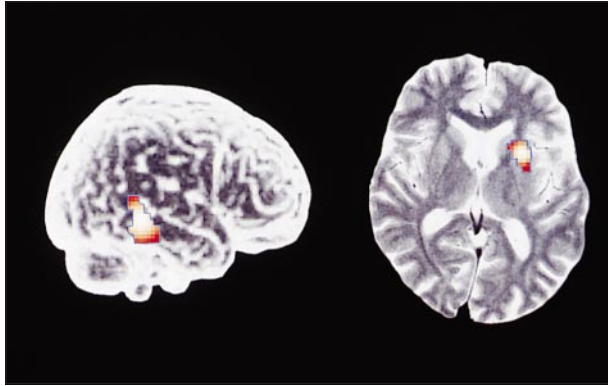
**Figure 1.** Regional cerebral blood flow activation with interpersonal psychotherapy (IPT) (n=13), venlafaxine (n=15), and whole sample (n=28) on statistical parametric mapping 96 analysis of variance “Z maps” (P=.01), for scan 2. For scan 1, the columns, left to right, show sagittal, coronal, and transaxial grids.

ganglia and limbic right posterior cingulate treatment activation (P=.01).

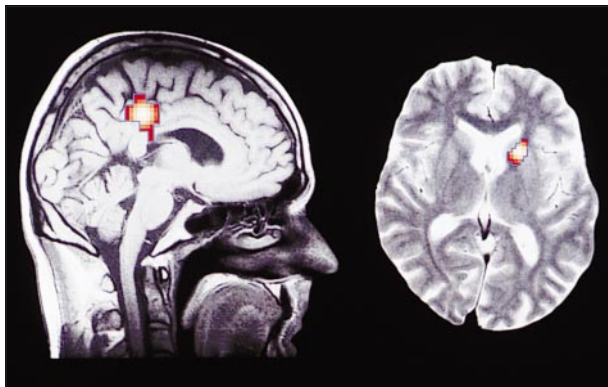
Comparing the 6-week scan with the baseline scan with respect to the whole group on both treatments, the areas that activated significantly (P=.01) were those for the venlafaxine group, but there was an additional acti-

vation pattern in the dominant hemisphere angular gyrus (P=.01), which is also shown on the Z map in the left inferior parietal region.

Comparing the 6-week scan with the baseline scans, there were nonsignificant basal diffuse patterns of brain blood flow reduction.



**Figure 2.** Patients receiving venlafaxine hydrochloride (n=15), showing activation of right basal ganglia and right posterior temporal cortex, using statistical parametric mapping 96 "Z map" ( $P = .01$ ), on 1-T normal magnetic resonance imaging template.



**Figure 3.** Interpersonal psychotherapy patients (n=13), showing activation of right basal ganglia and limbic right posterior cingulate cortex, using statistical parametric mapping 96 "Z map" ( $P = .01$ ), on 1-T normal magnetic resonance imaging template.

The question of single scans skewing SPM was checked by removing each one from these analyses. The posterior temporal activation pattern with venlafaxine was eliminated with 1 patient's exclusion.

#### COMMENT

Although preliminary, this investigation has found limbic right posterior cingulate blood flow to increase with IPT, yet not venlafaxine, while both treatments increased right basal ganglia blood flow. Our SPECT resolution was not fine enough to draw conclusions on striatal subregions. A posterior temporal activation with venlafaxine may have been a muscular artifact in a single patient.

This study produced unanticipated differential changes with psychotherapy and pharmacotherapy in areas in which previous investigators had, however, found abnormalities compared with controls. Some, but not all, of our a priori hypotheses with respect to potential areas of activation were met. There was no cingulate or frontal deactivation, which has been shown in some studies. Failure to detect dorsolateral prefrontal cortical activation over time in these data may reflect lower symptom severity in this new episode sample than in other studies.

Limitations of this study include a single IPT therapist who only became fully research-certified in the course of the project, yet who seemed to bring about rapid and significant clinical improvement. Thus, it is possible that the individual therapist's efficacy was measured rather than IPT. The week 6 scan interval may not have measured the maximum efficacy of the 2 treatments, particularly for IPT. Yet a single, postbaseline scan time had to be chosen, as United Kingdom Administration of Radiation of Radioactive Substances Advisory Committee only allows 2 such SPECT scans each year.

Medication returns were not formally monitored as a compliance measure and the clinical raters were not trained in a large group of raters for this particular project, as in many multicenter trials. It is possible that unmeasured degrees of supportive psychotherapy confounded the 15-minute follow-up sessions monitoring venlafaxine. It did not seem clinically natural to monitor venlafaxine weekly, which would have matched IPT frequency for better scientific control.

Even given the validity of SPM96 and the absence of meaningless significant sequential brain change, there is a chance that the activation patterns are physiological fluctuations.

An intention-to-treat analysis was not done, as this did not relate meaningfully to sequential SPECT. Another discrepancy of the method here compared with trial methods is the absence of long-term follow-up data. There is a lack of absolute data and a lack of healthy control subjects.

A similar pattern to our findings was shown in patients who responded to antidepressants or cognitive behavioral therapy with significant initial right basal ganglia hypoperfusion,<sup>1</sup> although subsequent cingulate activation was bilateral, as opposed to our unilateral right finding. Right cingulate activation has, however, been shown in 10 elderly depressed patients with various medical treatments on sequential SPECT.<sup>8</sup>

The nonspecificity of right basal ganglia activation can only be speculative. With respect to neurotransmitter abnormalities in the basal ganglia in depression, a number of findings have implicated dopamine.<sup>42-45</sup> It is possible that mediation of dopamine receptors is affected indirectly by antidepressant treatment. High-dose venlafaxine has dopamine receptor affinity<sup>46,47</sup> yet there is no evidence for direct dopamine receptor action at the doses used here.

Pharmacodynamic research suggests that at this dose venlafaxine acts by inhibiting serotonin reuptake and, at higher doses, has a noradrenaline reuptake action in addition. The striatum seems to have complex inhibitory and disinhibitory functions of motor and mental control.<sup>48</sup> It has been suggested that cognitive functions are probably regulated in part by some specific areas of the dorsal striatum.<sup>49-51</sup> Why unilateral right activation patterns should emerge poses a major question for refutation or proof and explanation of their bearing on depression.

Despite numerous limitations, the strengths of this study are its large sample for a neuroimaging project, 2 treatment conditions associated with clinical improvement over time, and provocative, significant SPECT find-

ings that should be replicated, controlling for some of the above confounding factors.

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Corresponding author: Stephen D. Martin, MBBS, MRCPsych, Affinity Research Unit, Cherry Knowle Hospital, Ryhope, Sunderland, SR2 0NB, England.

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