

No Effect of Depression on [^{15}O]H $_2$ O PET Response to Intravenous *d*-Fenfluramine

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Objective: Subnormal prolactin responses to the serotonin-releasing agonist fenfluramine occur in depression. Since many measures of serotonin pathology occur in depression, abnormal responses to fenfluramine may occur in brain structures other than the hypothalamic-pituitary axis. One study compared six depressed and six healthy subjects' responses to oral *d,l*-fenfluramine by assessing [^{18}F]fluorodeoxyglucose uptake as detected by positron emission tomography (PET). That study showed several abnormalities within the cortex, and the authors concluded that low responsivity to *d,l*-fenfluramine is widespread in depression. In this study abnormalities in regional neuromodulation by serotonin in major depression were assessed with intravenous *d*-fenfluramine and [^{15}O]H $_2$ O PET. **Method:** Changes in regional cerebral blood flow (CBF) were detected by using [^{15}O]H $_2$ O PET after administration of intravenous *d*-fenfluramine to 13 depressed and 18 healthy women. The PET scans were done 20 and 5 minutes before and 20 and 35 minutes after *d*-fenfluramine administration. Differences between the depressed and healthy groups in change in regional CBF (mean postfenfluramine minus mean prefenfluramine) were analyzed by using statistical parametric mapping. **Results:** There were no significant differences between depressed and healthy subjects; in fact, changes in regional CBF after intravenous *d*-fenfluramine were remarkably similar. **Conclusions:** Degrees of neuronal responsivity to *d*-fenfluramine are similar in depressed and healthy subjects. Differences between the previous and current findings may be accounted for by greater specificity of intravenous *d*-fenfluramine to serotonin release, timing of scans, paucity of suicidal subjects in the current study, or greater variance in regional CBF from direct vascular effects of serotonin.

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There is significant evidence implicating low brain serotonin turnover in the pathophysiology of depression. Brain uptake of the serotonin precursor 5-hydroxytryptophan is low during depression (1). Depletion of the serotonin precursor tryptophan induces recurrence of sad mood in treated depressed subjects (2). The serotonin metabolite 5-hydroxyindoleacetic

acid in cerebrospinal fluid is often low in depression (3). These measures could reflect low serotonin turnover in specific brain regions or a more generalized hyposerotonergic state.

Measures of serotonin (5-HT) receptor binding are one approach to detecting focal changes; however, results are inconsistent. The best-replicated finding, greater than normal 5-HT $_2$ binding within the frontal cortex, was found in fewer than one-half (4, 5) of such studies (4–10). Furthermore, the laterality of this finding has not been well replicated: D'haenen et al. (7) found a high ratio of right to left frontal cortex 5-HT $_2$ binding, but Yates et al. (4) reported greater than normal 5-HT $_2$ binding in the left frontal cortex.

The endpoint of low prolactin response to oral *d,l*-fenfluramine (a serotonin-releasing agent [11, 12]) in depression (13–16) is a common finding that may reflect serotonin-based pathology. Since whole-brain measures and some receptor studies also have shown serotonin-based abnormalities, it is likely that brain re-

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gions other than the hypothalamic-pituitary axis respond differently to fenfluramine in depression. Such structures have a high potential for being pathophysiologically linked to depression.

The response of other brain structures to fenfluramine can be assessed by detecting changes in regional cerebral blood flow (CBF) or regional glucose uptake by means of positron emission tomography (PET) (17–20). Scanning with [^{18}F]fluorodeoxyglucose (FDG) PET after administration of oral *d,l*-fenfluramine, as compared to placebo, has been reported to be a valid method in at least two centers (17–20). Several changes were subsequently introduced to improve this method: intravenous administration, use of the more specific *d*- form of fenfluramine (11, 12), and a one-session format with [^{15}O]H $_2$ O PET scans before and after injection (18).

The older version of this technique ([^{18}F]FDG PET with oral *d,l*-fenfluramine) was applied by Mann et al. (19) to six depressed and six healthy subjects. Relative to global FDG uptake, increases in the left parietal-temporal cortex and the left medial frontal cortex and decreases in the right prefrontal cortex and the right parietal-temporal cortex were seen in the healthy subjects but not in the depressed patients. Mann et al. (19) concluded that serotonin neuromodulation is lower than normal throughout the brains of depressed persons.

Using the improved approach—intravenous *d*-fenfluramine with [^{15}O]H $_2$ O PET—with more subjects and more rigorous subject selection, we retested the theory of a generalized hyposerotonergic state in depression. We hypothesized that there are specific brain regions with abnormal responses to fenfluramine. The same differences previously reported by Mann et al. (19), between depressed and healthy subjects, should occur in the current study. Intravenous *d*-fenfluramine should have localized effects on healthy subjects (18) but none in the depressed group.

METHOD

This study was approved by the review committee on the use of human subjects at the University of Toronto. The subjects were 13 depressed and 18 healthy women aged 18 to 30 years who were recruited by advertisement. All were physically healthy, right-handed, nonsmoking, and not pregnant. All of them had been free of drugs (including psychotropic drugs) for the previous 6 weeks. The depressed subjects had been free of psychotropic medication for at least 3 months (see the following). After complete description of the study to the subjects, written informed consent was obtained.

The first eight healthy subjects have been previously described (18). The remaining healthy subjects were similarly screened by using the Structured Clinical Interview for DSM-IV (SCID) (21) and the Hamilton Depression Rating Scale (22). A score of less than 8 on the Hamilton scale was required for entry of the healthy subjects into the study.

For each depressed patient, a diagnosis of a major depressive episode was confirmed by the SCID, which was administered by a trained research assistant. Patients with psychotic symptoms or comorbid axis I diagnoses were excluded from the study. Ten subjects had a diagnosis of major depressive disorder, and three subjects had

a diagnosis of bipolar disorder, type II. Only one depressed subject, with bipolar disorder, had ever completed a 6-week trial of an antidepressant. This subject had been free of psychotropic drugs for 3 months. One subject, with major depressive episode, had a history of a previous deliberate suicide attempt. In addition, each patient received a psychiatric consultation (J.H.M., S.K., or G.M.B.). A score of greater than 17 on the Hamilton Depression Rating Scale was required for entry into the study. Each depressed subject had routine tests to rule out common medical causes of depression (thyroid function, electrolytes, complete blood cell count).

On the scan day, 0.3 mg/kg of intravenous *d*-fenfluramine was administered over 3 minutes. [^{15}O]H $_2$ O PET measurements of regional CBF were done 20 and 5 minutes before the *d*-fenfluramine injection and 20 and 35 minutes afterward. The latter two times coincide with the peak cortisol response to intravenous *d*-fenfluramine (18). Blood samples for determination of serum cortisol levels were drawn at –25, –10, 15, 30, 45, 60, and 75 minutes.

PET scanning was carried out with a GEMS-Scanditronix PC-2048 15B head scanner. Each subject received a bolus intravenously of 60 mCi of [^{15}O]H $_2$ O. Data acquisition began when the activity threshold exceeded 8,000 counts per second, which is approximately 30 seconds after the bolus. Data were taken in one 60-second frame for each scan. A ^{68}Ge transmission scan was used to correct attenuation.

To standardize cognitive activity, the subjects did a continuous performance task during scanning (18, 23). To maximize the reliability of the task-related activation, the continuous performance task began 20 seconds before the bolus (24).

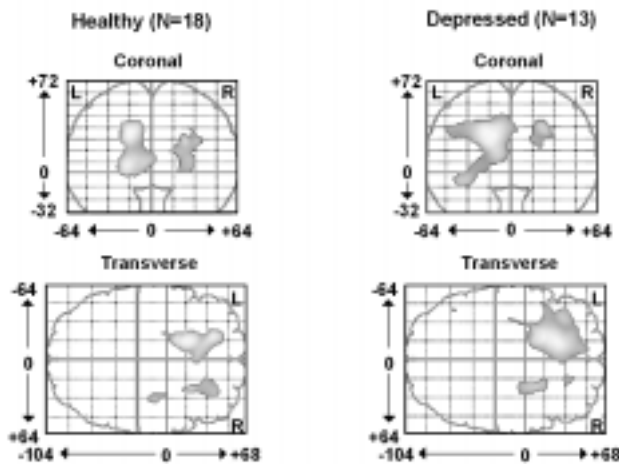
The PET scans were assessed with Statistical Parametric Mapping software, version 1995 (25–28). The threshold for each voxel was set at $p=0.001$. This threshold does not account for multiple comparisons. To correct for multiple comparisons, regional changes were considered significant only if both the spatial extent of suprathreshold voxels and the corrected peak voxel were significant ($p<0.01$ for each) (25).

RESULTS

The mean ages of the patients and healthy subjects were 25.1 and 25.7 years, respectively; the difference was not significant ($t=0.39$, $df=29$, $p=0.70$). The mean scores on the Hamilton Depression Rating Scale of the patients and healthy subjects, respectively, were 22.3 ($SD=4.4$) and 1.4 ($SD=1.9$); this difference was significant (Satterthwaite's method, $t=16.58$, $df=8$, $p<0.0001$). Three of the healthy subjects and four depressed subjects were in the luteal phase of the menstrual cycle, and the remaining subjects were in the follicular phase (Fisher's exact test, $p=0.45$, n.s.).

Change in regional CBF was defined as the mean of the values for the last two scans minus the mean of the values for the first two scans. With statistical parametric mapping (25–28), increases in regional CBF (relative to change in the whole brain) in the healthy and depressed subjects were found (figure 1). In the healthy subjects, relatively increased activity was found bilaterally in the medial frontal cortex both superiorly and inferiorly. For the left frontal cortex, the peak Talairach and Tournoux coordinates (29), z score, number of $2\times 2\times 4$ -mm voxels, p value for number of voxels by chance alone, and p value for peak voxel change were as follows: $x=-14$, $y=18$, $z=32$; z score=5.41; $N=894$; $p<0.001$; $p<0.001$. For the right frontal cortex, the respective values were as follows: $x=24$, $y=22$, $z=24$; z score=4.92; $N=298$; $p=0.02$; $p=$

FIGURE 1. Increases in Regional Cerebral Blood Flow After Administration of Intravenous *d*-Fenfluramine in Healthy Subjects and Depressed Patients^a



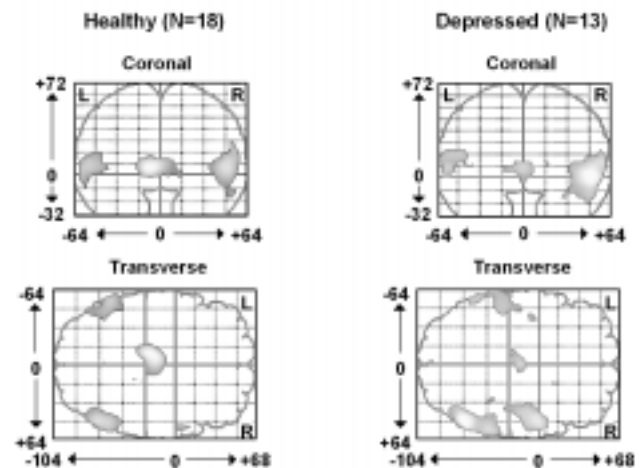
^a $p < 0.001$ for each voxel.

0.001. In the depressed subjects, relatively increased activity was found primarily in the left medial frontal cortex both superiorly and inferiorly. The peak coordinates, z score, number of voxels, p value for peak voxel change, and p value for this number of voxels were the following: $x = -18$, $y = 16$, $z = 32$; z score = 5.51; $N = 1,897$; $p < 0.001$; $p < 0.001$.

Decreases in regional CBF were also found in the healthy and depressed groups (figure 2). In the healthy subjects, relatively decreased activity was found in the bilateral posterior temporal cortex and in the left thalamus. For the left temporal cortex, the peak Talairach and Tournoux coordinates, z score, number of voxels, p value for number of voxels, and p value for peak voxel change were as follows: $x = -52$, $y = -54$, $z = 8$; z score = 4.53; $N = 385$; $p = 0.01$; $p = 0.008$. For the right temporal cortex, the values were $x = 46$, $y = -62$, $z = 8$; z score = 4.94; $N = 588$; $p = 0.003$; $p = 0.001$. For the left thalamus, the values were the following: $x = -10$, $y = -20$, $z = 4$; z score = 5.73; $N = 504$; $p = 0.005$; $p < 0.001$. Within the depressed group, relatively decreased activity was found bilaterally in the inferior parietal-superior temporal cortex. The peak coordinates, z score, number of voxels, p value for peak voxel change, and p value for this number of voxels were, for the left side, $x = -56$, $y = -50$, $z = 8$; z score = 4.11; $N = 386$; $p = 0.01$; $p = 0.04$. For the right side (two regions) they were as follows: $x = 50$, $y = -62$, $z = 0$; z score = 5.37; $N = 881$; $p < 0.001$; $p < 0.001$; and $x = 50$, $y = 2$, $z = 8$; z score = 4.55; $N = 484$; $p = 0.006$; $p = 0.007$.

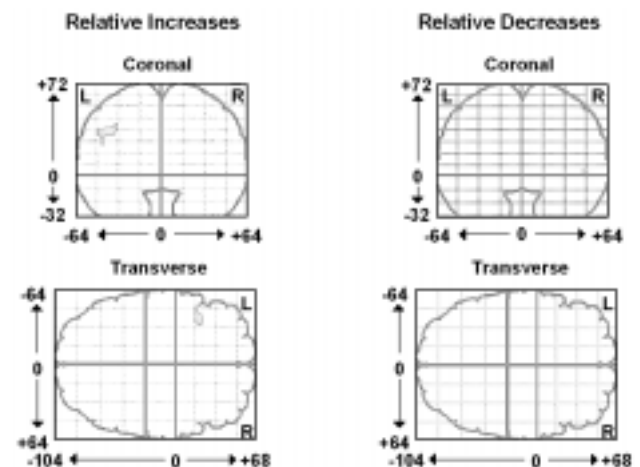
The effect of diagnosis on relative increases and decreases after intravenous *d*-fenfluramine was examined by using statistical parametric mapping (25–28). No significant differences were present. The depressed group had a nonsignificantly greater increase of regional CBF in the left frontal cortex (figure 3). This region was 72 voxels in size (not significant: $p = 0.18$ for size, $p = 0.19$ for peak voxel difference in change).

FIGURE 2. Decreases in Regional Cerebral Blood Flow After Administration of Intravenous *d*-Fenfluramine in Healthy Subjects and Depressed Patients^a



^a $p < 0.001$ for each voxel.

FIGURE 3. Increases and Decreases in Regional Cerebral Blood Flow After Administration of Intravenous *d*-Fenfluramine in Depressed Patients (N=13) Relative to Those in Healthy Subjects (N=18)^a



^a $p < 0.001$ for each voxel threshold uncorrected; not significant when corrected for multiple comparisons.

To eliminate any possibility that the difference between the healthy and depressed groups was a result of merely going through the procedure, relative decreases and increases in depressed as compared to healthy subjects from the first to the second baseline scan (before *d*-fenfluramine administration) were calculated. This would indicate changes in regional CBF between scan 1 and scan 2. No significant changes were found.

To demonstrate the consistency of our findings with those from other studies of regional CBF in depression (30), we examined the effect of diagnosis on regional CBF within the baseline condition. The baseline condition was defined as the two scans done before *d*-fenfluramine administration. The most significant findings

were that the depressed patients had significantly less regional CBF in the bilateral dorsal and ventral anterior cingulate cortex (left spatially greater than right). The Talairach and Tournoux coordinates, z score, and p value for peak voxel changes were, for the left side, $x=-12$, $y=24$, $z=28$; z score=7.03; $p<0.001$; and, for the right side, $x=12$, $y=20$, $z=28$; z score=7.68; $p<0.001$. The total (left and right) region included 1,705 voxels ($p<0.001$). The most inferior level of anterior frontal cortex included in the analysis corresponded to approximately $z=-12$ in Talairach-Tournoux space; hence, the analysis did not include the orbital cortex.

Repeated measures analysis of variance (ANOVA) for the rate of response in the cognitive performance task showed that the effect of diagnosis, effect of repeated performance, and interaction of diagnosis and repetition were all nonsignificant (diagnosis: $F=0.83$, $df=1, 29$, $p=0.37$; repeated performance: $F=0.21$, $df=3, 87$, $p=0.89$; repeated performance by diagnosis: $F=0.72$, $df=3, 87$, $p=0.54$). Repeated measures ANOVA for response accuracy showed that the effect of diagnosis, effect of repeated performance, and interaction of diagnosis and repetition were also all nonsignificant (diagnosis: $F=1.39$, $df=1, 29$, $p=0.25$; repeated performance: $F=1.31$, $df=3, 87$, $p=0.28$; repeated performance by diagnosis $F=0.66$, $df=3, 87$, $p=0.58$).

The intravenous *d*-fenfluramine challenge elicited hormone responses, as would be expected of a serotonergic agonist. Blood samples were drawn from 28 of the 31 subjects. Repeated measures ANOVA of serum cortisol found significant effects over time ($F=4.26$, $df=6, 156$, $p=0.001$), which reflected a rise in cortisol after fenfluramine administration. There was no interaction with diagnosis in this small study group ($F=0.63$, $df=6, 156$, $p=0.70$). Diagnosis was significant for mean cortisol level (of seven samples) only ($t=2.12$, $df=26$, $p=0.04$). The mean serum cortisol levels for the depressed and healthy groups were 137 ng/ml ($SD=45$) and 109 ng/ml ($SD=25$), respectively. Peak cortisol change, defined as the maximum cortisol level of the five postfenfluramine samples minus the mean of the two samples taken before *d*-fenfluramine, was 14 ng/ml ($SD=26$). The time of peak cortisol response was 37 minutes ($SD=15$).

DISCUSSION

The major finding was that intravenous *d*-fenfluramine had remarkably similar effects on regional CBF in depressed and healthy subjects. There was no evidence for global hyporesponsiveness to *d*-fenfluramine.

The differences between depressed and healthy subjects' responses to oral *d,l*-fenfluramine found by Mann et al. (19) were not replicated. The discrepancies may be explained by methodological differences. In the current study *d*-fenfluramine was used rather than *d,l*-fenfluramine. *d,l*-Fenfluramine is less selective for serotonin release because *l*-fenfluramine also has effects on

dopamine and norepinephrine (11). The current findings are secondary to serotonin release, whereas the findings reported by Mann et al. (19) may be secondary to the release of multiple monoamines.

A second major methodological difference between the current study and the one by Mann et al. (19) is that we used intravenous, not oral, administration of fenfluramine. Consequently, scanning occurred much earlier in the current study (at 20 and 35 minutes after fenfluramine dosing) than in the study by Mann et al. (3 hours).

The differences in timing between the two studies may be responsible for dissimilar results because fenfluramine initially releases serotonin and then depletes presynaptic serotonin. Reports of preclinical studies (31, 32) suggest that serotonin storage is depleted about 1 to 2 hours after intraperitoneal fenfluramine administration. In the current study, scanning may have occurred before presynaptic serotonin depletion in both the depressed and healthy groups. In the study by Mann et al. (19), at 3 hours after oral fenfluramine presynaptic serotonin may have been depleted in depressed patients but not in healthy subjects. This would explain the finding that the depressed patients showed no response to fenfluramine but the healthy subjects did.

Selection of patients may also explain discrepancies between our findings and those of Mann et al. In our study, only one of 13 depressed subjects had a history of a suicide attempt and there were no patients with bipolar disorder, type I. In the Mann et al. study, two patients had backgrounds of suicide attempts and type I bipolar disorder.

The design of the current study has some limitations common to PET work using challenges and regional CBF tracers. A separate placebo challenge was not done, but the difference between our results and those of Mann et al. is unlikely to be attributable to any confounding interaction between diagnosis and duration of time spent in the scanner: no such interactions were present when we compared changes between the first two scans (done before *d*-fenfluramine administration). The measure of difference in regional CBF is relative; thus, the absolute change within the frontal cortex could be a greater increase in CBF than in the rest of the brain or a milder decrease in CBF compared to the decrease in the rest of the brain. Arterial sampling could have provided absolute values, but this more invasive method was not necessary to test the hypothesis of hyporesponsivity to *d*-fenfluramine in depression.

Changes in regional CBF are highly responsive to change in neuronal activity. There is a question about whether *d*-fenfluramine directly influences CBF within localized blood vessels. The regions with significant changes found in the healthy subjects refute the question of direct serotonin effect because they do not reflect any pattern of vascular supply and they are similar in location to those found with our previous oral *d,l*-fenfluramine challenge (17), which used [^{18}F]FDG, a measure of glucose metabolism, as a radiotracer. The

available evidence does not indicate localized differences in vasoconstriction by serotonin agonists. Of the cerebral arteries assessed in humans—basilar (33), middle cerebral (34), and smaller arteries within the temporal-parietal cortex (35)—the rank potencies of vasoconstriction by specific agonists are similar. *d*-Fenfluramine may have a direct global effect on cerebral vasculature, but statistical parametric mapping accounts for this by using global CBF as a covariate. In an animal study (36), regional CBF remained highly correlated with regional cerebral glucose uptake after 5-HT_{1A} agonist administration, but to our knowledge correlations of regional CBF to regional glucose uptake have not been investigated with other selective 5-HT agonists or fenfluramine.

We did not find any differences between healthy and depressed subjects in regional CBF response to intravenous *d*-fenfluramine. This demonstrates that at least some postsynaptic serotonergic pathways are intact in depression. Differences between the findings in this study and the previous report (19) may be accounted for by greater specificity of intravenous *d*-fenfluramine to serotonin release, the timing of the scans, clinical differences in the depressed subjects recruited, or greater variance in regional CBF from direct vascular effects of serotonin. Future investigation with intravenous *d*-fenfluramine should focus on the effects of scan timing and should target subgroups of depressed subjects.

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