Article

Changes in Regional Brain Glucose Metabolism Measured With Positron Emission Tomography After Paroxetine Treatment of Major Depression

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Objective: Depression is commonly associated with frontal hypometabolic activity accompanied by hypermetabolism in certain limbic regions. It is unclear whether successful antidepressant treatments reverse these abnormalities or create new resting levels of metabolism. The aim of the present study was to assess the effects of successful paroxetine treatment on regional glucose metabolism in patients with major depression.

Method: Positron emission tomography with [^{18}F]fluorodeoxyglucose was performed on 13 male patients before and after 6 weeks of paroxetine therapy. Resting state scans were also acquired under similar conditions in 24 healthy male subjects for comparison.

Results: After successful paroxetine therapy, increased glucose metabolism occurred in dorsolateral, ventrolateral, and medial aspects of the prefrontal cortex (left greater than right), parietal cortex, and dorsal anterior cingulate. Areas of decreased metabolism were noted in both anterior and posterior insular regions (left) as well as right hippocampal and parahippocampal regions. In comparison to metabolism levels in a group of healthy volunteers, the increase in prefrontal metabolic activity represented a normalization of previously reduced metabolic activity, whereas the reduction in pregenual anterior cingulate activity represented a decrease from previously elevated metabolic levels.

Conclusions: These results provide further support for a dysfunction in cortical-limbic circuitry in depression, which is at least partly reversed after successful paroxetine treatment.

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Functional imaging studies in depression have consistently demonstrated regional blood flow and metabolic abnormalities. Most (1–5) but not all (6–8) investigators have reported a decrease in metabolic activity in the prefrontal cortex in individuals with major depression, particularly in the dorsolateral and medial areas. Regions of decreased metabolism in the inferior parietal and dorsal anterior cingulate as well as in paralimbic regions (anterior insula, inferior orbital, and inferior temporal cortex) have also been identified (9).

In contrast, there is less consensus on the changes in functional brain activity after antidepressant treatment. It is unclear whether antidepressant treatments act to reverse these abnormalities or create new resting levels of metabolism. The balance of evidence appears to support a return to normalcy in some but not all areas. Buchsbaum and colleagues (10) noted a significant correlation between the normalization of previously elevated activity in the anterior cingulate and the reduction in depressive symptoms in responders to sertraline treatment. Increased metabolic activity in left prefrontal, inferior parietal, dorsal anterior, and posterior cingulate areas was also associated with remission during fluoxetine treatment, as was a decrease below baseline metabolism in limbic and paralimbic regions, including the subgenual cingulate, insula, and hippocampus (11). In contrast, Brody and colleagues (12) did not confirm their hypothesis that activity in the dorsolateral prefrontal cortex would increase after paroxetine treatment, although they did report a significantly greater decrease in ventrolateral and orbitofrontal activity in responders than in nonresponders to paroxetine treatment. There are further reports of increased activity in the left prefrontal cortex (1, 13, 14), no change in activity (15), and decreased left prefrontal cortical activity (8) after treatment with disparate antidepressants. Differences in antidepressant agents (e.g., tricyclics or selective serotonin reuptake inhibitors [SSRIs]), concomitant benzodiazepine prescriptions, drug washout criteria, and diagnostic subtypes of depressed subjects, as well as differences in imaging techniques and methods of analysis, may explain these discrepant findings.

To date, no single positron emission tomography (PET) study has utilized methods that control for antidepressant drug type, concomitant medication, and gender. As a result, evidence concerning the functional neuroanatomy of antidepressant effects is derived from a set of studies that employed differing methods. In an effort to address these issues, we used [^{18}F]fluorodeoxyglucose (FDG) PET to ex-

TABLE 1. Characteristics and Plasma Levels of 13 Depressed Male Patients Receiving Paroxetine

		Depression		Hamilton Depression Scale Score			Paroxetine Status at Last Visit	
Subject	Age (years)	Number of Previous Episodes	Duration of Current Episode (weeks)	Pretreatment	Posttreatment	Decrease (%)	Dose (mg/day)	Plasma Level (ng/ml)
1	34	1	3	21	2	90	20	17.32
2	29	2	18	21	3	86	40	78.97
3	45	2	5	33	15	55	40	31.66
4	41	2	4	23	4	83	20	43.94
5	31	4	3	22	9	59	40	214.99
6	24	0	7	18	3	83	20	89.61
7	28	0	36	23	10	57	40	68.96
8	38	2	2	19	3	84	20	15.71
9	58	>15	32	23	5	78	20	52.97
10	48	0	28	24	6	75	20	6.45
11	37	3	19	23	1	96	20	31.28
12	35	1	21	23	6	74	40	57.51
13	30	5	8	25	11	56	40	43.42
Total								
Mean	36.76	2.84	14.3	22.42	6.0	75.08	29.23	57.91
SD	9.37	3.95	12.1	3.59	4.1	13.98	10.38	53.35

amine the neuroanatomical basis of paroxetine treatment in a well-defined homogeneous unipolar population of male patients. On the basis of converging evidence from previous studies, we hypothesized that antidepressant treatment with paroxetine for 6 weeks would be associated with 1) increased activity in both the prefrontal and inferior parietal cortices, as well as in the anterior and posterior cingulate, and 2) decreased activity in the subgenual cingulate and paralimbic regions.

Method

Subjects

Thirteen consecutively screened right-handed male patients (mean age=36.0 years, SD=10) who met DSM-IV criteria for a major depressive episode in the context of major depressive disorder and provided written informed consent to complete PET/FDG studies were examined. Inclusion criteria were a 17-item Hamilton Depression Rating Scale (16) score of >18, a body mass index within 20% of age-adjusted averages, and no recent exposure to antidepressant treatments (3 months for ECT, 8 weeks for fluoxetine, and 4 weeks for all other antidepressant agents).

None of the patients had a concurrent DSM-IV diagnosis, and none was receiving additional psychotropic medication at the time of study. Subjects were also required to be medically stable. However, one subject was receiving the angiotensin-converting enzyme inhibitor ramipril (10 mg/day) for hypertension and was treated with isophane insulin human (10 U b.i.d.).

Twenty-four healthy right-handed male volunteers (mean age= 31.7 years, SD=6.7) who provided written informed consent were also recruited as a comparison group. Volunteers were required to meet similar body mass index criteria, to have a score of 5 or less on the Hamilton depression scale, and to have no current or past psychiatric history, including psychotropic drug use or alcohol abuse. The psychiatric status for both groups was determined by using the Structured Clinical Interview for DSM-IV (SCID) (17).

Medication

After single-blind placebo dosing for a mean of 3 days (SD=1) and the first PET scan, paroxetine was administered at a dose of 20 mg/day. Two of the original 15 subjects were excluded at this time because of reductions in Hamilton depression scale scores (to 13 and 11, respectively). After 4 weeks of paroxetine therapy at a dose of 20 mg/day, clinicians had the option of increasing the dose to 40 mg/day. Blood was sampled for plasma paroxetine approximately 5 hours after the first dose of paroxetine and again at the same time after 42 days of treatment. It was analyzed by using high-performance liquid chromatography with mass spectrometric detection methods (18). Paroxetine plasma levels were measured as an index of compliance and are included in Table 1.

PET Procedure

PET scans were conducted at the PET Centre, the Centre for Addiction and Mental Health, University of Toronto. The first scan for depressed patients was conducted before the first dose of paroxetine and 5 hours after placebo ingestion. A second PET/FDG scan was completed after a mean of 42 days (SD=3) of paroxetine therapy at approximately the same time as the first PET scan. All PET sessions began at 8:00 a.m. The images were acquired by using a GEMS-Scanditronix (Uppsala, Sweden) PC 2048b brain PET scanner with 15 slices of 6.5-mm interslice distance and reconstructed in-plane resolution of approximately 8 mm. The images were acquired parallel to the anterior-posterior commissure line. The subjects were fitted with a customized thermoplastic face mask to minimize head movement for the initial scan and for accurate repositioning of the next scan. Five mCi of FDG, synthesized on the day of each scan, were injected in an intravenous bolus. After the injection, each subject remained in a resting state with eyes open in a dimly lit room with low ambient noise for a 45-minute uptake period. Emission data were acquired over a 35-minute period, at approximately 1 million counts per slice, followed by a 10-minute ^{68}germanium transmission scan for subsequent attenuation correction. The same procedure was followed after 6 weeks for the group with major depression and on a single occasion for the comparison group.

Image Analysis

After spatial realignment to minimize anatomical variance between the first and second scans for the depressed patients, the scans were spatially realigned to the Montreal Neurological Institute's 300 stereotactic template, based on Talairach and Tournoux's stereotaxic atlas (19), at nine parameters to correct for differences in the whole-brain global mean. The images were Gaussian-filtered to a final in-plane resolution of 8 mm full width at half maximum.

Two separate repeated analysis of covariance (ANCOVA) comparisons were carried out, with age as a covariate, by using the statistical parametric mapping technique, version 1996, developed by Friston et al. (20), to detect differences on a voxel-by-voxel basis 1) within subjects before and after treatment and

TABLE 2. Change in Relative Regional Brain Glucose Metabolism in 13 Depressed Male Patients After Paroxetine Treatment

Brain Region	Talairach Coordinates x	y	z	Brodmann's Area	Hemisphere	Rate of Glucose Metabolism (voxel score)[a] Pretreatment Mean	SD	Posttreatment Mean	SD	Change (%)[b]	Analysis of Change t (df=12)	p
Areas of increase												
Dorsolateral prefrontal	–28	40	0	10/44	Left	89.7	1.9	96.4	1.9	7.47	6.24	<0.001
	–38	14	38	9	Left	115.1	4.1	120.3	4.1	4.52	3.26	0.003
	–36	24	36	9	Left	149.3	2.3	154.0	2.3	3.15	3.67	0.003
Pregenual anterior cingulate	8	36	–4	24a	Right	123.1	8.5	139.4	3.1	13.24	6.40	<0.001
Medial frontal/dorsolateral anterior cingulate	16	18	38	32/24	Right	91.9	1.9	99.0	1.9	7.73	6.62	<0.001
	10	30	40	32	Right	134.0	3.2	142.3	3.2	6.19	4.72	<0.001
Ventrolateral prefrontal	–36	28	–2	47	Left	139.6	1.9	145.2	1.9	4.01	5.39	<0.001
Inferior parietal	–56	–18	26	40	Left	140.9	2.2	149.5	2.2	6.10	6.90	<0.001
	–48	–40	32	40	Left	122.3	2.6	132.9	2.6	8.67	7.33	<0.001
Ventral striatum	12	20	–6		Right	101.6	7.8	124.7	3.0	22.74	9.34	<0.001
Areas of decrease												
Anterior insula	–36	2	0		Left	139.9	1.1	135.4	1.1	–3.22	7.56	<0.001
	40	22	–2		Right	169.1	1.9	163.5	1.9	–3.31	5.44	<0.001
	34	12	14		Right	130.7	2.1	127.5	2.1	–2.45	4.90	<0.001
	44	–16	18		Right	141.5	1.7	136.7	1.7	–3.39	4.95	<0.001
Posterior insula	–38	–26	8		Left	153.9	2.5	146.8	2.5	–4.61	4.98	<0.001
Hippocampus	30	–28	–12		Right	108.2	1.9	101.7	1.9	–6.01	6.08	<0.001
Parahippocampus	22	–42	0		Right	106.1	2.4	98.3	2.4	–7.35	5.91	<0.001
	22	–54	4		Right	132.6	2.8	125.3	2.8	–5.51	4.75	<0.001

[a] Relative to whole-brain global mean.
[b] A positive number means increased metabolism; a negative number means decreased metabolism.

2) between depressed subjects and the comparison group before treatment. Brain regions that were identified as having 100 or more contiguous voxels and a cluster level of $p<0.05$ in within- or between-group comparisons were defined as significant at a threshold of $p<0.01$. In order to quantify the magnitude of change in relative glucose metabolism in these regions before and after treatment, mean values, standard deviations, and percent change in voxel scores in a priori regions were calculated and are presented in Table 2.

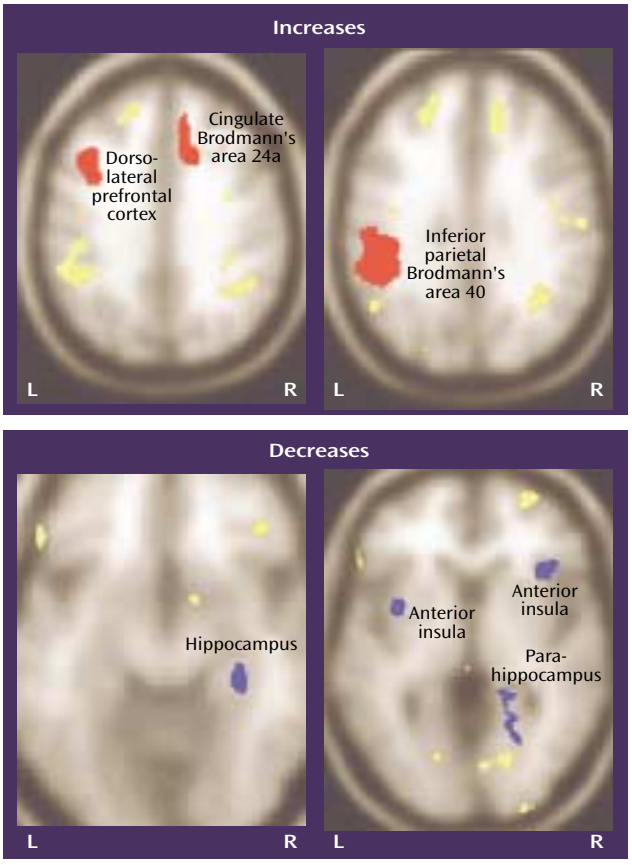
Results

Seven patients received paroxetine, 20 mg/day, throughout the trial, and six received paroxetine, 40 mg/day, for the final 2 weeks of the study. Higher plasma paroxetine levels were detected after 6 weeks of treatment in the 40-mg/day group (mean=82.6 ng/ml, SD=67.1) than in the 20-mg/day group (mean=36.8 ng/ml, SD=28.5). All patients had at least a 50% reduction in Hamilton depression scale scores. The mean Hamilton depression scale score was 22.42 (SD=3.59) before treatment and 6.0 (SD=4.1) after treatment (Table 1).

Changes in Metabolic Rates

Areas of increased metabolism after treatment were seen in the dorsolateral, ventrolateral, and medial prefrontal cortex, parietal cortex, and dorsal anterior cingulate (Figure 1, top), whereas areas of decreased metabolism occurred in both anterior and posterior insular regions (left) as well as right hippocampal and parahippocampal regions (Figure 1, bottom). There were more regions with increased activity in the left hemisphere and more regions on the right displaying decreased activity (Table 2).

FIGURE 1. Changes in Regional Brain Glucose Metabolism in 13 Depressed Male Patients After 6 Weeks of Paroxetine Therapy[a]



[a] Red areas represent significant increases in metabolism, blue areas represent significant decreases, and yellow regions represent changes that did not reach statistical significance.

Differences Between Patients and Comparison Subjects

At pretreatment, the depressed group demonstrated significantly higher metabolic activity in the right pregenual anterior cingulate (Brodmann's area 24a: 8, 36, –4) (t= 4.60, df=35, p<0.001) and significantly decreased metabolism in the ventral striatum (caudate and putamen: 12, 20, –6) (t=4.94, df=35, p<0.001) than the comparison group. No other regions met the statistical parametric mapping 96 threshold for significance.

Since our a priori hypothesis stated that untreated depressed patients would show hypometabolism in the prefrontal and anterior cingulate and inferior parietal cortices, we conducted a further post hoc analysis. Regions within depressed subjects that had shown increased activity after treatment were selected for direct comparison by using ANCOVA between groups. Mean voxel values of relative glucose metabolism were calculated for comparison subjects to best match the anatomical regions listed in Table 2 for pre- and posttreatment increases or decreases. The three regions within the dorsolateral prefrontal cortex (–28, 40, 0; –38, 14, 38; and –36, 24, 36) described in Table 2 had significantly lower metabolism in untreated patients than in the comparison group (t=6.24, df=12, p<0.001; t= 3.26, df=12, p=0.003; t=3.67, df=12, p=0.003, respectively).

Discussion

Successful antidepressant treatment with paroxetine was associated with significant increases in metabolic activity in dorsolateral, ventrolateral, and ventral prefrontal areas, as well as dorsal medial prefrontal, anterior cingulate, and inferior parietal regions. Increases were predominantly but not exclusively on the left side. Significant reductions in glucose metabolism were also noted in both anterior and posterior insular regions, hippocampus, and parahippocampus (right more than left).

These findings support the results of several previous reports involving different antidepressant agents. Tricyclic antidepressant treatment (with concomitant benzodiazepines) was associated with an increase in left-sided prefrontal activity, although medication status at the time of repeat testing was inconsistent in this study (14); increased parietal activity was similarly associated with response to sertraline (10). In contrast to our findings of increased ventrolateral activity after successful treatment with paroxetine, Brody and colleagues (12) reported a significant decrease in ventrolateral and orbitofrontal activity in paroxetine responders compared to nonresponders.

A similar pattern of dorsal frontal, dorsal anterior cingulate, and inferior parietal activation accompanied by reduced ventral, mid, and posterior insula activity as well as reduced hippocampal activity was also reported by Mayberg et al. (21). We also identified increased pregenual anterior cingulate (Brodmann's area 24a) activity in untreated depressed patients compared to healthy volunteers, replicating findings in reports by Mayberg et al. (11) and Wu et al. (22), who also reported increased baseline activity in responders to sleep deprivation. However, we failed to confirm that a decrease in metabolism below normal in this area is associated with treatment nonresponse (11, 12), since all our patients were treatment responders. Furthermore, anterior cingulate metabolism increased even further with successful treatment, a finding not previously reported.

Functional Considerations

Prefrontal cortex. The role of the prefrontal cortex in depression remains elusive (23–25). Patients with lesions of the ventral prefrontal cortex lose the ability to express emotion in combination with thoughts that would ordinarily provoke an emotional response. In contrast, their planning and intellectual working abilities appear to remain intact (26). In depressed subjects, impaired modulation of the left ventral prefrontal cortex has been associated with impairment in the ability to shift emotional and cognitive sets appropriately, such that they maintain a negative thought pattern or mood (24, 27, 28).

Decreased blood flow in the left dorsolateral prefrontal cortex, on the other hand, has been associated with the psychomotor and attentional deficits and executive functioning impairments of depression (29–31). Increased, primarily left-sided, prefrontal cortex metabolism after successful treatment with paroxetine may thus be the correlate of improved motor function, negative thinking, and cognitive abilities in our subjects.

Medial prefrontal cortex and cingulate gyrus. In the medial prefrontal cortex, the anterior cingulate cortex plays a critical role in the expression and modulation of emotion (30, 32). The functions of the anterior cingulate differ across its length, and electrical stimulation studies have identified arousal and heightened attention, simple motor movements, and affective changes such as euphoria, sadness, fear, or anguish depending on which portion of the cingulate was stimulated (26, 33, 34). In addition, bilateral cingulate ablation has been associated with akinetic mutism (26), whereas defined lesions within the anterior cingulate have been reported to improve depressive and anxiety symptoms (35). Consistent with these observations are findings of increased anterior cingulate activity in a range of PET activation studies involving attention, memory, response selection, language, and pain perception (34, 36–38), which have predominantly focused on Brodmann's areas 24 and 32.

Recently, Mayberg et al. (11) proposed a model of depression in which the pregenual anterior cingulate (Brodmann's area 24a) serves as a facilitator of interactions between limbic and frontal brain regions. Overall, we report similar bidirectional findings, although we did not find evidence of altered metabolism in the subgenual cingulate region (Brodmann's area 25).

Our findings of increased dorsal anterior cingulate metabolism after treatment of depression are in line with those of other studies, which suggest that changes in this region are a state phenomenon and are correlated with improvement of various dimensions of depressive symptom profiles (22, 29, 39–41). Our data only partially confirm the role of the pregenual anterior cingulate (Brodmann's area 24a) as a predictor of treatment response, because all our patients were responders and all showed pretreatment hyperactivity in this region compared to healthy volunteers. However, there was a further *increase* with treatment and not a decrease below normal, as found by Mayberg et al. (11) and Brody et al. (12).

Paralimbic structures. Reciprocal connections between paralimbic structures and the prefrontal cortex have been postulated (42–45) and are supported by our finding of decreased metabolism in these structures after paroxetine treatment. It is of interest that although we report decreased metabolic activity in the insula after treatment, it remained higher than in the comparison group. Mayberg et al. (11), on the other hand, found an increase in metabolism in these regions in fluoxetine nonresponders and a decrease from previously normal patterns in responders, which suggests that suppression or disconnection of paralimbic regions may be necessary for the normalization of those dorsal neocortical areas that are associated with recovery from depression. This hypothesis is of particular interest in light of treatment with SSRIs, because these drugs are known to exert their mechanism of action by means of the raphe nuclei, which have close connections to the hippocampus, amygdala, anterior insula, hypothalamus, and cingulate gyrus as well as to neocortical sites, including the prefrontal cortex and inferior parietal cortex (46, 47).

Parietal cortex. The parietal cortex has strong limbic and paralimbic connections, and it primarily receives input from the pulvinar and lateral posterior nuclei of the thalamus (31, 48, 49). Dolan and colleagues (31) reported significant associations between attention and memory deficits in untreated depressed patients and reduced cerebral blood flow in the inferior parietal region. Hence, evidence of increased activity after response to paroxetine therapy may reflect symptomatic improvement in our population.

Regional Serotonergic Dysfunction and Antidepressants

It is unclear whether abnormalities of metabolism in specific brain regions reflect neurochemical changes. In general, receptor ligand studies tend to show abnormalities in the prefrontal cortex (50, 51). However, at least one neurochemical study (52) has shown a global effect of paroxetine on serotonin 5-HT_2 receptor binding potential.

Limitations and Future Directions

There are several limitations to the current study. The fact that our comparison group had only one PET scan is a potential limitation. When Bartlett and colleagues (53) examined the test-retest variability of a measure of regional cerebral glucose metabolism, the average regional changes were no more than 1%. On the other hand, Stapleton and associates (54) reported a higher level of glucose utilization during the first PET scan than during the second in healthy male volunteers, a finding they attributed to anxiety changes in subjects with low trait anxiety. It should be noted, however, that we only compared first scans in the depressed group with our comparison group. We may also have had insufficient power to detect additional group differences since our group size was relatively small. This may have been particularly relevant in the comparison between depressed subjects and healthy volunteers. Because patient and comparison populations were male, any generalizations to female populations were prevented. On the other hand, the use of a single sex population, together with the unexpected uniformity of drug response, contributed to the homogeneity of this population. Further studies examining metabolic changes after 6–12 months of treatment will help to determine whether these changes remain stable in the remitted state.

In summary, treatment with paroxetine resulted in elevated levels of glucose metabolism in several frontal regions, including the dorsolateral prefrontal cortex, medial and ventral areas, anterior cingulate, and inferior parietal cortex. In some but not all cases, there was evidence of reduced metabolism in these areas in untreated depressed subjects compared to that of healthy volunteers. Paroxetine treatment also reduced metabolic activity in several paralimbic regions.

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