Cerebral metabolic correlates as potential predictors of response to anterior cingulotomy for treatment of major depression

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Object. Neurosurgical procedures are a viable intervention for severe, treatment-refractory major depression, although they have been associated with only modest rates of efficacy. The purpose of this study was to identify possible neuroimaging predictors of treatment response to anterior cingulotomy in patients with major depression.

Methods. Thirteen patients underwent stereotactic anterior cingulotomy for treatment-refractory major depression. Symptom severity was measured using the Beck Depression Inventory (BDI) both before and approximately 12 months after surgery. The authors performed [18F]fluorodeoxyglucose–positron emission tomography (PET) studies in all patients preoperatively. Statistical parametric mapping methods were used to test for loci of significant correlation between preoperative regional cerebral metabolism and postoperative reduction in BDI scores. The mean (± standard deviation) change in the BDI score from the preoperative period (43.7 ± 7.8) to the postoperative period (30.5 ± 21.3) was 33.1 ± 45.4%. Two loci—the left subgenual prefrontal cortex and left thalamus—were identified as sites at which preoperative metabolism was significantly correlated with subsequent improvement in depressive symptom severity following cingulotomy. Specifically, higher preoperative rates of metabolism at these loci were associated with better postoperative results.

Conclusions. Possible PET scanning predictors of treatment response were identified in patients with major depression who had undergone anterior cingulotomy. Further research will be necessary to determine the reproducibility of this finding. If confirmed, the availability of an index for noninvasively predicting a patient’s response to cingulotomy for the treatment of major depression would be of great clinical value.

Key Words: neurosurgery • positron emission tomography • prefrontal cortex • thalamus • neuroimaging

Most patients with major depression can be successfully treated with some combination of psychotherapy, pharmacotherapy, and ECT. A subset of patients with very severe forms of major depression fail to respond to these conventional therapies; thus, these patients are sometimes considered for surgical intervention. Unfortunately, neurosurgical treatment for psychiatric illness is an invasive procedure with only modest success rates. Specifically, data from MGH indicate that 53% of patients with major affective disorders respond to bilateral anterior cingulotomy (one type of limbic system surgery). Additionally, although surgical risks following cingulotomy are not common (~5%) of patients suffer enduring sequelae), they can include intracranial hemorrhage, infection, and postoperative seizures as well as occasional urinary incontinence and cognitive dysfunction. Therefore, any test that could accurately predict the likelihood of a response to surgery in patients with major depression would be of tremendous clinical value. In particular, a neuroimaging evaluation that could reliably predict outcome would enhance patient selection, help avoid unnecessary surgery, and improve the overall response rate.

Neuroimaging research has contributed a great deal to the formation of contemporary neurobiological models of major depression. Convergent findings have implicated a network of brain regions, including dorsal and ventral regions of the prefrontal cortex, anterior cingulate cortex, amygdala, hippocampus, and related components of the striatum and thalamus in the pathophysiology of major depression. Some of the observed regional brain abnormalities appear to be mood state–dependent, whereas others persist following remission of symptoms.

In addition to elucidating the underlying pathophysiological features of the disease, another potential clinical application entails the use of neuroimaging to study treatment
Predictors of response to cingulotomy for depression

**TABLE 1**

Demographic and clinical data in 13 patients who underwent cingulotomy for treatment of major depression*

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age (yrs), Sex</th>
<th>Indication for Cingulotomy</th>
<th>Comorbid Dx</th>
<th>Preop BDI Score</th>
<th>Postop BDI Score</th>
<th>% Improvement in BDI Score</th>
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<tbody>
<tr>
<td>1</td>
<td>54, F</td>
<td>BD</td>
<td>none</td>
<td>34</td>
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<td>100.0</td>
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<td>30, F</td>
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</tr>
<tr>
<td>3‡</td>
<td>37, F</td>
<td>MDD</td>
<td>dys</td>
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<td>5</td>
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<td>6</td>
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<tr>
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<td>MDD</td>
<td>SoP, dys</td>
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<td>29</td>
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<tr>
<td>6‡</td>
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<td>SoP, SP</td>
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<td>27</td>
<td>43.8</td>
</tr>
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<td>48</td>
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<td>AG, PD</td>
<td>59</td>
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<td>GAD</td>
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<td>MDD</td>
<td>PD</td>
<td>45</td>
<td>60</td>
<td>−33.3</td>
</tr>
</tbody>
</table>

* AG = agoraphobia; AN = anorexia nervosa; BD = bipolar disorder; Dx = diagnosis; dys = dysthymia; GAD = generalized anxiety disorder; PD = panic disorder; PTSD = posttraumatic stress disorder; SoP = social phobia; SP = specific phobia.
† Patients are ordered by degree of clinical response.
‡ Study performed on Siemens HR+ PET scanner.

response. In one such study, pretreatment FDG-PET data obtained in depressed patients were grouped according to response or nonresponse following treatment with antidepressant medications. These investigators found baseline hypermetabolism in the rostral anterior cingulate cortex in the patient group that subsequently responded to treatment with antidepressant agents. They postulated that an adaptive hypermetabolic change in the rostral anterior cingulate cortex might be required for a positive response to treatment. Since then, similar studies have demonstrated that baseline hyperactivity in the anterior cingulate cortex and, in some cases, the medial prefrontal cortex have correlated with subsequent response to a wide variety of treatments.

A recent study in our laboratory was conducted with the aid of FDG-PET scanning to acquire data from patients with treatment-refractory OCD before they underwent bilateral anterior cingulotomy for their symptoms. Results demonstrated that higher preoperative rCMRG within the right posterior cingulate cortex correlated with improvement in OCD symptom severity following cingulotomy. Given success rates of approximately 50% for anterior cingulotomy for OCD, these findings highlight the potential for neuroimaging data to guide treatment decisions in psychiatric practice.

We report on the initial results of an analogous study in which we examined PET-derived cerebral metabolic correlates of response to anterior cingulotomy in patients with major depression. A priori, we hypothesized that loci of cerebral metabolic correlates with subsequent treatment outcome would be found within the principal brain structures implicated in major depression (dorsolateral and ventromedial prefrontal cortex, anterior cingulate cortex, posterior or cingulate cortex, amygdala, hippocampus, striatum, and thalamus).

**Clinical Material and Methods**

This study was conducted with the approval of the Sub-committee on Human Studies of the MGH. Written informed consent was obtained from each patient for the cingulotomy and associated procedures in the context of clinical care. In the context of this study, clinical data including patient demographics, diagnostic information, and FDG-PET images were obtained retrospectively from the hospital records of 13 patients (four men and nine women) who had undergone bilateral stereotactic anterior cingulotomies at MGH for severe, treatment-refractory major depression (Table 1). An MDD was the indication for cingulotomy in 11 of the patients, and major depression within the context of bipolar disorder was the indication in the remaining two patients. The mean (± standard deviation) age at cingulotomy was 49.7 ± 12 years (range 30–65 years), and the mean interval between preoperative and postoperative clinical assessments was 11.8 ± 10.7 months (range 6–41 months). Most patients had comorbid psychiatric illness and were otherwise without major neurological disorders. In particular, all patients were free of histories of significant head trauma, stroke, or other known neurological lesions. No patient in this study had received any prior neurosurgical treatment for psychiatric illness; however, most patients were taking a variety of psychotropic medications at the time of surgery as well as during the postoperative follow-up period.

Patients were accepted as candidates for cingulotomy and treated postoperatively in accordance with a clinical protocol that had been developed by the MGH Cingulotomy Assessment Committee. Briefly, in each case we conducted an initial review of patient records and any correspondence with the referring psychiatrist to establish the following: 1) The patient had active major depression. 2) The major depression was chronic, severe, and debilitating. 3) The debility was principally a consequence of the major depression rather than a comorbid condition. 4) Prohibitive contraindications to surgery were not present (for example, active substance use disorder or traumatic brain injury). 5) An exhaustive array of nonsurgical treatments had been tried without sustained relief. 6) The referring psychiatrist and patient were committed to complying with the prescribed postoperative treatment recommendations. To elaborate, with regard to past treatment trials, all patients had failed to respond to the following: 1) a minimum of two
documented trials of tricyclic antidepressant agents, with
the highest recommended dose being tolerated for at least 6
to 8 weeks; 2) a minimum of two documented trials of se-
lective serotonin reuptake inhibitors, with the highest rec-
ommended dose being tolerated for at least 6 to 8 weeks; 3)
a minimum of one trial of a standard monoamine oxidase
inhibitor, with the highest recommended dose being toler-
ated for at least 6 to 8 weeks; 4) a minimum of one trial of
an atypical antidepressant agent (for example, bupropion,
venlafaxine, nefazodone, trazodone, mirtazapine), with the
highest recommended dose being tolerated for at least 6 to
8 weeks; 5) the augmentation of antidepressant treatments
with lithium, thyroid hormone, and dopaminergic agents (at
least one); and 6) a minimum of one course of bilateral ECT
consisting of at least 10 to 12 treatments (unless intolerable
side effects emerged).

Following a review of records and correspondence, can-
idates who appeared to meet the criteria for cingulotomy
were next assessed onsite at the MGH. Here, all patients
were examined by at least one psychiatrist, one neurolo-
gist, and one neurosurgeon. The presurgical assessment
included a comprehensive physical examination, a com-
prehensive neurological examination, an MR imaging study
of the brain to rule out gross structural abnormalities, an
FDG-PET study of the brain to assess baseline regional dys-
function, and routine preoperative tests including elec-
trocardiography, blood glucose, electrolytes, and complete
blood counts. Standardized instruments were administered,
including the BDI4 and the Structured Clinical Interview for
DSMIII-R.43

Patients were routinely followed up approximately 12
months postoperatively by using the same standardized in-
struments. Follow-up data in the current study were ac-
quired between 6 and 12 months postoperatively in all pa-
tients except two (Cases 4 and 12) for whom such data were
not available until 41 and 29 months, respectively. Patients
who lived locally or who returned to Boston for a second
surgical procedure were evaluated onsite (two patients),
whereas the remainder were interviewed by telephone (11
patients).

With regard to postoperative treatment, all patients were
maintained on the combination of medication that had been
previously determined to be optimal in their case. Typical-
ly, this entailed a combination of medications that were at
least partially effective in controlling comorbid conditions
and, in some cases, effective in minimally ameliorating
the major depression. Occasionally, in cases in which pa-
tients showed no improvement in major depression several
months after cingulotomy or in those in which comorbid
conditions worsened, the referring psychiatrist might make
modifications to the medication regimen before the approx-
imate 12-month follow-up time point.
Predictors of response to cingulotomy for depression

**Surgical Technique**

The procedure for MR imaging–guided stereotactic anterior cingulotomy has been described in detail previously. Briefly, a pair of burr holes is made bilaterally, each 9.5 cm posterior to the nasion and 1.5 cm lateral to the midline. Electrically insulated thermistor electrodes are positioned stereotactically into the anterior cingulate gyrus with the aid of MR imaging guidance. Initial targets are located 0.7 cm lateral to the midline, 2 cm posterior to the most anterior aspect of each frontal horn, and 1 mm above the roof of the ventricles. Lesions are created by heating the uninsulated tip of the electrode (1 cm in length) to 80 to 85°C for 90 seconds by using radiofrequency current. The electrode is then withdrawn 1 cm and another lesion is made immediately dorsal to the first. The procedure is then repeated on the contralateral side. This operation is intended to produce lesions of approximately $1 \times 1 \times 2$ cm within the anterior cingulate cortex of each hemisphere (that is, a total lesion volume ~4 cm$^3$).

**Positron Emission Tomography Studies**

The $^{18}$FDG (~370 MBq or 10 mCi) was injected intravenously into the patient, who remained in a quiet room with his or her eyes open. After a 45-minute uptake period, the patient’s head was immobilized with a custom fabricated head-holder (Tru-Scan Imaging, Inc., Annapolis, MD) and positioned so that the imaging plane was parallel to the orbitomeatal line. Emission data for the first 10 patients were acquired with a Scanditronix PC4096 PET camera (General Electric, Milwaukee, WI), in a single bed position for 30 minutes. The primary imaging parameters of the PC4096 camera are in-plane and axial resolutions of 6 mm FWHM and 15 contiguous slices of 6.5-mm separations. The PC4096 images were reconstructed using a conventional filtered back-projection algorithm to an in-plane resolution of 6 mm FWHM. Emission data for the last three patients were acquired with a Siemens HR+ PET scanner (CTI, Knoxville, TN), in a single bed position for 30 minutes. The primary imaging parameters of the HR+ scanner are in-plane and axial resolutions of 4.5 mm FWHM and 63 contiguous slices of 2.5-mm separation. The HR+ images were reconstructed using a conventional filtered back-projection algorithm to an in-plane resolution of 4.5 mm FWHM. Projection data from both cameras were corrected for nonuniformity of detector response, dead time, random coincidences, and scattered radiation. An analytic attenuation correction was applied to the data, based on an estimate of slice contour and the assumption of a uniform attenuation coefficient equal to that of water.

Following reconstruction, movement-corrected,$^3$ whole-brain normalized images reflecting rCMRG were transformed to MNI space (http://www.bic.mni.mcgill.ca). Following spatial normalization, scans were filtered with a 20-mm FWHM two-dimensional gaussian filter.

**Statistical Analysis**

Analysis of whole-brain, voxel-wise PET data followed the theory of statistical parametric mapping$^{19,21,45}$ and was performed with SPM99 software (Wellcome Department of Cognitive Neurology, Institute of Neurology, London, UK). Across the entire cohort of subjects, three sets of statistical parametric maps were generated: the principal maps reflected the relationship between rCMRG and percentage of improvement in the BDI score; two sets of control maps were also generated to test for confounding relationships between rCMRG and age, and rCMRG and BDI score at pre-treatment. For each map, the covariates-only option was selected, so that a regression analysis was performed to test the linear relationship between rCMRG and the external clinical variable (across subjects), yielding a z score at each voxel in space. For ease of discussion, we refer to the findings in terms of significant correlations, although the analysis used formally involved linear regression rather than assessment of correlation per se. Both direct and inverse relationships were assessed.

The statistical parametric maps were inspected to identify all foci of significant correlations. Given that this study represents the first of its kind, we used relatively liberal statistical thresholds in the hope of generating more refined hypotheses for future studies; more stringent thresholds together with more circumscribed hypotheses are recommended for follow-up experiments. Although a $z$ score greater than 3.09 ($p < 0.001$), uncorrected for multiple comparisons) was selected a priori as the threshold for statistical significance, such findings should not be taken as strong evidence of reliable effects before confirmation, ideally by independent replication.

**Results**

**Treatment Response**

Clinical data are presented in Table 1. The mean change in the BDI score from the preoperative (43.7 ± 7.8) to the postoperative interval (30.5 ± 21.3) was 33.1 ± 45.4%, with four (31%) of 13 patients exhibiting a greater than 50% reduction in the severity of depressive symptoms. In addition, improvement in the BDI score was significant for the entire group ($t_{12} = 2.65; p = 0.021$).

**Predictors of Treatment Response on PET Scanning**

First, the relationship between rCMRG and percentage of improvement in the BDI score was assessed. Loci of significant correlations were found within two of the principal regions implicated in the pathophysiology of major depression. Loci of significant correlation were not found in any of the other a priori regions. One locus of significant correlation was found within the left subgenual prefrontal cortex (peak $z$ score 3.32; MNI coordinates $-8, 24, \text{and} -8$; this peak locus was surrounded by 23 contiguous voxels exceeding $z = 3.09$, or $p < 0.001$ uncorrected; Fig. 1). Another locus of significant correlation was found within the left posterior thalamus (peak $z$ score 4.18; MNI coordinates $-16, -32, \text{and} 12$; this peak locus was surrounded by 230 contiguous voxels exceeding $z = 3.09$, or $p < 0.001$ uncorrected; Fig. 2). Specifically, a higher preoperative rCMRG at these loci was associated with a greater postoperative percentage of improvement in BDI score (that is, a better outcome). A complete search of the entire brain region revealed no other locus of significant correlation.

Next, control analyses were performed to assess whether the loci of significant correlation that had been found in the
initial analysis might be confounded by age or preoperative severity of depressive symptoms. Neither of these control analyses yielded significant correlations at the loci identified in the initial analysis.

Finally, for the purposes of statistical and graphic illustration, Pearson product-moment correlation analyses were performed using the rCMRG of the voxels of peak statistical significance and the percentage of improvement in BDI score. The correlation analysis for the left subgenual prefrontal cortex yielded an $r^2(11)$ of 0.81 ($p = 0.001$; Fig. 1), whereas that for the left thalamus yielded an $r^2(11)$ of 0.9 ($p < 0.001$; Fig. 2). As seen in Figs. 1 and 2, the points on these graphs are broadly distributed; however, we sought to confirm that these statistically significant correlations were not being driven by points at the extremes. Hence, in three separate analyses for each region of interest, we repeated this Pearson product-moment correlation analysis, excluding the best responder, the worst responder, and both the best and worst responders. In all three cases for each region of interest, the correlation analysis remained significant at a probability value less than 0.05, indicating that the significant correlation was not being driven by data points at the extremes. Last, we repeated these Pearson product-moment correlation analyses for both regions of interest, excluding the two patients with bipolar disorder, and again found that the correlation analyses remained significant at a probability value less than 0.05.

**Discussion**

All treatment decisions involve assessing the potential risks and benefits of available options. Because limbic system surgical procedures such as anterior cingulotomy are associated with only modest efficacy in the treatment of psychiatric illness and involve an irreversible lesion with potential side effects, any presurgical data that may better predict outcome following those procedures would be tremendously valuable. Currently, there are no such reliable predictors of response. Thus, efforts to identify a neuroimaging-based predictor of treatment response are warranted to aid clinical decision making in these cases. Data from our previous FDG-PET study of patients with treatment-refractory OCD indicated that higher preoperative rates of metabolism in the right posterior cingulate cortex correlate with improvement in OCD symptom severity following cingulotomy. To our knowledge, however, the current study represents the first conducted in patients with major depression who underwent limbic system surgery.

Contemporary neurocircuitry models have emphasized the role of dorsal and ventral regions of the prefrontal co-
Predictors of response to cingulotomy for depression

text, anterior cingulate cortex, amygdala, hippocampus, and related components of the striatum and thalamus in the pathophysiology of major depression.12,14,27 In the current study our data indicate that in this cohort of patients with major depression, preoperative rCMRGl within two of these regions—the left subgenual prefrontal cortex and left thalamus—predicted a subsequent reduction in depressive symptom severity following anterior cingulotomy. These statistical results do not appear to be attributable to confounding factors such as age or severity of depression at the time of PET data acquisition. Although preliminary, these findings provide a strong case for conducting subsequent research to assess the reproducibility and generalizability of the results.

Multiple neuroimaging studies have demonstrated increases in CBF in the subgenual prefrontal cortex with the induction of sadness in healthy volunteers.10,22,30 Conversely, decreased metabolism and CBF have been demonstrated in the subgenual prefrontal cortex during depressive episodes in patients with unipolar or bipolar disorders when compared with healthy volunteers.8,17 In addition, data from both morphometric MR imaging6,17,24 and postmortem studies34 have revealed that the volume of the left subgenual prefrontal cortex is decreased in patients with unipolar major depression and bipolar disorder. These findings are especially relevant to the current study given that the indication for cingulotomy in two of the 13 patients was depression within the context of bipolar disorder. Although data in the current study indicate that those patients with treatment-refractory major depression with lower-magnitude decrements in metabolism within the subgenual prefrontal cortex are more likely to experience symptom improvement following anterior cingulotomy, alternative explanations are possible. Results of studies in which researchers used techniques to correct for partial volume effects of the reduced volume of the subgenual prefrontal cortex of depressed patients indicate that, following correction, the metabolism in the subgenual prefrontal cortex may actually be increased when compared with that in healthy volunteers.15 This partial volume-corrected finding of increased metabolism in the subgenual prefrontal cortex of depressed patients provides some explanation for data from multiple investigations demonstrating that treatment with antidepressant medications results in metabolic decreases in this region.7,8,17,29,30 If metabolism in the subgenual prefrontal cortex is actually increased in depressed patients compared with that in healthy volunteers and if depressed patients with higher preoperative metabolism in the subgenual prefrontal cortex would be more likely to respond to anterior cingulotomy, then activity in this region would have to decrease further in responders than nonresponders to normalize or return to a metabolic state comparable to that in healthy volunteers.

Data from other neuroimaging studies of predictors of treatment response in depressed patients have demonstrated that greater hyperactivity in the rostral anterior cingulate cortex may predict treatment response;25,28,36,40 increased hyperactivity in the posterior cingulate cortex may predict treatment response to anterior cingulotomy in patients with severe treatment-refractory OCD.37 There are at least two explanations for why hyperactivity in brain structures with elevated metabolism associated with the pathophysiology of the illness may predict a positive treatment response. First, it is possible that the elevated metabolism in these brain regions is associated with a compensatory response to primary pathological features in other brain regions. Thus, the ability to mount a compensatory response in the absence of treatment may be predictive of a better treatment response. Second, it is possible that the regions where hyperactivity predicts a positive treatment response represent the neural substrate where the treatment exerts its effect. Therefore, patients without hyperactivity in these regions in the absence of treatment will not respond to therapies that may exert their effect within these regions.

Results from the current study also demonstrate that depressed patients with higher preoperative metabolism in the left posterior thalamus are more likely to respond to anterior cingulotomy. The thalamus is a component of the CSTC circuits that are hypothesized, among other things, to mediate emotion and affect.1,2 Converging evidence reveals that dysfunction of the components of these CSTC circuits is implicated in the pathophysiology of major depression.12,26,27 Structural neuroimaging studies in which researchers have examined the thalamus in depressed patients have yielded conflicting results.41 Functional neuroimaging data have demonstrated increased CBF in the thalamus in depressed patients18,39 as well as decreased metabolism in the thalamus following treatment with fluoxetine.29 Interestingly, findings in the current study involve a territory in the posterior thalamus in the region of the pulvinar. It has been demonstrated that posterior nuclei of the thalamus have monosynaptic connections to the central nucleus of the amygdala in rodents44 and that this direct thalamoamygdala connection plays a central role in classic fear conditioning.40 Data from studies conducted in humans have indicated that analogous connections exist and that the resulting neural pathway is capable of processing visual fear-related stimuli independent of both the striate cortex and normal visual awareness.32,33 This posterior thalamoamygdala connection is especially relevant given that results of other studies have demonstrated increased left-sided amygdaloid metabolism in patients with major depression, compared with controls.6,18 Of course, the amygdala also has extensive connections with the prefrontal cortex, including the subgenual prefrontal cortex.11,35 Given that amygdaloid metabolic abnormalities in major depression have been predominantly demonstrated to be left sided, that there are known connections between the amygdala and both the prefrontal cortex and posterior thalamus, and that the findings in the current study involve territories of the left subgenual prefrontal cortex and left posterior thalamus, one may posit that the findings in the current study involve components of a left-sided corticothalamoamygdala network that is dysfunctional in patients with major depression.

Although most depressed patients will ultimately respond to medication, psychotherapy, or ECT, a small subset will experience no alleviation of their depressive symptoms. Study data have indicated that a poor response to antidepressant treatment may be associated with an inability to suppress ventral paralimbic regions.28 In this small subset of treatment-refractory patients, ablative lesions within the limbic system may suppress activity within essential ventral paralimbic regions, so that response is possible. Although such limbic system surgical procedures are an effective treatment for a subset of patients with treatment-refractory major depression, the precise mechanism of action remains unclear. Future studies in which researchers com-
pare neuroimaging data acquired before and after limbic system surgery will be needed to elucidate these mechanisms. Nonetheless, one might speculate that cingulotomy, like other surgical procedures for depression, such as anterior cingulotomy and subcaudate tractotomy, facilitates clinical improvement by disrupting connections linking critical limbic–cortical and limbic–subcortical circuits. Systematic examination of common regional metabolic changes among the various surgical approaches may help better define these critical targets.

Interpretations of results of the current study should be considered in the context of acknowledged limitations. First, this preliminary study was conducted with a modest number of patients. Given the heterogeneity of the overall population with treatment-refractory major depression, replication of the current findings is essential before seeking to generalize from these results to future candidates for cingulotomy. Moreover, in the absence of additional data, generalization to other indications for cingulotomy or to other neurosurgical treatments for major depression is entirely unfounded. Second, as we acknowledged previously, the statistical threshold applied is somewhat liberal, further underscoring the need for replication. Third, it is possible that the significant relationship between measured rCMRG and BDI score improvement is confounded by variables that cannot be readily accounted for within the general linear model, such as diagnostic comorbidity or medication effects.

Conclusions

Results of the current study indicate that cerebral metabolism within territories of the left subgenual prefrontal cortex and the left thalamus was significantly correlated with subsequent improvement in depressive symptom severity following anterior cingulotomy in a cohort of patients with severe, treatment-refractory major depression. Future studies will be necessary to assess the reproducibility and generalizability of these findings. Last, studies are needed to assess whether the use of neuroimaging methods to identify predictors of treatment response may have broader applications for clinical practice in the future.

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References

Predictors of response to cingulotomy for depression


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