# Targeting the Affective Component of Chronic Pain: A Case Series of Deep Brain Stimulation of the Anterior Cingulate Cortex

**Sandra G.J. Boccard, PhD*‡**
**James J. Fitzgerald, PhD*‡**
**Erlick A.C. Pereira, MD‡**
**Liz Moir, RGN‡**
**Tim J. Van Hartevelt, MSc§**
**Morten L. Kringelbach, DPhil§**
**Alexander L. Green, MD‡**
**Tipu Z. Aziz, FMedSci‡**

‡Oxford Functional Neurosurgery and Experimental Neurology Group, Nuffield Departments of Clinical Neuroscience and Surgery; §Department of Psychiatry, University of Oxford, United Kingdom

*These authors contributed to the manuscript equally.

**Correspondence:**
Sandra G.J. Boccard-Binet, PhD,
Department of Neurosurgery,
Level 6, West Wing,
John Radcliffe Hospital,
Oxford, OX3 9DU, UK.
E-mail: sandra.boccard@ndcn.ox.ac.uk

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**BACKGROUND:** Deep brain stimulation (DBS) has shown considerable promise for relieving nociceptive and neuropathic symptoms of refractory chronic pain. Nevertheless, for some patients, standard DBS for pain remains poorly efficacious. Pain is a multidimensional experience with an affective component: the unpleasantness. The anterior cingulate cortex (ACC) is a structure involved in this affective component, and targeting it may relieve patients' pain.

**OBJECTIVE:** To describe the first case series of ACC DBS to relieve the affective component of chronic neuropathic pain.

**METHODS:** Sixteen patients (13 male and 3 female patients) with neuropathic pain underwent bilateral ACC DBS. The mean age at surgery was 48.7 years (range, 33-63 years). Patient-reported outcome measures were collected before and after surgery using a Visual Analog Scale, SF-36 quality of life survey, McGill Pain Questionnaire, and EQ-5D (EQ-5D and EQ-5D Health State) questionnaires.

**RESULTS:** Fifteen patients (93.3%) transitioned from externalized to fully internalized systems. Eleven patients had data to be analyzed with a mean follow-up of 13.2 months. Post-surgery, the Visual Analog Scale score dropped below 4 for 5 of the patients, with 1 patient free of pain. Highly significant improvement on the EQ-5D was observed (mean, +20.3%; range, +0%-+83%; $P = .008$). Moreover, statistically significant improvements were observed for the physical functioning and bodily pain domains of the SF-36 quality-of-life survey: mean, +64.7% (range, −8.9%-+276%; $P = .015$) and mean +39.0% (range, −33.8%-+159%; $P = .050$), respectively.

**CONCLUSION:** Affective ACC DBS can relieve chronic neuropathic pain refractory to pharmacotherapy and restore quality of life.

**KEY WORDS:** Anterior cingulate cortex, Deep brain stimulation, Neuropathic pain

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Chronic pain, with a prevalence of as high as 8% of the general population, costs at least $150 billion per year in the United States alone and remains difficult to treat.[1] Deep brain stimulation (DBS) for pharmacoresistant neuropathic pain was first introduced more than 60 years ago.[2] Over time, several brain structures have been targeted, including the periventricular/periaqueductal gray area (PAG)[3] and the ventral posterior medial and lateral nuclei of the sensory thalamus (VP).[4] The mechanisms of action of DBS for chronic pain are not yet clear, but it has been proposed that PAG DBS may exert its effects through opioidergic or autonomic mechanisms in the pain neuromatrix.[5] On the other hand, VP stimulation may work through non-opioid mechanisms and is therefore more likely to be useful for central pain.[6] Combined electrical stimulation of PAG and VP has been used to synergistically optimize chances of reaching good pain relief. As described in recent case series from Oxford and Porto, DBS for chronic pain has been used with varying degrees of success for facial pain, poststroke neuropathic pain, brachial plexus injury, and phantom limb pain.[7]

**ABBREVIATIONS: ACC,** anterior cingulate cortex; **DBS,** deep brain stimulation; **PAG,** periventricular/periaqueductal gray area; **VP,** ventral posterior medial and lateral nuclei of the sensory thalamus

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Despite the increasing use of DBS for chronic pain, the underlying mechanisms remain poorly understood and its efficacy is variable.[8] Pain is a multifaceted phenomenon with at least 3 dimensions: sensory (pain intensity), affective (pain unpleasantness), and cognitive, all of which generate an integrated pain experience.[9] Some pain may benefit from targeting regions involved in the affective dimension of chronic pain such as the anterior cingulate cortex (ACC).[10] Changes in activity in distinct regions of the ACC have been linked to many psychological and motor functions[11] and have also been shown to be involved in pain expectation and empathy.[12]

Historically, neurosurgical lesioning of the anterior cingulate has been performed to relieve intractable pain, in particular, in cancer. Cingulectomy was first performed in 1948 by Cairns group in Oxford[13] and later popularized stereotactically in Massachusetts by Ballantine et al.[14] We recently reviewed published series, noting that the efficacy of the procedure varied from 32% to 83% in 8 studies for pain of malignant origin.[15]

Here we describe the first case series of ACC DBS to relieve the affective component of chronic neuropathic pain.

## METHODS

### Patients

Patients were referred by clinicians nationally to a single-center multidisciplinary team consisting of pain specialists, neuropsychologists, and neurosurgeons whose clinical protocol is detailed elsewhere.[8] Neuropsychological evaluation excluded psychiatric disorders and ensured minimal cognitive impairment. A definable organic origin for pain was sought, with the patient refractory to or poorly tolerant of pharmacological treatments. In 1 case, the patient's pain was of unknown cause but was clearly neuropathic in character and, after careful assessment, underlying psychiatric morbidity was thought to be extremely unlikely. Neuropathic pain refractory to medication for at least 2 years together with the absence of surgical contraindications such as coagulopathy permitted application for treatment funding. Informed consent was obtained from all patients proceeding to surgery. Other surgical treatments may have been previously unsuccessful such as DBS of PAG and/or VP (patients A, C, F, G, I, M, O). For other patients, widespread, poorly localized pain (patients B, D, E, H, J, K, L, N, P) led to ACC DBS being offered in the first instance.

### Surgical Methods

Our surgical technique for DBS was previously described.[8,16] Before surgery, each patient underwent a T2-weighted magnetic resonance imaging (MRI) scan with 1-mm slice thickness parallel to the anterior commissure-posterior commissure line for surgical planning. A Cosman-Roberts-Wells base ring (Radionics Inc, Burlington, Massachusetts) was applied to the patient's head while under local anesthesia. With the localizer frame attached to the base ring, a computed tomography scan with 1-mm slice thickness was performed and volumetrically fused with the MRI using the Neuroinspire planning system (Renishaw Inc, Bristol, United Kingdom). This system was then used to calculate target coordinates and define lead trajectory. The ACC target used was 20 mm posterior to the anterior tip of the frontal horns of the lateral ventricles Figure 1. The trajectory was chosen to position the contacts mostly in white matter, the cingulum bundle, with the deepest contact in the corpus callosum. For each lead, a 2.5-mm cranial perforation was made using a twist drill. A Radionics TC electrode (Cosman Medical Inc, Burlington, Massachusetts) was passed to target to create a tract and then removed and replaced with a Medtronic model 3387 depth lead (Medtronic Inc, Minneapolis, Minnesota). This lead is 1.27 mm in diameter and has 4 platinum-iridium contacts near its end, each occupying 1.5 mm of the lead length and spaced from the next by 1.5 mm. A postoperative computed tomography scan, fused to the preoperative MRI, confirmed electrode position. Leads were externalized via temporary extensions. The implanted pulse generator was introduced under the skin of the patient's upper chest after a 1-week trial period of stimulation on the ward.

### Pain Assessments

Pain and health-related quality of life measures were assessed before surgery and during follow-up. The Visual Analog Scale (VAS) and the McGill Pain Questionnaire were used.[17] The VAS extends from "no pain" (0) to "the worst pain you can imagine" (10), and the McGill Pain Questionnaire gives additional qualitative information in domains of

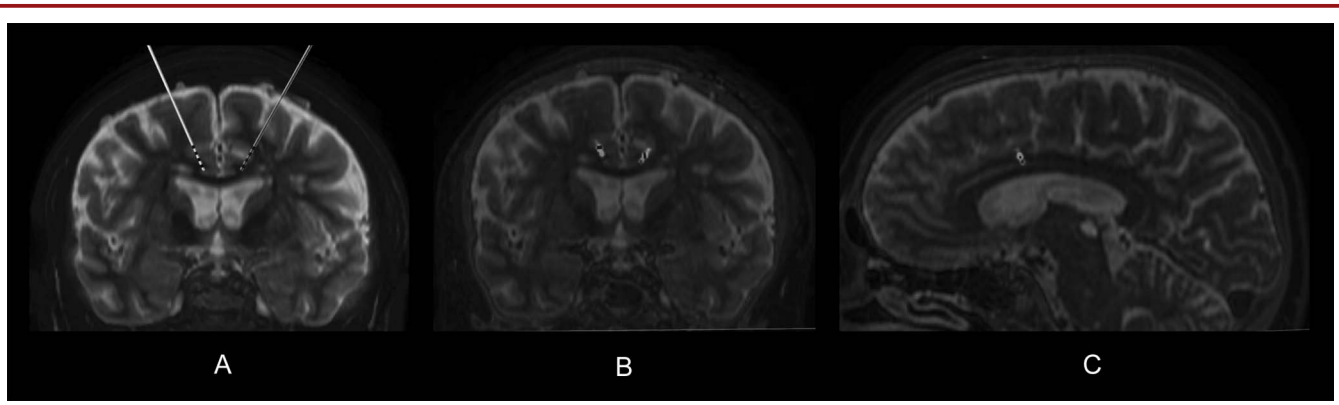


**FIGURE 1.** *Views of bilateral electrodes in the anterior cingulate cortex.* **A**, *preoperative trajectory planning.* **B**, *coronal view on a postoperative fused magnetic resonance/computed tomography (MR/CT) images.* **C**, *sagittal view on a postoperative fused MR/CT images.*

"sensory," "affective," "evaluative" and "miscellaneous" pain severity. Patients recorded their VAS scores during their good, bad and average days, pre-surgery and post-surgery. The VAS scores were reviewed to ensure consistency and the mean was then calculated. The McGill Pain Questionnaire was also completed before and after surgery and analyzed using the ranked pain rating index.[17]

Patients also completed the SF-36 and EQ-5D quality of life questionnaires alongside the pain questionnaires. SF-36 responses were regrouped into 8 domains of physical functioning, role - physical, bodily pain, general health, vitality, social functioning, role - emotional, and mental health. Results were scored using online tools.[18] Norm-based scores allowed comparison between studies. The SF-36 scores ranged from 0, an extreme of dysfunction or symptom severity, to 100, optimal function. The health state of patients was evaluated by EQ-5D. Its 2 sections evaluate first the health state in 5 dimensions (mobility, self-care, usual activities, pain, and anxiety) and second on a health VAS, with 0 being the worst state that they can imagine and 100 the best. EQ-5D scores were calculated as detailed elsewhere.[19]

Pre- and postoperative scores were compared using the Wilcoxon signed rank test, with a $P$ value of $<.05$ taken as statistically significant. For each patient, the time point for the postoperative data used in the analysis is given in Table 1.

### Stimulation Settings

Before implantation of the pulse generator, an evaluation of the effect of stimulation was performed with the following settings: 4 to 6.5 V, 130 Hz, and 450 μs. The deepest contact was used as the cathode and the most superficial as the anode.

## RESULTS

### Patients

Sixteen patients were treated: 13 men and 3 women, with a mean age of 48.7 years (range, 33-63 years). Causes of pain are shown in Table 2 and included failed back surgery syndrome (6 patients), poststroke pain (4 patients), brachial plexus injury (3 patients), cervical spinal cord injury (1 patient), head injury (1 patient), and pain of unknown cause (1 patient). Pain was located in the whole body (2 patients), hemibody (4 patients), back (2 patients), chest (1 patient), arms/hands (5 patients), or legs/feet (2 patients). The overall mean VAS score was 8.5 (range, 5-10) before surgery.

### Outcome

Of the 16 patients treated, 15 (93.8%) went on to full implantation. During the follow-up period, 5 patients had their DBS electrode removed for various reasons: insufficient pain relief (patients A, E, and G), inability to comply with treatment (patient C), and infection (patient D). Among them, 4 patients (all but patient D) were excluded from analysis because of insufficient data. Mean follow-up of outcomes was 13.2 months (range, 1-36 months) for the 11 patients whose results were analyzed. Figure 2 and Table 3 summarize their pain and quality of life.

### Main Results

Post-surgery, VAS score improved by 24.5% (range, −42% to +100%; $P$ = .083). It dropped below 4 for 5 patients (patients H, B, N, O, and K), with 1 patient free of pain at 17 months (patient K). The SF-36 score was not noticeably increased (7.3%; range, −40.1% to +46.6%; $P$ = .48), but the physical functioning and bodily pain domains had a statistically significant increase of 64.7% (range, +8.9%-+276%; $P$ = .015) and 39.0% (range, −33.8% to +159%; $P$ = .050). A significant improvement in EQ-5D scores was observed after surgery (+20.3%; range, 0%-+83%; $P$ = .008). There were nonsignificant improvements in McGill Pain Questionnaire mean score (+16.0%; range, −77% to +100%; $P$ = .23) and overall health state as self-reported on the VAS (+30.0%; range, −80% to +150%; $P$ = .24).

### Stimulation Parameters

Mean stimulation parameters were 5 V (range, 4-6.9 V), at 128.6 Hz (range, 120-130 Hz). A pulse width of 450 μs across all 4 electrode contacts was used.

### Affective Component of Pain

In keeping with the theory that the ACC is involved in processing the affective component of pain, improved patients did not always describe a decrease in their pain intensity. VAS scores did not correlate with quality-of-life improvements. Several patients described feeling as if their pain was separate from them physically and said that they did not think about it anymore, although they could still sense it.

## DISCUSSION

### Background and Rationale

Chronic pain is a multifaceted experience, with cognitive, affective, and sensory-discriminative aspects. The ACC has been shown to be involved in the affective aspects of pain.[10] Suffering has general effects on mood, disability, and employment. Assessing quality-of-life and psychological factors in addition to measuring VAS is desirable to capture the improvement seen by relieving distress, anticipation, misery, and incapacity. We found that quality of life improved with ACC DBS to a greater extent than pain VAS scores.

The dorsal ACC is a heterogeneous brain region that, among other things, is involved in conferring emotional valence to pain. It also has roles in sensory, motor, and cognitive processing, including visceromotor, skeletomotor and endocrine outflow, maternal behavior, vocalization, attention to action, and responses to painful stimuli.[20] Brodmann area 24 within the dorsal ACC can be subdivided into a rostral part more involved in affective processing and a more caudal region subserving cognition and motor functions with projections to the spinal cord and red nucleus.[11]

Dissociation of nociception from the suffering of pain was first noted during surgery for psychiatric disorders. Besides Cairns' cingulotomies, Watts and Freeman[21] observed that their patients with frontal lobotomy were not bothered by their pain. Later, cingulotomy by electrocoagulation, performed by Foltz and coworkers,[22] decreased the unpleasantness of patients' pain but did not affect their ability to discern pain intensity, reporting

**TABLE 1.** Pre- and Postoperative Data: Individual Pain Assessment Scores of Each Patient Preoperatively and Throughout Follow-up[a]

| Patient | Follow-up, mo | VAS | Sensory | Affective | Evaluative | Misc. | MPQ Total | PF | RP | BP | GH | VT | SF | RE | MH | SF-36 Total | EQ-5d | Health State[b] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| B | 0 | 6.7 | 28 | 1 | 4 | 10 | 43 | 15.2 | 28 | 29.3 | 27.5 | 49.1 | 19.1 | 23.7 | 50.4 | 242.3 | 5 | 20 |
| | **17** | **3** | **25** | **0** | **0** | **0** | **25** | **15.2** | **28** | **33.2** | **19.5** | **51.4** | **19.1** | **23.7** | **57.3** | **247.4** | **5** | **50** |
| | 30 | 5 | N/A | | | | | 19.4 | 28 | 33.2 | 24.2 | 51.4 | 24.6 | 23.7 | 59.5 | 264 | N/A | |
| D | 0 | 8.3 | 17 | 4 | 4 | 13 | 38 | 15.2 | 28 | 19.9 | 28.9 | 37.2 | 30 | 44.8 | 39.1 | 243.1 | 6 | 25 |
| | **6** | **8** | **25** | **2** | **7** | **9** | **43** | **57.1** | **35** | **24.2** | **34.5** | **23** | **35.4** | **55.3** | **48.2** | **312.7** | **5** | / |
| E | 0 | 8 | 6 | 6 | 5 | 10 | 27 | 15.2 | 28 | 25.1 | 21.9 | 23 | 13.7 | 23.7 | 20.9 | 171.5 | 8 | 15 |
| | 5 | 8 | 23 | 1 | 3 | 5 | 32 | 19.4 | 28 | 25.1 | 33.6 | 32.5 | 19.1 | 23.7 | 39.1 | 220.5 | 7 | 25 |
| | 12 | 7 | 17 | 9 | 4 | 2 | 32 | 15.2 | 28 | 29.3 | 36.8 | 32.5 | 24.6 | 23.7 | 36.8 | 226.9 | 6 | 25 |
| | 18 | 8 | 19 | 3 | 3 | 11 | 36 | 15.2 | 28 | 25.1 | 26.5 | 23 | 13.7 | 23.7 | 20.9 | 176.1 | 7 | 25 |
| | **36** | **8** | **15** | **5** | **4** | **11** | **35** | **15.2** | **28** | **29.3** | **28.9** | **27.8** | **19.1** | **23.7** | **32.3** | **204.3** | **7** | **20** |
| H | 0 | 10 | 22 | 4 | 5 | 5 | 36 | 15.2 | 28 | 19.9 | 54.6 | 32.5 | 24.6 | 55.3 | 34.5 | 265 | 6 | 77 |
| | 6 | 3 | 15 | 1 | 1 | 4 | 21 | 48.8 | 35 | 33.2 | 53.2 | 49.1 | 46.3 | 44.8 | 48.2 | 359 | 4 | 78 |
| | 8 | 3.5 | 6 | 0 | 3 | 2 | 11 | 42.5 | 28 | 37.5 | 55.6 | 51.4 | 46.3 | 34.3 | 59.5 | 355.1 | 1 | 95 |
| | **20** | **5.5** | **17** | **3** | **4** | **7** | **31** | **44.6** | **28** | **37.5** | **57.9** | **49.1** | **35.4** | **55.3** | **50.4** | **358.2** | **2** | **83** |
| J | 0 | 8 | 18 | 1 | 5 | 7 | 31 | 23.6 | 28 | 19.9 | 19.5 | 39.6 | 30 | 23.7 | 39.1 | 223 | 6 | 20 |
| | **5** | **10** | **12** | **3** | **5** | **8** | **28** | **21.5** | **28** | **19.9** | **17.2** | **30.1** | **24.6** | **23.7** | **20.9** | **186** | **6** | **20** |
| | 18 | N/A | 17 | 3 | 5 | 6 | 31 | 21.5 | 28 | 19.9 | 17.2 | 30.1 | 19.1 | 23.7 | 23.2 | 182.7 | 6 | 10 |
| K | 0 | 10 | 6 | 4 | 4 | 6 | 20 | 17.3 | 56.2 | 24.2 | 38.2 | 37.2 | 30 | 55.3 | 36.8 | 295.2 | 7 | 90 |
| | 3 | 0 | 1 | 1 | 0 | 3 | 5 | 17.3 | 56.2 | 62.7 | 43.9 | 44.3 | 46.3 | 55.3 | 50.4 | 376.4 | 4 | 60 |
| | **17** | **0** | **0** | **0** | **0** | **0** | **0** | **21.5** | **28** | **62.7** | **36.8** | **46.7** | **35.4** | **23.7** | **48.2** | **303** | **4** | **90** |
| L | 0 | 6.7 | 29 | 0 | 1 | 5 | 35 | 21.5 | 28 | 37.9 | 54.6 | 63.3 | 51.7 | 55.3 | 50.4 | 362.7 | 6 | 100 |
| | 5 | 8 | 18 | 17 | 0 | 9 | 44 | 38.5 | 28 | 37.9 | 45.3 | 42 | 35.4 | 23.7 | 34.5 | 285.3 | 5 | 70 |
| | **14** | **9.5** | **33** | **8** | **4** | **17** | **62** | **36.2** | **28** | **19.9** | **45.3** | **30.1** | **24.6** | **23.7** | **9.6** | **217.4** | **6** | **20** |
| M | 0 | 9 | 19 | 6 | 5 | 10 | 40 | 15.2 | 28 | 19.9 | 26.5 | 23 | 19.1 | 23.7 | 30 | 185 | 6 | 20 |
| | 1 | 5 | 11 | 0 | 3 | 3 | 17 | 23.6 | 28 | 25.1 | 28.9 | 25.4 | 24.6 | 23.7 | 34.5 | 214 | 6 | 15 |
| | **12** | **8** | **25** | **2** | **4** | **11** | **42** | **23.6** | **28** | **25.1** | **19.5** | **25.4** | **24.6** | **23.7** | **43.6** | **213.5** | **6** | **20** |
| N | 0 | 6 | 5 | 3 | 6 | 9 | 23 | 17.3 | 28 | 19.9 | 36.8 | 23 | 13.7 | 23.7 | 32.3 | 194.7 | 7 | 30 |
| | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 36.2 | 28 | 25.1 | 41.5 | 34.9 | 13.7 | 23.7 | 34.5 | 237.6 | 2 | 70 |
| | **9** | **3** | **5** | **2** | **2** | **5** | **14** | **27.8** | **35** | **37.5** | **40.6** | **30.1** | **24.6** | **55.3** | **34.5** | **285.4** | **6** | **60** |
| O | 0 | 5 | 15 | 16 | 8 | 18 | 57 | 27.8 | 28 | 29.3 | 41.5 | 32.5 | 35.4 | 55.3 | 34.5 | 284.3 | 5 | 25 |
| | 1 | 1 | 8 | 6 | 8 | 8 | 30 | 34.1 | 28 | 19.9 | 48.5 | 30.1 | 24.6 | 23.7 | 25.5 | 234.4 | 4 | 15 |
| | **8** | **3** | **32** | **6** | **3** | **8** | **49** | **29.9** | **28** | **37.5** | **46.2** | **39.6** | **30** | **34.3** | **36.8** | **282.3** | **4** | **35** |
| P | 0 | 9 | 32 | 0 | 5 | 8 | 45 | 34.1 | 28 | 19.9 | 61.7 | 56.2 | 24.6 | 55.3 | 57.3 | 337.1 | 6 | 30 |
| | 1 | 8 | 18 | 4 | 5 | 6 | 33 | 42.5 | 28 | 29.3 | 31.2 | 58.5 | 24.6 | 34.3 | 52.7 | 301.1 | 5 | 40 |

[a]VAS, Visual Analog Scale; Misc., miscellaneous; MPQ, McGill Pain Questionnaire; PF, physical functioning; RP, role-physical; BP, bodily pain; GH, general health; VT, vitality; SF, social functioning; RE, role-emotional; MH, mental health; N/A, not available. Numbers in bold numbers are follow-up data analyzed.
[b]Health State self-reported preoperatively and at follow-up.

**TABLE 2. Patients Demographic Characteristics and Preoperative Pain Data**[a]

| Patient | Sex | Age at Surgery, y | Pre- op VAS Score | Previous DBS | Pain | | Date of Surgery |
|---|---|---|---|---|---|---|---|
| | | | | | Location | Origin | |
| A | M | 49 | 9 | Bilateral PVG | Back | FBSS | Feb 07 |
| B | M | 49 | 6.7 | | Whole body | FBSS | Jan 09 |
| C | F | 42 | 8 | Bilateral PVG-VPL | Right leg | Post stroke | Jul 09 |
| D | M | 44 | 8.3 | | Both arms | SCI, tetraplegia | Jul 10 |
| E | M | 51 | 8 | | Right leg | FBSS | Oct 10 |
| F | M | 33 | 10.0 | Bilateral PVG-VPL | Left arm | Brachial plexus injury | Sep 11 |
| G | M | 52 | 10 | Bilateral PVG-VPL | Chest | Unknown | Nov 11 |
| H | F | 46 | 10.0 | | Whole spine | FBSS | Mar 12 |
| I | F | 58 | 9 | Bilateral VPL | Right hemibody | Head injury | May 12 |
| J | M | 53 | 8.0 | | Right hand | Post stroke | May 12 |
| K | M | 49 | 10 | | Right hemibody | FBSS | Jun 12 |
| L | M | 63 | 9.0 | | Right hemibody | Post stroke | Sep 12 |
| M | M | 46 | 6.7 | Bilateral PVG-VPL | Right arm | Brachial plexus injury | Nov 12 |
| N | M | 58 | 6.0 | | Left arm | Brachial plexus injury | Feb 13 |
| O | M | 48 | 5 | Right PVG | Right hemibody | Post stroke | Mar 13 |
| P | M | 39 | 9.0 | | Whole body | FBSS | Nov 13 |
| Mean | | 48.7 | 8.5 | | | | |
| SD | | 7.5 | 1.6 | | | | |

| Patient | Sex | Complications | Follow-up Course | | | Data Analyzed | Comments |
|---|---|---|---|---|---|---|---|
| | | | Current State | Reason | Date | | |
| A | M | | IPG removed | No pain relief | Mar 09 | | Electrodes too anterior |
| B | M | | DBS on | | Jan 11 | 17 mo | No early follow-up available |
| C | F | | DBS removed | Unable to comply with treatment | Sep 09 | | |
| D | M | Infection | DBS removed | Infection | Apr13 | 6 mo | |
| E | M | Right wire broken | DBS on | | Nov 13 | 36 mo | |
| F | M | | DBS removed | Insufficient pain relief | May 12 | | |
| G | M | | DBS removed | Insufficient pain relief | May 12 | | |
| H | F | | DBS on | | Nov 13 | 20 mo | |
| I | F | | IPG not implanted | No pain relief before IPG implantation | May 12 | | |
| J | M | Infection + eczema | DBS on | | Nov 13 | 5 mo | |
| K | M | | DBS on | | Nov 13 | 17 mo | |
| L | M | | DBS on | | Nov 13 | 14 mo | |
| M | M | | DBS on | | Nov 13 | 12 mo | |
| N | M | Seizure | DBS on | | Nov 13 | 9 mo | |
| O | M | | DBS on | | Nov 13 | 8 mo | |
| P | M | | DBS on | | Dec13 | 1 mo | |
| Mean | | | | | | | |
| SD | | | | | | | |

[a]VAS, Visual Analog Scale; Pre-op, preoperative; DBS, deep brain stimulation; M, male; PVG, periventricular gray area; FBSS, failed back surgery syndrome; F, female; VPL, ventral posterolateral thalamus; SCI, spinal cord injury; IPG, implanted pulse generator.

good or excellent relief in 9 of 11 patients. Furthermore, cingulotomy was reported to induce indifference to pain[23] and apathy.[24]

Several studies performed with positron emission tomography or functional MRI showed pain-related activation of the ACC in humans.[25,26] Hutchison et al also found in humans neurons responding specifically to painful stimuli.[27] Interestingly, another study established that DBS of the thalamus in 5 patients with chronic pain generated activity in the rostral and dorsal ACC,[26,28] as did single-photon emission tomography and magnetoencephalography studies with human subjects receiving PAG, thalamic or dual PAG, and VP DBS.[28-30] Recently, our group has shown PAG activation with ACC DBS in addition to long-term changes in ACC activity with ACC DBS.[31]

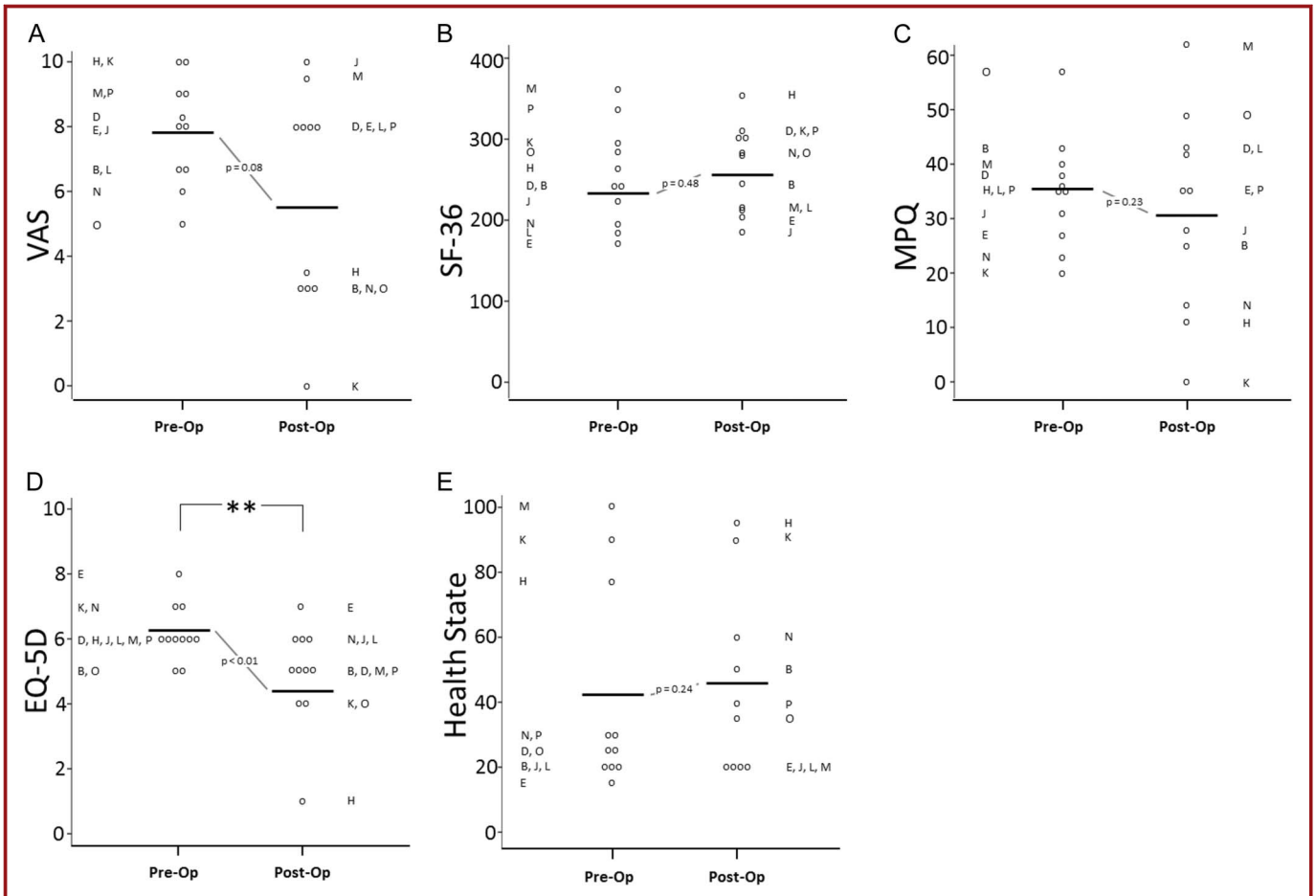


**FIGURE 2.** *Anterior cingulate cortex deep brain stimulation patient outcomes.* **A**, *Visual Analog Scale (VAS).* **B**, *SF-36.* **C**, *McGill Pain Questionnaire (MPQ).* **D**, *EQ-5D.* **E**, *EQ-5D health state self-reported, before (pre-op) and after surgery (post-op) (from 5 to 36 months after surgery). Each dot represents a patient, identified by a letter (B to O). The pre-op and post-op means are indicated by the horizontal line.*

The justification for targeting the ACC in this series derives both from the aforementioned neuroimaging evidence and successful case series of cingulotomy to relieve cancer pain.[14] A review by Cosgrove and coworkers a decade ago reported that this surgery was beneficial in 80 (52%), but not in 73 patients (48%).[32] Fallaice et al described 3 of 7 cancer pain patients improved for 3 days to 3 months,[33] and Hurt and Ballantine reported 12 of 32 patients with marked or complete pain relief at up to 3-month follow-up.[34] Hassenbusch found 6 of 12 patients with cancer pain gaining good or excellent analgesia after mean follow-up of 13 months, concluding it was useful as a palliative procedure for high-grade or late-stage malignancy and for severe pain of musculoskeletal origin and less beneficial for thalamic and other neuropathic pain syndromes.[35,36] Wong et al reported 3 patients with metastatic cancer pain improved by cingulotomy.[37] The largest reported case series of 35 patients with cancer pain by Ballantine et al reported 20 patients (57%) with satisfactory pain relief 3 months after surgery, with efficacious analgesia persisting in only 2 of 10 patients surviving longer.[38] Spooner et al, in 2007, reported the first dorsal ACC DBS. The patient with cervical spinal cord injury and whole-body pain showed greater improvements in pain and mood with bilateral ACC DBS compared with unilateral PAG DBS 4 months postoperatively. No long-term follow-up was recorded due to the patient's death from pulmonary complications 1 year after surgery.[39]

Neuromodulation of this area of the brain and its neighboring areas has also been performed for other affective and psychiatric disorders. DBS of the subgenual cingulate white matter is used for obsessive-compulsive disorder and depression,[40,41] and DBS of the anterior limb of internal capsule for obsessive-compulsive disorder was approved by the US Food and Drug Administration in 2009. In addition, the anterior limb of internal capsule/nucleus accumbens has been presented as a potential target for the affective component of central post stroke pain.[42] During the trial week before the implantation of the implanted pulse generator, the patients here preferred stimulation settings with

**TABLE 3. Pain Assessment Scores and Pain Improvement for the 11 Patients With Follow-up**[a]

| | | Preop | | | | Postop | | | | Pain Improvement | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | No. | Min | Max | Mean | No. | Min | Max | Mean | Min | Max | Mean | *P* Value[b] |
| VAS | | 11 | 5 | 10 | **7.9** | 11 | 0 | 10 | **5.8** | −42 | 100 | **24.5** | .083 |
| MPQ | Sensory | 11 | 5 | 32 | **17.9** | 11 | 0 | 33 | **17.8** | −150 | 100 | **−10.0** | .919 |
| | Affective | 11 | 0 | 16 | **4.1** | 11 | 0 | 8 | **2.9** | −200 | 100 | **20.8** | .501 |
| | Evaluative | 11 | 1 | 8 | **4.7** | 11 | 0 | 7 | **3.4** | −300 | 100 | **3.1** | .108 |
| | Miscellaneous | 11 | 5 | 18 | **9.2** | 11 | 0 | 17 | **7.0** | −120 | 100 | **18.3** | .229 |
| | Total | 11 | 20 | 57 | **35.9** | 11 | 0 | 62 | **31.1** | −77 | 100 | **16.0** | .230 |
| SF-36 | PF | 11 | 15.2 | 34.1 | **19.8** | 11 | 15.2 | 57.1 | **30.3** | −8.9 | 275.7 | **64.7** | **.015** |
| | RP | 11 | 28.0 | 56.2 | **30.6** | 11 | 28.0 | 35.0 | **29.3** | −50.2 | 25.0 | **0.0** | 1.000 |
| | BP | 11 | 19.9 | 37.9 | **24.1** | 11 | 19.9 | 62.7 | **32.4** | −33.8 | 159.1 | **39.0** | **.050** |
| | GH | 11 | 19.5 | 61.7 | **37.4** | 11 | 17.2 | 55.6 | **34.1** | −64.3 | 70.9 | **−1.1** | .929 |
| | VT | 11 | 23.0 | 63.3 | **37.9** | 11 | 23.0 | 58.5 | **37.6** | −59.9 | 58.2 | **6.8** | .624 |
| | SF | 11 | 13.7 | 51.7 | **26.5** | 11 | 19.1 | 46.3 | **28.0** | −52.4 | 88.2 | **16.9** | .366 |
| | RE | 11 | 23.7 | 55.3 | **40.0** | 11 | 23.7 | 55.3 | **32.3** | −57.1 | 133.3 | **−6.5** | .230 |
| | MH | 11 | 20.9 | 57.3 | **38.7** | 11 | 9.6 | 59.5 | **40.3** | −68.0 | 72.5 | **6.6** | .533 |
| | Total | 11 | 171.5 | 362.7 | **254.9** | 11 | 185.9 | 355.1 | **264.4** | −40.1 | 46.6 | **7.3** | .477 |
| EQ-5D | EQ-5D | 11 | 5 | 8 | **6.2** | 11 | 1 | 7 | **4.9** | 0 | 83 | **20.3** | **.008** |
| | Health State | 11 | 15 | 100 | **41.1** | 10 | 20 | 95 | **45.0** | −80 | 150 | **30.0** | .235 |

[a]Preop, preoperative; Postop, postoperative; Min, minimum; Max, maximum; VAS, Visual Analog Scale; MPQ, McGill Pain Questionnaire; PF, physical functioning; RP, role-physical; BP, bodily pain; GH, general health; VT, vitality; SF, social functioning; RE, role-emotional; MH, mental health. Health State part of EQ-5C self-reported before and at follow-up. Bold numbers indicate the follow-up data that was analyzed.
[b]Pre- and postoperative scores were compared using the Wilcoxon signed rank test.

the deepest contacts as active. These data suggest that the corpus callosum could play a role in the relief of neuropathic pain.

Interestingly, clinical improvement was usually not seen intraoperatively or immediately postoperatively in this ACC DBS cohort, but only after 2 to 3 days, in contrast with PAG or VP DBS.[8] Initial experience has guided our patient selection toward those patients without precise somatotopic localization of their pain, often with pain after stroke and with significant impairment to their quality of life.

In our study, electrodes were implanted mostly in the white matter, 20 mm posterior to the anterior tip of the frontal horns of the lateral ventricles, with the deepest contacts in the corpus callosum and the upper electrodes in the cingulum bundle. However, as efficacy varies between patients, individually tailored targeting may be desirable. We are currently using magnetic resonance tractography to investigate this possibility.

### Key Results

All patients but 1 transitioned from externalized to fully internalized systems. Postsurgery, pain, as reported on the VAS, was less than 4 for 5 patients, with 1 patient rendered pain free. A significant improvement in quality of life (EQ-5D) was observed. Moreover, statistically significant improvements were gained in some domains of the SF-36.

### Limitations

The study is a pilot study with limited follow-up, and there are inevitable "learning curves" to patient selection and surgical targeting. We expect that results will improve with a larger case series. The main limitations are those of an open-label trial, and randomization would be desirable, as described in the recent study protocol of DBS for thalamic pain syndrome.[23] Moreover, pain assessments targeting the affective component of pain may be preferable to evaluate improvements.

### Interpretation

Patients tend to describe that some pain is still present, but that it does not bother them anymore. Consequently, little or no improvement inf the pain VAS score does not necessarily equate to poor therapeutic efficacy. Furthermore, as the primary effect is not pain alleviation, patient satisfaction may appear lower. Nevertheless, a demonstrably improved performance in quality of life was seen in this cohort.

### Generalizability

Patients in this study were patients with intractable pain that prevented them from living a normal life. DBS of the ACC improved quality of life by lessening the impact of pain on them.

## CONCLUSION

Here we demonstrate that DBS of the ACC can significantly alleviate the suffering of patients with otherwise treatment-resistant chronic pain. This provides a promising avenue for patients for whom other treatments including PAG and VP DBS are ineffective.[8]

## Disclosure

The research was supported by the National Institute for Health Research (NIHR) Oxford Biomedical Research Centre based at Oxford University Hospitals NHS Trust and University of Oxford. The views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health. The authors have no personal financial or institutional interest in any of the drugs, materials, or devices described in this article.

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## COMMENTS

This is an interesting small cohort study of patients with refractory pain, even to most invasive pain treatment as deep brain stimulation in the somatosensory thalamus and the periaqueductal gray matter. The authors provide us with 15 of 16 patients who underwent long-term bilateral stimulation of the anterior cingulate cortex after trial stimulation. Although the pain relief was not significant in the cohort, considerable decreases in the VAS scores were observed in some of the patients, and significant changes were found for the whole cohort in different quality-of-life measures as SF-36 and EQ-5D. This leads to the assumption that stimulation in the secondary pain-processing areas of the pain matrix affective components of the pain and most likely the attention to pain can be treated by long-term stimulation. The long-

term effect, however, has to been awaited yet. Not unexpectedly in a series with highly selected patients, there are several limitations of this study. The number of patients is too small to formulate strong conclusions, especially because one-third dropped out for different reasons. The pain syndromes are very heterogeneous. The area within the ACC stimulated is quite large (large pulse width, high voltages, and stimulation over all contacts). It is not clear whether a blinded stimulation was performed. The role of the corpus callosum in pain suppression is highly speculative. Nevertheless this is a new approach in patients refractory to the conventional targets of DBS. We would recommend that the authors create a larger cohort and combine the findings with functional imaging as diffusion tensor imaging, resting-state MRI, and opioid receptor positron emission tomography.

**Volker Tronnier**
*Lübeck, Germany*

Chronic pain and central pain syndromes in particular are among the most challenging conditions facing the functional neurosurgeon. The response to medical therapy is often unsatisfactory, and the features can be severe and disabling. Several procedures targeting everything from the nerve to the cortex have been developed. Despite some advances, a clear understanding of underlying mechanisms and predictors of response remains elusive. Complicating the picture are the perceptual, cognitive, and affective components of pain, which contribute to its impact and persistence. The affective or suffering component has been especially underappreciated in the pain field, a fact that the authors of this paper try to remedy. This paper describes the authors' experience with deep brain stimulation (DBS) of the anterior cingulate in chronic treatment-refractory pain. Their prospective, open-label study in 15 patients is the first and largest series to date of DBS at this target for this indication. Their hypothesis is that targeting a limbic structure would influence the affective component of pain and contribute to reductions of the "unpleasantness" associated with pain. Cingulate lesioning surgery for pain has been performed for decades as has DBS in the thalamus and periventricular/periaqueductal system. The uniqueness and novelty here are the application of DBS for pain at the cingulotomy target. The authors are to be congratulated for their pioneering efforts to tackle this formidable problem. The strengths of this paper are its relatively large sample size and the diverse array of measures and scales used to assess pain and quality of life. In addition, the authors have leveraged several decades of experience with cingulotomy for pain, and in particular cancer pain, by positing an important role for the limbic system in the pain experience. The ability to titrate stimulation parameters with DBS is certainly an advantage, but it remains unclear whether lesioning the cingulate and stimulating it have the same underlying mechanisms and clinical effects. Although promising, it is important to also be aware of the limitations of the study. In keeping with the phase I nature, this study is not sham-stimulation controlled, so it is not possible to ascribe the observed effect to stimulation. There is clearly much room for additional investigation, and the authors have made a worthy and interesting contribution to our understanding of the pain experience and its management.

**Nir Lipsman**
**Andres M. Lozano**
*Toronto, Ontario, Canada*

The authors present an interesting case series in which they used deep brain stimulation (DBS) of the anterior cingulate cortex (ACC) to improve quality of life in patients with treatment-resistant pain. The ACC was considered a good target for neuromodulation due to earlier reviews showing the effectiveness of cingulotomy in controlling malignant pain. For this study, patients had been refractory to pain medications for at least 2 years, and in some patients previous DBS of the periventricular gray (PVG) and/or ventral posterolateral thalamus (VPL) had failed. Before ACC-DBS surgery, the mean pain intensity was determined with a visual analog scale (VAS) conducted twice daily for 14 days. Patients also completed the McGill Pain Questionnaire (MPQ), the SF-36 quality of life survey, and the EQ-5D quality of life questionnaire. Of the 16 patients found suitable for ACC-DBS, 15 had the devices fully implanted, and 11 patients completed follow-up testing including the VAS, MPQ, SF-36, and EQ-5D. VAS scores did not significantly improve for the group as a whole, although 5 patients saw their scores drop below 4, and 1 patient was free of pain at follow-up testing. MPQ scores also did not significantly improve. In contrast, both the physical functioning and bodily pain domains of the SF-36 significantly increased, and the EQ-5D scores also significantly improved. VAS scores did not correlate with quality-of-life improvements, and the authors noted that patient reports suggested that patients may still feel the same pain intensity but saw that pain as separate from themselves. Together, these results led to the conclusion that ACC-DBS was improving patient quality of life despite not significantly lowering pain intensity and that this action may be due to ACC-DBS dampening the affective component of pain. The authors are to be complimented on including this variety of pain and quality-of-life scales in the design of this study. Pain is known to be a multifaceted experience brought about through several parallel pathways,[1] and reliance on a single measure limits the scope of our understanding of the pain experience. Further, as the authors note in this study, a lack of improvement in 1 measure of pain (VAS, pain intensity) does not mean that the treatment lacks efficacy. Here, we see that patients experienced improved quality of life without a significant reduction in pain intensity. We have had difficulties in our own assessments using VAS, both because it only assesses pain intensity and because patients tend to answer in the moment rather than giving a global score. The authors of this study tried to account for the latter by having patients keep a 2-week preoperative VAS diary that allowed the determination of a mean VAS score. Alternatively, we augment our own VAS by using 10- or 100-point scales to describe pain intensity at its worst, at its best, during the majority of the day, and currently. We also ask patients to score their global impression of how much their pain has changed since device implantation, as patient global impression of change scores are still the gold standard for determining meaningful clinical change in many areas of research.[2] Much like the authors, we too use a variety of questionnaires to assess outcomes beyond pain intensity and strongly encourage other pain researchers to do the same. A final concern is that chronic pain patients may have relief of 1 area of pain that unmasks pain in a different region, an effect that could conceal any effects of a treatment on pain intensity. Patient self-reports in this study suggest that ACC-DBS could be improving quality of life, in part or full, by changing the affective component of pain. Confirmation of this potential ACC-DBS mechanism will require more sensitive affective measures than were included, for example, by adding a structured interview pre- and postoperatively on the affective component of pain to the current MPQ measure. If this mechanism is confirmed, it will emphasize the importance of assessing patient for all

facets of the pain experience. In all, this study was an excellent first step in showing quality-of-life improvements after ACC-DBS.

**Joannalee C. Campbell**
**Julie G. Pilitsis**
*Albany, New York*

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## CME QUESTIONS:

1. The dorsal anterior cingulate cortex (dACC) is responsible for what aspect of pain?
   A. Affective
   B. Nociceptive
   C. Somatosensory
   D. Neurogenic
   E. Psychosomatic

2. What white matter bundle is located immediately inferior to the cingulate cortex?
   A. Cingulum
   B. Corpus callosum
   C. Anterior commissure
   D. Fornix
   E. Corona radiata

3. What deep brain structure is most commonly targeted for deep brain stimulation for chronic nociceptive pain?
   A. Subthalamic nucleus (STN)
   B. Globus pallidus internus GPi
   C. Anterior limb of the internal capsule (ALIC)
   D. Ventral intermediate nucleus (VIM)
   E. Periaqueductal grey (PAG)