Deep brain stimulation of the subcallosal cingulate gyrus for depression: anatomical location of active contacts in clinical responders and a suggested guideline for targeting

Clinical article

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Object. Deep brain stimulation (DBS) of the subcallosal cingulate gyrus (SCG), including Brodmann area 25, is currently being investigated for the treatment of major depressive disorder (MDD). As a potential emerging therapy, optimal target selection within the SCG has still to be determined. The authors compared the location of the electrode contacts in responders and nonresponders to DBS of the SCG and correlated the results with clinical outcome to help in identifying the optimal target within the region. Based on the location of the active contacts used for long-term stimulation in responders, the authors suggest a standardized method of targeting the SCG in patients with MDD.

Methods. Postoperative MR imaging studies of 20 patients with MDD treated with DBS of the SCG were analyzed. The authors assessed the location of the active contacts relative to the midcommissural point and in relation to anatomical landmarks within the medial aspect of the frontal lobe. For this, a grid with 2 main lines was designed, with 1 line in the anterior-posterior and 1 line in the dorsal-ventral axis. Each of these lines was divided into 100 units, and data were converted into percentages. The anterior-posterior line extended from the anterior commissure (AC) to the projection of the anterior aspect of the corpus callosum (CCa). The dorsal-ventral line extended from the inferior portion of the CC (CCi) to the most ventral aspect of the frontal lobe (abbreviated “Fr” for the formula).

Results. Because the surgical technique did not vary across patients, differences in stereotactic coordinates between responders and nonresponders did not exceed 1.5 mm in any axis (x, y, or z). In patients who responded to the procedure, contacts used for long-term stimulation were in close approximation within the SCG. In the anterior-posterior line, these contacts were located within a 73.2 ± 7.7 percentile distance from the AC (with the AC center being 0% and the line crossing the CCa being 100%). In the dorsal-ventral line, active contacts in responders were located within a 26.2 ± 13.8 percentile distance from the CCi (with the CCi edge being 0% and the Fr inferior limit being 100%). In the medial-lateral plane, most electrode tips were in the transition between the gray and white matter of SCG.

Conclusions. Active contacts in patients who responded to DBS were relatively clustered within the SCG. Because of the anatomical variability in the size and shape of the SCG, the authors developed a method to standardize the targeting of this region. (DOI: 10.3171/2008.10.JNS08763)

Key Words • Brodmann area 25 • cingulate gyrus • cingulotomy • deep brain stimulation • depression • psychiatry

One of the most promising emerging indications for DBS is for the treatment of MDD.5,9,12 Several targets are being considered as of this writing, including the SCG (a region that encompasses Brodmann area 25), the inferior thalamic peduncle,3 the nucleus accumbens,12 and the internal capsule. Our group has focused on the SCG, based on the premise that DBS could modulate the increased activity observed in this region in patients with depression.2,3,8–10,14 In our initial trial, 4 of 6 patients receiving DBS of the SCG responded to the procedure at 6 months. We have subsequently treated 14 additional patients. At 1 year, 55% of the 20 patients treated in our center were considered to be responders, based on a ≥ 50% improvement in their depressive symptoms.7

Because DBS of the SCG is an emerging therapy for MDD, prognostic factors and the optimal placement of the electrodes to achieve a good outcome have not yet been established. In our first study, surgical targeting was
accomplished through direct MR imaging visualization of the subgenual cingulum. We did not rely on coordinates relative to the MCP due to the significant variability in the anatomy of the medial prefrontal cortex across patients. One problem with targets derived directly from imaging, however, is the potential variation that may occur across centers. As a result, we created a standardized way of targeting the SCG. For this, we initially subdivided our patients into 2 groups: responders and nonresponders to therapy. Subsequently, we assessed the location of the contacts used for long-term stimulation relative to the internal anatomy of the medial frontal lobe in patients who responded to DBS surgery. Based on these findings, we designed a grid to standardize the targeting of the SCG relative to internal landmarks of the medial frontal lobe.

Methods

Patient Population

Twenty patients with MDD treated with SCG DBS at the Toronto Western Hospital were included in this study. To be considered a surgical candidate, the following criteria had to be met: 1) a diagnosis of MDD according to the Diagnostic and Statistical Manual (ed. IV-TR); 2) current major depressive episode persisting for at least 1 year; 3) HAMD-17 scores > 20 and Global Assessment of Function scores ≤ 50; and 4) failure to respond to 4 different antidepressant therapies, including medications and evidence-based psychotherapy. In 17 of the patients, electroconvulsive therapy had also failed. Exclusion criteria included suicidal plans during the recruitment phase, other Axis I or II disorders, or neurological or clinical conditions that could interfere with the technique or safety of the surgical procedure (that is, coagulopathy).

A significant response to DBS was considered to have occurred when HAMD-17 scores were reduced by > 50% at 12 months. According to this criterion, 11 patients (55%) were considered to be responders and 9 (45%) were nonresponders to the therapy (Table 1).

Surgical Technique and Programming

A stereotactic frame (Leksell model G, Elekta, Inc.) was placed after induction of local anesthesia, and axial 3D SPGR and T2-weighted stereotactic MR imaging sequences were acquired (Signa 1.5-T unit, General Electric, Inc.). Images were then uploaded onto a neuronavigation system with frame-based software (FrameLink 4.1, StealthStation, Medtronic, Inc.) for anatomical targeting.

The SCG was initially identified on reconstructed sagittal images, representing the cingulate region lying ventral to the genu of the CC (Fig. 1A). This often corresponded to a coronal section in which the initial aspect of the anterior horns of the lateral ventricles could be appreciated (Fig. 1B). In the medial-lateral plane, the selected target was the transition between gray and white matter of the SCG (Fig. 1B and C). In a few cases, the region was characterized by more complex or bifid gyri (Fig. 1B). Under these circumstances, we preferred to target the more ventral aspect of the SCG to permit maximum electrode coverage of the region.

In the operating room, after induction of local anesthesia, bilateral bur holes were made 1–2 cm anterior to the coronal suture and 2 cm lateral to the midline. Microelectrode recording commenced 10 mm above the target, and was used mainly to localize the junction between gray and white matter. This could be clearly ascertained, because the gray matter was characterized by neuronal activity, whereas the white matter was electrophysiologically silent.

Once the physiological target was determined, DBS quadripolar electrodes (model 3387, Medtronic, Inc.) were implanted in this region. Individual contacts were tested consecutively to evaluate acute effects of stimulation, and were subsequently secured in place. Thereafter, the head frame was removed and a dual-channel internal pulse generator (Kineta, Medtronic, Inc.) was implanted in the right subclavicular region after induction of general anesthesia.

Programming of the internal pulse generator was started ~ 2 weeks postsurgery. Initial settings were a monopolar configuration (contact cathode and case anode) 2.5–3.5 V, 90 μsec of pulse width, and 130 Hz. The contacts initially selected for stimulation were the ones closer to the SCG, as assessed on postoperative MR imaging studies. Most commonly these included contacts 1 and 5 and 2 and 6 (0 and 4 were the most ventral contacts; 0–3 were right hemisphere and 4–7 were left hemisphere). Patients were then seen on a weekly basis and the voltage was optimized. If clinical improvement was not seen after a few weeks of stimulation, a new pair of homologous contacts was tested (for example, 0 and 4, 1 and 5, 2 and 6, or 3 and 7). Once the best clinically effective contact was chosen, patients were reassessed only during regular follow-up visits. At long-term follow-up, most patients were using monopolar stimulation at 3.0–5.0 V, 90 μsec of pulse width, and 130 Hz, with either contacts 1 and 5 or 2 and 6 serving as the cathodes and the case as the anode.

Location of the Active Contacts Through MR Imaging

To locate the active contacts in each patient, postoperative 3D SPGR and T2-weighted axial MR images were transferred to a workstation. Using the FrameLink 4.1 software (March 4.1, StealthStation, Medtronic, Inc.) these 2 studies were fused, and coronal and sagittal planes were reconstructed based on axial images. The AC and PC were targeted in the axial plane and 3 additional points were plotted in the midline. Images were then reformatted parallel to the AC-PC plane and orthogonal to the midline. Pitch, roll, and yaw were corrected in the StealthStation. The DBS electrodes were visualized in all 3 planes, and their tips were targeted. For this study, we defined the tip of the electrode as the distal portion of the electrode artifact. Even though this does not represent the actual tip of the device, it was a standard measurement that could be compared across the groups being studied. Thereafter, we determined the entry point of the leads into the cortex, the location of the tip of the electrodes, and the distance between the MR imaging artifacts of
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Each of the contacts. For the purpose of our study, we have considered the center of the sphere-shaped artifacts corresponding to the electrode contacts to be the center of the contacts. In this study, active contacts were defined as those being used as the cathodes, because all patients were receiving monopolar stimulation.

Coordinates of the contacts and tips of the electrodes were derived from the MCP and the medial-lateral edge of the cortical surface (x, medial-lateral plane; y, anterior-posterior plane; and z, dorsal-ventral plane). Coordinates from the cortical surface were calculated because in some cases we observed asymmetries in the region of the subgenual cingulum, with one of the hemispheres crossing over the midline to the other side. In addition, we have also calculated the euclidean distance from the active contacts to the center of the AC. In a 3D “xyz” system, with p1 being AC (x1, y1, z1) and p2 being the center of the active contacts (x2, y2, z2), the euclidean distance between p1 and p2 was represented by \( \sqrt{(x_1 - x_2)^2 + (y_1 - y_2)^2 + (z_1 - z_2)^2} \).

Due to the variability in the anatomy of the prefrontal cortex, we not only calculated the distance of the contacts to the MCP but also relative to internal anatomical landmarks. To standardize the location of the electrodes across patients, we have initially traced a projection line abutting the most rostral aspect of the CC (the CC line) that was perpendicular to the base of the frontal lobe (Fig. 2). Thereafter, we drew 2 straight lines perpendicular to the projection line described above. The first connected the center of AC and the CC line and was called the AC-CCa line. The second connected the center of AC to the center of the active contact (AC-Ct). The percentage obtained with the formula AC-Ct/AC-CCa × 100 represented the relative distance of the center of the active contact from AC and CCa. In the dorsal-ventral plane, a line perpendicular to the base of the frontal lobe was drawn from the CCi to the edge of the frontal lobe (abbreviated “Fr” for the formula). A second line was then drawn parallel to CCi-Fr from the inferior aspect of CC to the center of the active contact (CCI-Ct). The percentage obtained with the formula CCI-Ct/CCi-Fr × 100 represented the relative distance of the center of the active contact to CCI and Fr.

**Statistical Analysis**

A Student t-test was used to compare the following variables: 1) the location of the contacts and tip of the electrodes relative to the MCP and medial-lateral edge of the cortical surface; 2) the location of the contacts relative to the AC-CCa and CCI-Fr lines; and 3) the euclidean distance between AC and the active contacts. Correlation analysis was used to assess whether there was a relationship between the location of the active contacts and outcome.

For the Student t-test, a probability value < 0.05 was considered statistically significant. A correlation was considered to be strong when \( r \geq 0.75 \), moderate when \( r \geq 0.5 \), weak when \( r \geq 0.25 \), and nonexistent when \( r < 0.25 \). All values in the text are expressed as the mean ± SD.

**Results**

**Electrode Location in Responders and Nonresponders to DBS of the SCG**

A summary of our results may be found in Table 2. Because no differences in electrode placement were found

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**TABLE 1: Clinical outcome in patients with major depression who responded or did not respond to DBS of the SCG**

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>No. of Patients</th>
<th>Preop HAMD-17 Score</th>
<th>Postop (1 yr FU) HAMD-17 Score</th>
<th>% Improvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>responders</td>
<td>11</td>
<td>24.3 ± 3.7</td>
<td>8.2 ± 2.5</td>
<td>66.4 ± 9.0</td>
</tr>
<tr>
<td>nonresponders</td>
<td>9</td>
<td>24.1 ± 3.2</td>
<td>18.0 ± 4.8</td>
<td>26.1 ± 13.8</td>
</tr>
<tr>
<td>all</td>
<td>20</td>
<td>24.2 ± 3.4</td>
<td>12.6 ± 6.2</td>
<td>48.2 ± 23.2</td>
</tr>
</tbody>
</table>

* Results are expressed as the mean ± SD. Abbreviation: FU = follow-up.
responders to DBS of the SCG were as follows: 6.3 ± 2.0 lateral (x [5.6 ± 1.3 from the edge of the cortical surface]; 34.0 ± 2.7 anterior (y); and 2.6 ± 3.1 inferior (z). The euclidean distance from the center of the active contacts to the center of AC in these patients was 22.9 ± 2.2.

A schematic representation of the location of the active contacts relative to internal anatomical landmarks in responders to surgery is presented in Fig. 3B. On average, these contacts were located in the 73.2 ± 7.7 percentile of the AC-CCa line in the anterior-posterior axis (0% being the center of the AC and 100% the line crossing the CCa) (Fig. 3C). In the dorsal-ventral plane, active contacts in responders to the therapy were located in the 26.2 ± 13.8 percentile of the CCI-Fr line (0% being the inferior edge of the CC and 100% the inferior limit of the frontal cortex) (Fig. 3C).

**Discussion**

The main objective of our study was to develop a standardized way of targeting the SCG. Because the anatomy of the medial prefrontal lobe is quite variable, the placement of DBS electrodes based on coordinates relative to the AC, PC, and MCP is often inadequate. In our first article, we reported that a suitable location for the electrodes would be the midpoint between the most anterior edge of the CC and the AC. In the patients who underwent operations subsequently, however, we realized that the target selected through direct visualization of the SCG on MR images was often more anterior than the one we previously published.

To develop a standardized way of targeting the SCG, we undertook 2 main steps. The first was to subdivide our patients into responders (a decrease in HAMD-17 scores of > 50% at 12 months) and nonresponders to DBS. Subsequently, we assessed the location of the contacts used for long-term stimulation relative to the internal anatomy of the medial frontal lobe in patients who responded to surgery.

In the first part of the analysis, we initially attempted to assess whether there were any differences in the anterior-posterior location of the electrodes between responders and nonresponders to DBS of the SCG. The premise was that the placement of electrodes in distinctive regions along this axis could lead to variable outcomes due to the recruitment of different fiber systems by stimulation. Our results did not corroborate this hypothesis, because the only difference we found was that the electrode array in nonresponders was significantly more dorsal than the one in patients who responded to the procedure. This difference, however, was on the order of millimeters and not likely to be of clinical significance. In addition, active contacts in responders were relatively clustered within the SCG and not in more ventral aspects of the frontal lobes. Because all nonresponders had at least 1 electrode contact placed within the SCG, it is unlikely that the small dorsal-ventral differences observed in our analysis were responsible for the lack of clinical response in these patients.

A few caveats of our analysis have to be taken into account. We have only explored a small portion of the sub-
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Almost all contacts in our series were within 65–80% of the AC-CCa line (0% being the center of AC and 100% the projection line crossing the CCa). It is possible that electrodes placed more anteriorly or posteriorly than our general target could yield different results. By moving the electrodes more anteriorly we would probably affect more fibers from the cingulate bundle, whereas by moving it more posteriorly we would theoretically affect a more complete set of projections to and from the SCG (including not only the cingulate bundle but also those involving the uncinate fascicle as well as fibers innervating subcortical and brainstem structures, the thalamus, and hypothalamus). The problem of targeting more posterior aspects of the SCG is surgical safety, because the anterior cerebral arteries are very close to that region. What we can conclude based on our findings is that within the small targeted region of the SCG, the location of the electrode contacts did not determine outcome. Also important to consider for anatomical, and eventually physiopathological reasons, is whether electrodes were in the white or gray matter of the SCG. In both responders and nonresponders, most contacts were located in the border gray/white matter. Moreover, contacts that were not in this anatomical region were only 1–2 mm into either the SCG gray or white matter. The only exceptions to this rule were the upper contacts in some patients, which were more dorsal and closer to the white matter of the CC.

<table>
<thead>
<tr>
<th>Electrode Contacts &amp; Subgroup</th>
<th>Parameter</th>
<th>Coordinate</th>
<th>Contact Position</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>x</td>
<td>xcx</td>
<td>y</td>
</tr>
<tr>
<td>0 &amp; 4</td>
<td>responders</td>
<td>5.6 ± 2.2</td>
<td>5.0 ± 1.3</td>
</tr>
<tr>
<td>nonresponders</td>
<td>6.2 ± 2.3</td>
<td>6.1 ± 1.8</td>
<td>33.1 ± 1.8</td>
</tr>
<tr>
<td>p value</td>
<td>0.4</td>
<td>0.06</td>
<td>0.2</td>
</tr>
<tr>
<td>1 &amp; 5</td>
<td>responders</td>
<td>5.6 ± 3.5</td>
<td>5.6 ± 1.3</td>
</tr>
<tr>
<td>nonresponders</td>
<td>6.7 ± 2.4</td>
<td>6.0 ± 1.7</td>
<td>33.0 ± 1.9</td>
</tr>
<tr>
<td>p value</td>
<td>0.2</td>
<td>0.4</td>
<td>0.1</td>
</tr>
<tr>
<td>2 &amp; 6</td>
<td>responders</td>
<td>6.9 ± 2.0</td>
<td>6.0 ± 1.3</td>
</tr>
<tr>
<td>nonresponders</td>
<td>7.3 ± 2.4</td>
<td>6.7 ± 1.7</td>
<td>33.0 ± 2.0</td>
</tr>
<tr>
<td>p value</td>
<td>0.6</td>
<td>0.1</td>
<td>0.06</td>
</tr>
<tr>
<td>3 &amp; 7</td>
<td>responders</td>
<td>7.5 ± 2.0</td>
<td>6.6 ± 1.9</td>
</tr>
<tr>
<td>nonresponders</td>
<td>6.5 ± 5.4</td>
<td>7.2 ± 2.2</td>
<td>33.1 ± 2.1</td>
</tr>
<tr>
<td>p value</td>
<td>0.5</td>
<td>0.4</td>
<td>0.06</td>
</tr>
</tbody>
</table>

* Values represent the mean ± SD. No differences in electrode placement were noticed when the right and left hemispheres were compared, and therefore, data from both sides were grouped for the analysis. Probability values were obtained with a t-test comparing responders and nonresponders to treatment. Abbreviation: ED = euclidean distance.
† Definitions of coordinates: x, medial-lateral coordinate of the contacts relative to the MCP; xcx, medial-lateral coordinate of the contacts relative to the cortical surface; y, anterior-posterior coordinate of the contacts relative to the MCP; z, dorsal-ventral coordinate of the contacts relative to the MCP.
‡ Definitions of contact positions: AC-ct, the anterior-posterior line connecting the AC to the contact; CCI-ct, the dorsal-ventral line connecting the inferior edge of the CC to the contact (see text for details).

TABLE 3: Correlation between electrode contacts 1 and 5 and stereotactic coordinates relative to the MCP and anatomical landmarks within the medial frontal lobe*

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Coordinate</th>
<th>Lines (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>% improvement in HAMD-17 scores</td>
<td>x</td>
<td>xcx</td>
</tr>
<tr>
<td>-0.27</td>
<td>-0.18</td>
<td>0.17</td>
</tr>
</tbody>
</table>

* Values represent the Pearson correlation coefficient (r). We have chosen to demonstrate results of the correlation analysis only for contacts 1 and 5 for the sake of clarity. Nevertheless, similar r values were obtained when the homologous contacts 0 and 4, 2 and 6, and 3 and 7 were considered. See Table 2 for definitions of the coordinates. Abbreviations: AC-CCa = anterior-posterior line connecting AC to the anterior edge of the CC; CCI-Fr = dorsal-ventral line connecting the inferior edge of the CC to the base of the frontal lobe.
after DBS of the SCG are still unclear. Because the location of the electrode contacts was similar in responders and nonresponders to DBS, one could hypothesize that differences in outcome could be related to variations in the clinical characteristics of depression across patients. Against this assumption, however, baseline total HAMD-17 scores and symptom cluster subscores in our series were similar in responders and nonresponders to surgery. Yet, one caveat in this regard is that our study so far has only included 20 patients. It is possible that future multicenter trials recruiting a larger number of patients may yield different results. In summary, at present we cannot ascertain why certain patients did not respond to DBS of the SCG.

Proposed Method for Targeting the SCG

Based on the location of the active contacts in patients who responded to surgery in our series, we conceived a more standardized method for targeting the SCG compared with our initial description.

The first step is to visualize the subgenual cingulum on a midline sagittal section (Fig. 4A). Thereafter, a line parallel to the base of the frontal lobe and a perpendicular line abutting the CCa should be traced. The next step would be to draw AC-CCa and CCI-Fr lines parallel and perpendicular to the base of the frontal lobe, respectively. Both lines should be divided into quartiles (25, 50, 75, and 100%) (Fig. 4B and C). Axial and/or coronal planes of a region corresponding to 70–75% in AC-CCa and 25–30% in CCI-Fr should then be selected to define the anatomical gray/white matter junction of the SCG (Fig. 4D). In most of our cases, this region corresponded to a coronal plane that was 4–8 mm posterior to the rostral aspect of the anterior horns of the lateral ventricles. In addition, this plane often corresponded to the last section in which we did not see basal ganglia structures or in which a small crescent of caudate nucleus could be appreciated. According to the results in our 20 initial patients, at least 1 contact should ideally be placed in the region described above. One question that may emerge is whether one type of MR imaging sequence is better than others for targeting. At present, we are mainly using 3D SPGR images for preoperative targeting. In this study, we have chosen to illustrate our targeting method only in T2-weighted sections because the contrast between gray and white matter can be better appreciated.

Finally, we would like to emphasize that the strategy discussed above only represents a guideline for targeting. Refinements should be conceived and implemented for each individual patient as the surgeon visualizes the...
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region. In summary, this was the first article attempting to standardize the targeting of the SCG. Our method provides a general guideline and has to be corroborated by other authors performing psychiatric surgery for depression as well as in future prospective studies.

Conclusions

Because of the anatomical variability in the size and shape of the medial prefrontal lobe, we developed a standardized method for targeting the SCG. Based on the location of the active contacts in patients who responded to surgery in our series, we designed a grid that takes into account internal anatomical landmarks for each individual patient.

Disclosure

Drs. Mayberg, Giacobbe, Lozano, and Hamani are consultants for, Dr. Kennedy receives research support from, and Dr. Mayberg holds a patent licensed to Advanced Neuromodulation Systems, Inc. Dr. Lozano owns stock in Medtronic. The authors report no other conflicts of interest concerning the materials or methods used in this study or the findings specified in this paper.

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