Caudate Glucose Metabolic Rate Changes With Both Drug and Behavior Therapy for Obsessive-Compulsive Disorder

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- We used positron emission tomography to investigate local cerebral metabolic rates for glucose (LCMRGlc) in patients with obsessive-compulsive disorder before and after treatment with either fluoxetine hydrochloride or behavior therapy. After treatment, LCMRGlc in the head of the right caudate nucleus, divided by that in the ipsilateral hemisphere (Cd/hem), was decreased significantly compared with pretreatment values in responders to both drug and behavior therapy. These decreases in responders were also significantly greater than right Cd/hem changes in nonresponders and normal controls, in both of whom values did not change from baseline. Percentage change in obsessive-compulsive disorder symptom ratings correlated significantly with the percent of right Cd/hem change with drug therapy and there was a trend to significance for this same correlation with behavior therapy. By lumping all responders to either treatment, right orbital cortex/hem was significantly correlated with ipsilateral Cd/hem and thalamus/hem before treatment but not after, and the differences before and after treatment were significant. A similar pattern was noted in the left hemisphere. A brain circuit involving these brain regions may mediate obsessive-compulsive disorder symptoms.

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Obsessive-compulsive disorder (OCD) is characterized by recurrent, unwanted thoughts (obessions) and conscious, ritualized acts (compulsions) usually attributed to attempts to deal with anxiety generated by the obsessions. There is now ample evidence that both medications that are strong serotonin re-uptake inhibitors and specific behavioral therapies that employ the principles of exposure and response-prevention are highly effective in reducing the symptoms of OCD, although the latter may be more effective for compulsions than for obsessions. Based on a wide variety of evidence, many investigators have postulated a role for the basal ganglia, along with limbic, thalamic, and cortical brain regions, in the mediation of OCD symptoms. We postulated previously that the head of the caudate nucleus plays a central role in OCD symptom mediation and that successful treatment of OCD by either medication or behavior therapy would be accompanied by a change in caudate nucleus function that might be detected with positron emission tomography (PET) and the 18-F-fluorodeoxyglucose (fludeoxyglucose F 18 [FDG]) method. Cerebral glucose metabolism is a sensitive indicator of brain function.

We decided, therefore, to study OCD patients with FDG-PET before and after drug or behavior therapy. We chose fluoxetine hydrochloride as our treatment drug, knowing a similar study was in progress using clomipramine hydrochloride.

PATIENTS, SUBJECTS, AND METHODS

This study was conducted in accordance with guidelines established by the UCLA Human Subjects' Protection Committee.

Patients

There were initially 10 patients with OCD in each of the two treatment groups, but a computer failure led to the loss of data for the initial scan of one subject in each group. The nine subjects remaining in each treatment group are included in the analyses reported herein.

All patients were clinical outpatients and/or inpatients in the UCLA Neuropsychiatric Hospital Mood and Anxiety Disorders Treatment Program who were asked to undergo PET scanning before and after the clinical treatment they elected (after a careful discussion of all available treatment options), which was either fluoxetine hydrochloride or behavior therapy without drugs. All had a current primary diagnosis of DSM-III-R OCD which had been present for at least 1 year. Diagnoses for each patient were made based on both a nonstructured psychiatric interview and the Schedule for Affective Disorders and Schizophrenia—Lifetime

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version (SADS-L). All patients were drug free for at least 2 weeks before their initial PET scan.

In the drug treatment group, there were concomitant diagnoses of cyclothymic disorder, panic disorder, Tourette's disorder (mild), and social phobia in one subject each. In the behavior therapy group, there were concomitant diagnoses of cyclothymic disorder, panic disorder, and acrophobia in one subject each. Many patients in each group had had major depression in the past, but all were euthymic now, as determined by both clinical assessment and the SADS-L. All patients denied substance abuse; we did not do urine drug screens. Patient demographics and rating scale scores are given in Table 1.

### Normal Control Subjects

Subsequent to analyses of patient PET data, a small group of normal control subjects were collected for comparison. These were two men and two women with a mean (±SD) age of 29±8 years who were judged to be healthy by history and recent physical examination. None had any personal or family history of an DSM-III Axis I disorder. All were drug free by history for at least 1 month before initial PET scanning. They were rescanned 10±2 weeks after initial scanning.

### Symptom Severity Ratings

Subject behaviors were rated with the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS), the 17-item Hamilton Depression Rating Scale (HAM-D), the Hamilton Anxiety Rating Scale (HAM-A), and the Global Assessment Scale (GAS) at the time of each PET scan. Responders to treatment were defined as priori as those who were rated as either "much improved" or "very much improved" on item 18 of the Y-BOCS (which is taken from the Clinical Global Impression Scale) at the time of the second PET scan. Nonresponders were those who scored "no change" or "minimally improved" on the same item.

### Treatments

**Drug Treatment.**—Patients in this group were treated with oral fluoxetine hydrochloride, started at 20 mg/d and titrated within 2 weeks to 60 to 80 mg/d, as tolerated, before the second PET scan was obtained. This is our standard clinical treatment for OCD with this drug. All patients enrolled in drug treatment were able to attain this dosage range with minimal side effects and stay on it for the duration of the study. No other drugs were used, and patients were not in behavior therapy or formal psychotherapy. If they asked about how they should respond to obsessions and compulsive urges, these patients were advised to see if they could refrain from these behaviors, as comfort permitted, if they wished. All did receive supportive advice from their therapists (L.R.B., M.P.S., and J.M.S.), with whom they met once or twice a week.

**Behavior Therapy.**—These patients elected to have behavior therapy consisting of exposure and response-prevention, which was individualized for the patient. Exposure and response-prevention exercises were facilitated by cognitive techniques. Patients met once or twice a week with their therapist (J.M.S., K.S.B., or L.R.B.) for approximately 1 hour to review assignments for exposure and response-prevention, which they did as homework and self-monitored with diaries and/or graphs. Homework was reviewed and evaluated with the patients at the next meeting. Some had occasional therapist-aided exposure and response-prevention sessions. Six also attended a cognitive-behavioral therapy group for patients with OCD run by one of us (J.M.S.). None took any psychoactive medications during the study. All received supportive advice from their individual therapists.

All patients had 10±2 weeks of the therapy they elected before undergoing a second PET scan. Those treated with behavior therapy abstained from medications from the first through the second scan, while those having drug treatment were all on fluoxetine at the time the second scan, with the last dose given the day before scanning.

### PET Methods

All subjects were injected with FDG while in the supine position in a room with no conversation, low ambient light, and environmental noise (mostly from the scanner gantry), as previously described. The subjects' ears and eyes were open, and they were instructed to look at the diffusely lit white ceiling above the tomograph. Each subject received 185 to 370 mBq (5 to 10 mCi) of FDG, prepared as previously described. "Arterialized" venous blood was obtained by having the subject's hand in a hand warmer. Blood sampling and determinations of plasma glucose and FDG concentrations have been described in detail previously.

Scanning was performed with a PET tomograph (831 Neuro ECAT III, Siemens-CTI, Knoxville, Tenn). Fifteen transverse sections of the brain, spaced 6.75 mm apart, were acquired simultaneously at an angle parallel to the canthomeatal plane. Each subject's head was held in a special head holder during scanning to allow accurate positioning using the low-power laser marker of the tomograph.

Before injection of the tracer, a 2-minute transmission scan with radiation from a germanium Ge 68 (68Ge) ring source was performed to obtain similar planes for intersubject comparisons and to allow accurate repositioning for follow-up scans done after treatment. Next, data for measured attenuation correction were obtained by means of a 20-minute transmission scan using the ring source. Emission scanning commenced 60 minutes after injection of FDG. Total imaging time was 40 minutes, and each image was reconstructed from 2 million to 3 million counts. 18F-Fluorodeoxyglucose was injected between 10:00 and 15:00. Images were reconstructed by filtered back-projection using a Shepp filter with a cutoff of 0.6 of the Nyquist frequency (0.95 cycles/cm). The in-plane resolution used in these studies was 6×6 mm, and the axial resolution was 6.75 mm.

Images were displayed on a video display (SuperMac Technology, Sunnyvale, Calif) in a 256×256 pixel display, with a black-on-white format. Neuroanatomic regions of interest (ROIs) were identified in all tomographic planes in which they occurred, and the glucose metabolic rates were determined as described previously (rate constants used for gray-matter metabolic rate determinations were k1=0.102, k2=0.13, k3=0.062, k4=0.0068, and the lumped constant was 0.52±0.29) to accomplish this, each scan was compared with template sets obtained from normal anatomic and PET studies with the same tomograph. The size and site of the ROI were then copied from these templates in a standardized fashion appropriate to the individual brain at hand, as previously
Table 2.—OCD Patient Treatment Response*

<table>
<thead>
<tr>
<th>Treatment Response by Group†</th>
<th>Drug Treatment</th>
<th>Behavior Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pretreatment Score</td>
<td>Posttreatment Score</td>
</tr>
<tr>
<td>Responders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Y-BOCS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>25.8±3.7</td>
<td>13.0±2.9</td>
</tr>
<tr>
<td>Obsessive (items 1-5)</td>
<td>13.3±2.2</td>
<td>6.6±1.5</td>
</tr>
<tr>
<td>Compulsive (items 6-10)</td>
<td>12.5±1.7</td>
<td>6.4±1.7</td>
</tr>
<tr>
<td>HAM-D</td>
<td>10.3±3.2</td>
<td>5.6±2.2</td>
</tr>
<tr>
<td>HAM-A</td>
<td>24.2±4.2</td>
<td>20.1±4.3</td>
</tr>
<tr>
<td>GAS</td>
<td>57.5±7.7</td>
<td>68.2±6.9</td>
</tr>
<tr>
<td>Nonresponders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Y-BOCS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>24.0±2.0</td>
<td>19.5±0.5</td>
</tr>
<tr>
<td>Obsessive (items 1-5)</td>
<td>12.0±2.0</td>
<td>8.5±0.5</td>
</tr>
<tr>
<td>Compulsive (items 6-10)</td>
<td>12.0±0.0</td>
<td>11.0±1.0</td>
</tr>
<tr>
<td>HAM-D</td>
<td>10.0±9.0</td>
<td>5.5±2.2</td>
</tr>
<tr>
<td>HAM-A</td>
<td>32.5±16.5</td>
<td>19.5±3.5</td>
</tr>
<tr>
<td>GAS</td>
<td>56.0±13.0</td>
<td>59.0±11.0</td>
</tr>
</tbody>
</table>

*OCD indicates obsessive-compulsive disorder.
†In the drug treatment group, seven of nine subjects were responders and two of nine were nonresponders; in the behavior treatment group, six of nine subjects were responders and three of nine were nonresponders. Values are means±SDs. See Table 1 for expansion of abbreviations. NS indicates not significant.

...described.32 For patients, this was done by one of us (A.A.), who was blind to subject identity, diagnosis, scan sequence, and the hypothesis being tested. Patient scans were scattered among 85 from a variety of studies being processed at the same time. Supratentorial hemispheric values were obtained in a similar fashion and included ventricles. The scans of control subjects analyzed subsequently had their ROIs defined by a technician who was also blind to scan sequence and the hypothesis being tested. For each subject, an average local glucose metabolic rate value (LCMRGlc) was determined for each structure by weighing that structure's planar metabolic value by its cross-sectional area using the following formula:

\[
\text{LCMRGlc} = \sum_{i=1}^{N} (MR)A_i / \sum_{i=1}^{N} A_i
\]

where N indicates the number of planes that include the structure, A indicates the cross-sectional area of the structure in plane i, and MR indicates the metabolic rate of the structure in plane i. The LCMRGlc is expressed in milligrams of glucose used per 100 g of brain tissue per minute. LCMRGlc for each ROI was "normalized" by dividing the LCMRGlc of that region by that of the ipsilateral cerebral hemisphere (ROI/hem), which yielded a dimensionless ratio. Using this metabolic ratio, rather than absolute values, reduces the variance in the resultant data set and gives a measure of activity relative to that in the rest of the hemisphere.

Statistical Analyses

All results are presented as the mean±SD. We had made a clear a priori prediction that metabolic rates in the caudate nuclei, normalized to the ipsilateral hemisphere (Cd/hem), would differ significantly before and after treatment for responders to both drug and behavior therapy. In addition, the degree of change in responders would show significantly more change in Cd/hem than in nonresponders or controls, in whom change would not occur after a similar time interval. This was our primary hypothesis.

Statistical comparisons for parametric measures (eg, ROI/hem values) were made with the paired t test for data from the same individual at the two times of scanning. Student's t test was used for comparisons between groups. However, because of low subject numbers and concerns about normal distributions, we also performed the nonparametric Wilcoxon test on critical results that were significant by Student's t test, and the Wilcoxon Signed-Rank test for similar intrasubject evaluations. The report by Benkelfat et al16 and doubts about our previous report6 concerning direction of caudate metabolic nucleus change after an unconventional drug treatment of depressed OCD patients (see below) led us to use two-tailed statistical tests to identify a difference, regardless of direction, in Cd/hem values before and after successful treatment.

We also examined the orbital gyrus/hem, putamen/hem, anterior cingulate gyrus/hem, and thalamus/hem, given the findings and theories of others,5,7,16,17,32 as secondary hypotheses. No corrections were made for multiple tests. Other brain ROIs (anterior lateral prefrontal cortex, sensory-motor region, parietal cortex, lateral temporal lobes, hippocampus-parahippocampal gyrus complex, amygdaloid nuclei complex, and cerebellar hemispheres), available for analysis as part of the ROI protocol for scans from the various studies undergoing processing at the time, were examined in an a posteriori survey, with no corrections made for multiple tests.

For comparisons among more than two groups, the nonparametric Kruskal-Wallis analysis of variance was used, since normal distributions and equal variances did not obtain. Post hoc Wilcoxon tests were used to distinguish between relevant pairings of OCD treatment responders and normal controls.

The nonparametric Kendall's τ, with a correction for tied values, was used for rank-order correlations between percentage change in the nonparametric behavioral rating scale scores and percentage change in normalized regional metabolic rates. (The Kendall's τ is valid with n≥8.32) The τ was also used for parametric data (metabolic rates), because normal distributions, as determined by visual inspection of frequency histograms, did not obtain for many brain regions.

RESULTS

Drug-treated patients underwent their second PET scanning after 10.5±1.3 weeks of treatment; patients undergoing behavior therapy did so after 10.8±1.1 weeks. Normal control subjects were rescanned after 9.8±1.3 weeks.
Fig 1.—Percent change after drug or behavior therapy ([posttreatment value—pretreatment value]/pretreatment value\times 100) in glucose metabolic rate in the right head of the caudate nucleus, divided by that of the ipsilateral hemisphere (Cd/hem) for responders and nonresponders to treatment, as well as normal controls scanned twice with a between-scan interval similar to that of the patients. Differences between responders and nonresponders to treatment are significant (P<.05) for both treatment groups, as are differences between treatment responders and normal controls. Arrows indicate data for subjects illustrated in Fig 2.

Seven of the drug-treated patients and six of the behavior therapy patients were judged to be responders by the preestablished criterion; the rest were nonresponders. Rating scale scores before and after treatment for these groups are presented in Table 2. Although not the determinant of response here, there was no overlap between responders and nonresponders in percentage change in the total Y-BOCS score before and after treatment: responders decreased scores by 30% or more and nonresponders by less than 30%, comparable with the differences between responders and nonresponders on the Y-BOCS in other studies.36

Table 3 presents pretreatment and posttreatment ROI/hem values obtained in those patients judged treatment responders for the brain regions postulated on a primary and secondary a priori basis. Whole-hemisphere LCMRGluc values did not change significantly from before to after treatment in either group of responders (percent change in drug treatment group: left hemisphere, 9.2%±63.8\% [t=3.2, df=6, P=not significant]; right hemisphere, 12.1%±69.4\% [t=3.9, df=6, P=not significant]; percent change in behavior therapy group: left hemisphere, 11.6%±16.9\% [t=1.5, df=5, P=not significant]; right hemisphere: 14.1%±18.3\% [t=1.73, df=5, P=not significant]).

Although right anterior cingulate gyrus/hem and left thalamus/hem showed significant changes with successful drug treatment, only the head of the right caudate nucleus showed a significant change with both successful drug and behavior therapies—values decreased. While responders changed right caudate nucleus ratios by 5.2%±2.3\% for drug treatment and −8.0%±4.8\% for behavior therapy, nonresponders changed only 0.3%±1.0\% (P=not significant) and 2.6%±3.2\% (P= not significant), respectively. Normal controls changed only 0.4%±2.0\% (P= not significant). Individual subject values for percentage change in right Cd/hem are represented in Fig 1. The Kruskal-Wallis analysis of variance, applied to right Cd/hem among all groups, was significant (Kruskal-Wallis test statistic, 14.17; P=0.007). Differences between responders and nonresponders were significant for both drug treatment (t=2.84, df=7, P=0.025; Wilcoxon z=1.90, P=0.06) and behavior therapy (t=3.15, df=7, P=0.02; Wilcoxon z=2.19, P=0.03). Right Cd/hem percentage changes for normal controls were less than those for drug treatment (z=2.17, df=9, P=0.03) and behavior therapy (z=2.24, df=8, P=0.025) responders. For illustration, Fig 2 presents FDG-PET scans of representative OCD treatment responders before and after each treatment.

Contrary to our expectations of significant Cd/hem results for both sides of the brain, the left Cd/hem did not show a statistically significant change with either treatment. Therefore, separate analyses of results in relationship to handedness were conducted. Results were unchanged when left and right caudate nucleus
values for the one left-handed patient in each treatment group (both responders) were switched, and when they were excluded from the analyses.

There was a significant, positive rank-order correlation between percentage change in total Y-BOCS score before and after treatment and the percentage change in right Cd/hem when considering all nine subjects having drug therapy ($\tau=.48$, $P=.04$) and a trend for those patients undergoing behavior therapy ($\tau=.37$, $P=.09$).

None of the other brain regions surveyed that are not listed in Table 3 showed significant changes in pretreatment to posttreatment results in the treatment responders (all $P>.10$).

Since there were significant changes with both successful drug and behavior treatment only for right Cd/hem, and we have always observed high correlations between normalized left and right head of caudate nucleus values in normal controls (J.C.M. and L.R.B., unpublished data, 1982 to 1992), we wondered what happened to such a correlation in the OCD treatment responders before and after treatment. To have adequate numbers for valid correlation coefficients, we had to combine responders to both treatments.

As shown in Table 4, before treatment there was not a significant correlation of left and right Cd/hem in responders. After successful treatment there was a significant positive correlation between left and right Cd/hem. At this point, since we and others have postulated pathology in brain circuits involving the caudate, thalamus, orbital, and cingulate gyrus brain regions in OCD, we examined correlations among these regions, too (Table 4).

Right orbital cortex/hem was significantly correlated with ipsilateral Cd/hem and thalamus/hem before treatment but not after, and the differences before and after treatment were clearly significant ($P<.05$). There was a similar pattern of correlation among these structures on the left side. Also of interest, there was no significant correlation between left cingulate/hem and left Cd/hem before treatment, but a clearly significant change to a significant positive correlation obtained after successful treatment. No other correlations between ROIs were calculated. Numbers of nonresponders and controls were too small for valid correlation coefficients.

**COMMENT**

Although subject numbers are small, and our findings clearly in need of replication, we were able to provide evidence that glucose metabolic rates in the right head of the caudate nucleus change when OCD is treated successfully with either fluoxetine or behavior therapy. Normal subjects scanned twice under similar conditions hours to days apart have not shown such changes in other laboratories, nor did our small group of normal subjects with a time interval between scans similar to that of our patients with OCD.

We also found evidence for significant correlations of orbital cortex activity with both the caudate nucleus and the thalamus before treatment in treatment responders. These correlations disappeared with successful treatment. Left cingulate glucose metabolism was not significantly correlated with left caudate nucleus activity before treatment but was significantly correlated after treatment.

Although half of our primary a priori hypothesis concerning the caudate nuclei was fulfilled, we did not provide evidence that left Cd/hem changes with effective OCD treatment. We had expected similar findings for both left and right Cd/hem. This seems all the more confusing in that Benkelfat et al. observed a statistically significant decrease in the normalized left caudate nucleus of OCD responders vs nonresponders, but did not do so for the right caudate nucleus in a group of patients with OCD undergoing FDG-PET before and after clomipramine hydrochloride treatment. They did, however, find a similar mean percentage decrease in right caudate nucleus glucose metab.

**Table 4.—Normalized Region of Interest Rank-Order Correlations (Kendall’s $\tau$) Before and After Treatment for Responders to Either Treatment**

<table>
<thead>
<tr>
<th></th>
<th>$\tau$ Value Before Treatment</th>
<th>$\tau$ Value After Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>L to R caudate</td>
<td>.28</td>
<td>.77*</td>
</tr>
<tr>
<td>L to R orbit</td>
<td>.54†</td>
<td>.59†</td>
</tr>
<tr>
<td>L to R thalamus</td>
<td>.67†</td>
<td>.69*</td>
</tr>
<tr>
<td>L to R cingulate</td>
<td>.17</td>
<td>.03</td>
</tr>
<tr>
<td>L caudate to L orbit</td>
<td>.49‡</td>
<td>.00</td>
</tr>
<tr>
<td>R caudate to R orbit</td>
<td>.44‡</td>
<td>-.03</td>
</tr>
<tr>
<td>L orbit to L thalamus</td>
<td>.33</td>
<td>-.21</td>
</tr>
<tr>
<td>R orbit to R thalamus</td>
<td>.41‡</td>
<td>-.21</td>
</tr>
<tr>
<td>L caudate to L thalamus</td>
<td>.28</td>
<td>.33</td>
</tr>
<tr>
<td>R caudate to R thalamus</td>
<td>.21</td>
<td>.46‡</td>
</tr>
<tr>
<td>L caudate to L cingulate</td>
<td>-.10</td>
<td>.41‡</td>
</tr>
<tr>
<td>R caudate to R cingulate</td>
<td>-.04</td>
<td>-.03</td>
</tr>
<tr>
<td>L cingulate to L orbit</td>
<td>.00</td>
<td>.33</td>
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<td>R cingulate to R orbit</td>
<td>.12</td>
<td>.03</td>
</tr>
<tr>
<td>L cingulate to L thalamus</td>
<td>-.05</td>
<td>.00</td>
</tr>
<tr>
<td>R cingulate to R thalamus</td>
<td>-.01</td>
<td>.05</td>
</tr>
</tbody>
</table>

*P<.001 (two-tailed).
†P<.01 (two-tailed).
‡P<.05 (two-tailed).
bolic rates in responders (−7.4% ± 18.6%) vs nonresponders (0.07% ± 8.7%), as we did, but the variance in their data for the right caudate nucleus was much greater than that obtained for the left caudate nucleus, and, thus, results were not significant for the right side. Clomipramine has significant direct interactions with the dopamine system in addition to its better-known serotonin reuptake blockade properties. Both dopamine agonists and antagonists have been shown to have strong effects on caudate nucleus glucose metabolic rates, and Benkelfat et al acknowledged that such effects, unrelated to OCD symptom response, could have confounded their caudate nucleus findings. Fluoxetine itself, however, has indirect effects on the dopamine system, as should all agents affecting serotonin.

Likewise, in our data, despite the fact that some cases that showed a clear response-related change in the right Cd/hem had a visible lack of similar effects on the left (Fig 2), it should be emphasized that we did observe an overall mean decrease in left Cd/hem with both OCD treatments, even though this change was not statistically significant. Also, our correlational analysis implicates the left caudate nucleus almost as strongly as the right.

Our study findings should not be taken as evidence against the findings of Benkelfat et al. Both studies had a high probability of Type II error, and taken together they are complementary in showing a similar change in caudate nucleus glucose metabolism after treatment with two chemically different drugs and after behavior therapy. It is noteworthy, however, that Hollander et al found increased right compared with left brain neurologic soft signs in their population of patients with OCD, perhaps implying that right brain function is more disordered than left in OCD.

Type II error is also possible in the evaluation of the other brain regions we surveyed. Surrounded by white matter and ventricular space, the head of the caudate nucleus is one of the easiest brain regions to determine visually with high-resolution FDG-PET scanning. The boundaries of most of the other brain regions we examined are not as distinct. Both Benkelfat et al and Swedo et al report significant changes in normalized orbital cortex after OCD treatment, yet we note that only subregions of orbital cortex showed this change; we did not attempt such subdivisions. We did find significant changes in correlations between orbital gyrus and caudate nucleus and thalamus before and after successful treatment, however. We also note that Swedo et al did not find caudate nucleus changes with OCD treatment. Differences in treatment duration might account for these seeming disparities among the three studies of OCD before and after treatment. We have suggested that orbital brain function changes with OCD treatment would occur some time after caudate nucleus changes.

Further, work in our laboratory has demonstrated that as an individual learns to perform a motor task more efficiently, the critical brain structures mediating the behavior show a reduction in both spatial extent and magnitude of activation on PET scanning while performing the task than when the task was new. With time, might the caudate nucleus become "more efficient" in controlling OCD symptoms and its change(s) in critical functions no longer be detectable with present PET methods? Swedo et al restudied their subjects after at least 1 year (mean, 20 months), Benkelfat et al did so after a mean of 16 weeks, and we did so after only 10 weeks. It is interesting that the study of intermediate length found both caudate nucleus and orbital changes, while the shorter and longer ones found only caudate nucleus and orbital changes, respectively. Whether those who respond to OCD treatment show various regional brain changes before, at the time of, or after clinical response could be investigated with FDG-PET.

We also found decreases in right anterior cingulate gyrus/hem and left thalamus/hem with successful drug treatment but not behavior therapy. These findings may be specific to OCD treatment with fluoxetine vs exposure and response-prevention, but could also be related to other factors in those patients who chose drug treatment over behavior therapy. Other studies are needed to resolve this issue.

In our first report of FDG-PET findings in OCD, we reported increases in both left and right Cd/hem ratios after treatment with trazodone hydrochloride and tranlycypromine sulfate. However, most of those subjects had major depression as well as OCD. We had previously reported a similar increase in Cd/hem with treatment of unipolar major depression and observed that the change in depression scores in the depressed patients with OCD gave a significant negative correlation with the change in Cd/hem, while the change in the OCD scale used did not.

Nevertheless, we associated this increase in Cd/hem with improvement in OCD symptoms, not just depression. We now believe that that conclusion was in error and that both the increases in Cd/hem and the decreased OCD symptoms observed in that study population were secondary to an improvement in depression, rather than a primary improvement in OCD per se. Obsessive-compulsive disorder often worsens when major depression is superimposed.

The findings of Benkelfat et al in a group of nondepressed patients with OCD, and our own failure to show significant improvement in a placebo and doxepin hydrochloride controlled treatment study of trazodone hydrochloride in nondepressed patients with OCD (L.R.B., J.M. Thompson, MD, and J. M. Schwartz, MD, unpublished data, 1990) led us to suspect this error. Consequently, we used a two-tailed hypothesis and statistics in the present study.

It should be pointed out, however, that a decrease in Cd/hem does not imply a "decrease" in some critical caudate nucleus "function." There are so many interacting excitatory and inhibitory circuits in the caudate nucleus that all one can say is that there is a change in function; the critical element(s) in the behavioral mediation may be either increasing or decreasing.

Known functions of the caudate nucleus, however, do seem to fit the symptomatology of OCD. Rapoport and colleagues have pointed out the similarities between the behaviors commonly seen in compulsive rituals and innate, species-specific behavioral routines that may be released when the caudate nucleus is dysfunctional. (Also, see Villablanca and Olmstead for a detailed review of relevant behaviors in cats with caudate nucleus lesions.) Another basal ganglia function, "gating," by which certain motor, sensory, and perhaps cognitive impulses are either allowed to proceed through to perception and behavior or are held back ("filtered") and dissipated, seems to speak to the psychodynamic concept of disordered "repression" in OCD. In this regard, it seems appropriate to note that individuals likely to develop Huntington's disease, who have Cd/hem values that are significantly below those of normals, have increased expressions of "anger and hostility" on the Profile of Mood States compared with siblings with normal Cd/hem values who are less likely to develop this neurologic disorder. Obsessive-compulsive disorder symptoms have often been viewed as the result of attempts...
to overcontrol these same emotions. Further, specifically in regard to the localization of this brain change after behavior therapy for OCD, there is now a wealth of data implicating the caudate nucleus in "procedural" or "process learning," including the ability to acquire new habits and skills necessary for the successful initiation of approach or avoidance behaviors.30-33

Although our findings are consistent with the idea that the head of the caudate nucleus is involved in the mediation of OCD's symptomatic expression,3 and there is an attractive theory as to how caudate nucleus dysfunction may develop in OCD and related disorders,34 our data do not prove that caudate nucleus dysfunction is the "cause" of OCD. That may be further up the afferent stream. Indeed, brain glucose metabolic rates largely reflect the work of neuronal firing at synaptic nerve terminals, and not the metabolic demands of cell bodies in and processes efferent from a structure.35 The orbital region of the brain has been demonstrated to be abnormal in OCD with FDG-PET5,33,36,37 and sends extensive efferent projections to both the head of the caudate nucleus and the thalamus.7 Our correlational analysis of brain region activity suggests that in symptomatic, treatment-responsive OCD activity in the orbital region is closely coupled with that in the caudate nucleus and thalamus, while with symptom improvement these relationships are broken, perhaps through a change in caudate nucleus function.

Although it seems hazardous to tally pluses and minuses among the multiple excitatory and inhibitory elements in orbital-basal ganglia-thalamic circuits to predict a final outcome, we will now invoke our data to support proposed theories.6,7,10 of OCD symptom mediation by elements in these same circuits6-11 (Fig 3B). According to our present view, before effective treatment a deficit in caudate nucleus function leads to inadequate "filtering" (or "repression") of orbital "worry" inputs, and thus allows them to drive the relevant fraction of inhibitory caudate nucleus output to the globus pallidus. This results in decreased pallidal inhibitory output to relevant parts of the thalamus. Consequently, orbital worry inputs may also come to have an undue, rigid influence on thalamic outputs to other brain regions mediating OCD symptoms that are not localized to the orbit. Further, excitatory thalamic input to the orbit makes this a potentially self-reinforcing loop that is difficult to "break." With effective treatment, however, adequate filtering activity in the caudate nucleus damps out this self-driving circuitry, and thereby allows the individual to better limit OCD symptoms once an obsessive worry is "launched" from the orbital region. These orbital-basal ganglia-thalamic circuits may have evolved to allow significant threats involving OCD themes (violence, contamination, etc) to capture and direct attention for needed action—and to rivet behavior to those concerns until the danger is judged passed. In treatment-responsive OCD the threshold for system "capture" may be too low. Caution is warranted about the generalizability of these ideas, however, since we do not have adequate subject numbers to examine drug treatment and behavior therapy separately or to comment on treatment nonresponders. In addition to further human PET work, PET studies and simultaneous electrophysiologic recordings from these same brain regions in animal models of OCD, before and after effective drug treatment,39 are warranted.

Based on reported effects of cingulotomy in OCD40 and theory put forward by others,6 we expected significant cingulate-caudate correlations before but not after effective treatement. Instead, we observed the opposite. This may have been a chance occurrence, although we have some ideas as to how cingulate-mediated "will" and/or "suppression" functions might be operating.22 Such discourse is beyond space limitations here.

A significant input to the caudate nucleus comes from seratonin neuron bodies in the dorsal raphe.61 Serotonin is highly implicated in the pathophysiology of OCD.60 We believe it unlikely, however, that changes in the activity of these serotonin terminals themselves are what is being measured directly when Cd/hem changes with successful treatment of OCD. These terminals are but a tiny fraction of those in the caudate nucleus,41 and changes in glucose utilization in serotonin terminals alone are thus not likely to be directly responsible for as large a percentage change
in Cd/hem as measured in our study. A more specific PET neurotracer than FDG may be needed to detect changes in activity at serotonin synapses. (A comparable situation exists with dopamine terminals in Parkinson’s disease where FDG-PET does not show consistent striatal abnormalities but 18F-fluoro-DOPA-PET does.63) It seems more likely that the changes in Cd/hem we observed are a reflection of changes in the activity of one or more of the many neurochemically diverse populations of small interneurons in the caudate nucleus.64 Our correlational analysis suggests the possibility, however, that loss of a key modulating process in the caudate nucleus may allow inputs from the orbital region to drive interneuron activity in the caudate nucleus and that with successful treatment adequate regulatory control is (re)established. Serotonin agonists have generally been observed to decrease brain glucose metabolic rates in animals, but effects in the caudate nucleus are complex, presumably dependent on the classes of serotonin receptors that may be most affected by any given agent, and are not easily interpreted.65 Critical interneuron function changes with OCD treatment could be effected by serotonin afferents to the caudate nucleus acting on other, larger populations of neurons, but there are many possible candidates for the title of “critical element” in the neurochemical mosaic of the caudate nucleus.

The “serotonin hypothesis” of OCD rests most firmly on evidence that chemically diverse drugs that are strong serotonin reuptake inhibitors are effective in the treatment of OCD, while similar agents that affect other neurotransmitters are ineffective.66,67 Some may wonder how behavior therapy could produce brain function changes similar to neurochemically specific drugs. Even in lower animals, such as the sea slug, Aplysia, however, it is changes at synapses that use serotonin that seem to mediate learned changes in stimulus-response behavior (see Kandel68 for review). Further, direct applications of serotonin at these synapses can produce the same lasting changes in synaptic function and behavior as seen with behavior modification in Aplysia.66,67 Thus, the possibility of both a serotonin reuptake inhibitor and behavior modification treatments having the same neural effects is not as farfetched as it might seem to some at first glance.

Unipolar major depression66–70 and the panic/agoraphobia disorder complex7–5 can also be treated with either drugs or behavior therapy, although, as in OCD, certain symptoms may respond better to one intervention than to another. Positron emission tomography has provided significant, replicated findings in mood disorders (see Baxter76 for review) and anxiety disorders.53,55,56,59–79 Positron emission tomographic studies that compare and contrast the effects of these vastly different treatment interventions may provide a powerful method for investigating the brain mediation of symptoms in these disorders, too.

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