Deep brain stimulation of the anterior cingulate cortex: targeting the affective component of chronic pain

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Deep brain stimulation (DBS) has shown promise for relieving nociceptive and neuropathic symptoms of refractory chronic pain. We assessed the efficacy of a new target for the affective component of pain, the anterior cingulate cortex (ACC). A 49-year-old man with neuropathic pain underwent bilateral ACC DBS. Patient-reported outcome measures were collected before and 2 years after surgery using a Visual Analogue Scale, Short-Form 36 quality of life survey, McGill pain questionnaire, EuroQol-5D questionnaires (EQ-5D; Health State) and neuropsychological assessments. The patient improved with DBS. Two years after surgery, the Visual Analogue Scale decreased from 6.7 to 3.0, McGill pain questionnaire improved by 42% and EQ-5D Health State increased by 150%. Stimulating the ACC at 130 Hz, 330 μs and 3 V facilitated neuropathic pain relief. The DBS remained efficacious during the 2-year follow-up period. Affective ACC DBS can relieve chronic neuropathic pain refractory to pharmacotherapy and restore quality of life. *NeuroReport* 25:83–88 © 2014 Wolters Kluwer Health | Lippincott Williams & Wilkins.

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Introduction

Chronic pain poses a huge disease burden, with a prevalence of up to 8% in the general population [1]. Deep brain stimulation (DBS) has provided an alternative for pharmacoresistant neuropathic pain since it was first introduced over 60 years ago [2]. As described in a recent comprehensive case series [3], DBS of periaqueductal gray area (PAG) and of the sensory thalamus (VP) has been utilized with various degrees of success for diverse types of pain.

Pain is an integrated experience with sensory, affective and cognitive dimensions [4]. Some patients may benefit from targeting limbic structures implicated in modulating the affective component – the suffering – mainly responsible for the pain-related disability. The anterior cingulate cortex (ACC) is one of these structures [5] and it is involved in pain expectation [6]. Its neurosurgical destruction has been performed to relieve intractable pain, in particular cancer pain [7,8].

Here, we report the first case of long-term bilateral ACC DBS to relieve the affective component of chronic neuropathic pain.

Patient and methods

Medical history

A 49-year-old man presented with a 20-year history of chronic pain traceable to several motorcycle accidents beginning 10 years earlier. His injuries led to a brachial plexus injury of the right arm. He underwent reconstructive surgery and a few years later, an anterior cervical decompression. Subsequently, he developed a cervical myelopathy that was treated by a laminoplasty with fusion. Later, he started to feel pain in his legs and feet. The pain was unrelieved by dihydrocodeine and high-dose gabapentin. He then underwent a lumbar laminectomy that improved his pain and mobility. The patient progressively developed an almost whole-body pain, predominantly severe burning, itching joint pain and pain that felt like a 'vice' in his groin. Pain was all along his spine, legs and feet, with a Visual Analogue Scale score for pain (VAS) of 10/10 most of the time. He was referred to a pain relief unit, where many drugs and transcutaneous electrical nerve stimulation were tested, without success. He became depressed and suicidal. He was then offered DBS of the ACC for the affective component of his pain.

Preoperative neuropsychological results confirmed predominantly average cognitive and memory functioning, with nonverbal intelligence quotient falling in the middle of the average range. Cognitive processing speed was impaired (Symbol Digit Modality Test first centile, written and oral). Normal performance was evident on tests of verbal memory, visuospatial function and on tests of executive function, apart from the Stroop Task, where performance was very poor (first centile).

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Deep brain stimulation procedure

Before surgery, the patient underwent a T2-weighted MRI scan with 1 mm slice thickness parallel to the AC-PC line for surgical planning. A Cosman-Roberts-Wells base Ring (Radionics Inc., Burlington, Massachusetts, USA) was applied to the patient's head under local anaesthesia. 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, UK). This system was then used to calculate target coordinates and define the lead trajectory. The ACC target used was 20 mm posterior to the anterior tip of the frontal horns of the lateral ventricles (Fig. 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 skull perforation was made using a twist drill. A TM probe was passed to create a tract and then removed and replaced with a Medtronic model 3387 depth lead (Medtronic Inc., Minneapolis, Minnesota, USA). This lead is 1.27 mm in diameter and has four 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 by temporary extensions.

Before implantation of the generator, an evaluation of the effect of stimulation was performed with the following settings: 3 V, 130 Hz and 330 μs. The deepest contact was used as the cathode and the most superficial one was the anode.

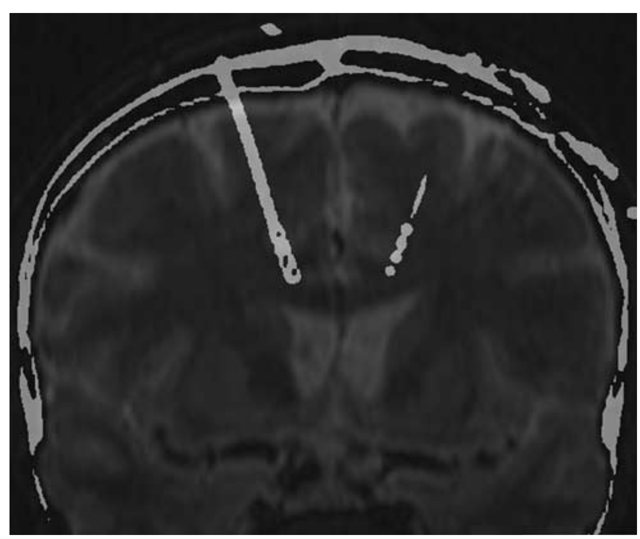
Pain and neuropsychological assessments

Pain and health-related quality-of-life measures were assessed before surgery and during follow-up. The VAS and the McGill pain questionnaire (MPQ) were used [9]. The VAS extends from 'no pain' (0) to 'the worst pain you can imagine' (10) and the MPQ provides additional qualitative information in domains of 'sensory', 'affective', 'evaluative,' and 'miscellaneous' pain severity.

The patient also completed Short-Form 36 (SF-36) and Euroqol 5 domain (EQ-5D) quality-of-life questionnaires alongside the pain questionnaires. SF-36 responses were regrouped into eight domains of Physical Functioning, Role – Physical, Bodily Pain, General Health, Vitality, Social Functioning, Role – Emotional and Mental Health. Results were scored using online tools [10]. Norm-based scores allowed comparison between studies. The SF-36 scale ranged from a score of 0, an extreme of dysfunction or symptom severity, to 100, optimal function. The health state of patients was evaluated by EQ-5D. Its two sections evaluate first the health state in five dimensions (mobility, self-care, usual activities, pain and anxiety) and second on a 'health' VAS, with 0 being the worst state they can imagine and 100 the best. EQ-5D scores were calculated as detailed elsewhere [11].

The neuropsychological assessment protocol is administered routinely to pain patients undergoing DBS in Oxford and includes a semistructured interview. The protocol also includes the following tests: Raven's Standard Progressive Matrices; categorical verbal fluency; phonetic verbal fluency; articulation rate; story recall from the Adult Memory and Information Processing Battery; word and face recognition tests from the Camden Recognition Memory Test; Repeatable Episodic Memory Test; Medical College of Georgia Complex

Fig. 1



Coronal view of bilateral electrodes in the anterior cingulate cortex.

Table 1 Pain score for each assessment at consecutive follow-up times

		McGill Pain Questionnaire					SF-36-norm-based scale scores									EQ-5D	
	VAS	Sensory	Affective	Evaluative	Miscellaneous	Total	PF	RP	BP	GH	VT	SF	RE	MH	Total	EQ-5D	Health state
Pre-Op	6.7	28	1	4	10	43	15.2	28.0	29.3	27.5	49.1	19.1	23.7	50.4	242.3	5.0	20
1 year	4.0	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
2 years	3.0	25	0	0	0	25	15.2	28.0	33.2	19.5	51.4	19.1	23.7	57.3	247.4	5.0	50

BP, Bodily Pain; EQ-5D, EuroQol-5D Questionnaire; GH, General Health; MH, Mental Health; PF, Physical Functioning; Pre-op, presurgery; RE, Role – Emotional; RP, Role – Physical; SF-36, Short-Form 36-Question quality-of-life survey; SF, Social Functioning; VAS, Visual Analogue Scale for pain; VT, Vitality.

Table 2 Frontal system behaviour scale from the patient's and his wife's perspective

Frontal system behaviour scale	Wife		Patient	
	Pre-Op	1 year	Pre-Op	1 year
1. Speaks only when spoken to	1	1	1	1
2. Angered or irritated	3	2	1	2
3. Repeat actions or get stuck	3	4	1	3
4. Impulsivity	2	1	1	2
5. Get confused when doing several things in a row	3	4	1	3
6. Laughs or cries easily	2	4	1	1
7. Makes the same mistakes again and again	4	5	1	2
8. Lack of initiative, motivation	2	3	1	3
9. Too flirtatious	1		1	1
10. Does or says embarrassing things	3	4	1	1
11. Neglects intimate hygiene	2	3	1	1
12. Hyperactive	2	3	1	1
13. Unaware having problems/denies them	4	4	1	2
14. Sits around doing nothing	2	5	1	2
15. Disorganized	5	5	1	3
16. Loses control of urine or bowels and seems unconcerned	1	1	1	1
17. Cannot do two things at once	2	4	1	2
18. Talks out of turn	5	5	1	1
19. Shows poor judgment	3	3	1	1
20. Makes up fantastic stories when can't remember something	1	1	1	1
21. Lost interest in things that used to be important/fun to him	1	5	1	2
22. Says one thing and then does another	3	5	1	2
23. Starts things but fails to finish them	3	5	1	3
24. Shows little emotion, unconcerned or unresponsive	3	3	1	1
25. Forgets to do things but then remembers when prompted	3	5	1	4
26. Inflexible, unable to change routines	2	5	4	3
27. Gets in trouble with law or authorities	1	1		
28. Does risky things just for the heck of it	3	1	3	1
29. Slow moving, lacks energy, inactive	1	5	1	4
30. Oversilly, childish sense of humour	3	5	1	2
31. Complains that food has no smell or taste	2	1	1	1
32. Swears	5	5	2	2
33. Apologizes for misbehaviour	1	1	1	1
34. Pays attention	1	1	1	3
35. Thinks things through before acting	3	4	1	2
36. Uses strategies to remember important things	1	1	1	2
37. Is able to plan ahead	1	1	1	3
38. Is interested in sex	5	3	4	3
39. Cares about his appearance	3	4	4	2
40. Benefits from feed-back	1	1	5	2
41. Gets involved with activities spontaneously	4	2	3	1
42. Does things without being requested to do so	3	3	4	2
43. Sensitive to the needs of other people	3	3	4	4
44. Gets along well with others	4	5	5	5
45. Acts appropriately for his age	3	3	3	3
46. Starts conversation spontaneously	3	5	4	4

Each item is rated on a five-point likert scale (minimum score = 1 and maximum score = 5).
Pre-op, presurgery.

Figures; the Stroop Colour-Word Test; the Judgement of Line Orientation Test; digit span from the Wechsler Adult Intelligence Scale; the Symbol Digit Modalities Test; Intra/Extra-Dimensional Set-Shifting Test, Spatial Span and Spatial Working Memory tests from the Cambridge Neuropsychological Automated Battery. Self and carer forms of the Frontal Systems Behaviour Scale (FrSBE) were completed by the patient and his wife.

Results

After several days of stimulation, the burning body pain had resolved but the patient complained of extreme tenderness to the soles of his feet. Settings were altered to 2.5 V, 130 Hz and 330 μs. Two months after surgery, pain was considerably reduced and the patient's mood had improved considerably. At 4 months of follow-up, pain in the heels was 'warm', not burning anymore. Ten months after surgery, the patient reported himself '300% better', with no burning pain. His mobility and his sleep had also improved. Moreover, medication was no longer needed. However, 1 year after surgery, the pain increased, the patient's feet were 'burning' again and his mobility became problematic. As headaches appeared, the DBS was switched off for a month. The implanted pulse generator was then switched on again with new settings: 4 V, 130 Hz and 450 μs. The patient felt a 'rushing

Table 3 **Neuropsychological assessments before surgery (pre-op) and at the 2-year follow-up**

			Pre-op		Two-year follow-up	
MSVT			Passed all three stages			
NART	Errors	Nart_e	31		–	
	Predicted FIQ	Nart_iq	92		–	
	Predicted VIQ	Nartviq	92		–	
SPM	A-C raw	Spm_raw	25	−0.42	26	−0.25
	Total raw	Spm_tot	32	−0.64	34	−0.44
	Predicted SPM from NART errors	Pr_spm	40		39.37	
	IQ	Spm_iq	101		104	
Fluency	Animals raw	Flu_an	22	0.52	26	1.48
	Tools raw	Flu_tl	16	0.90	26	3.40
	FAS raw	FAS	45	0.42	36	−0.42
	Predicted FAS from NART errors	Pr_FAS	33.94		33.94	
Speech motor	Mean articulation	Artic	10.70	0.04	10.67	0.02
Digit span	Raw	Ds_raw	12		10	
	Age scaled score	Ds_ass	8		7	
	Forward	Ds_for	5		5	
	Backward	Ds_back	4		4	
AMIPB	Immediate *z*-score	Stry_ir	30	−0.38	30	0.67
	Delay *z*-score	Stry_dr	36	0.35	27	0.57
	% Retention *z*-score		−0.81		0.11	
REMT	Total raw correct	Remt_ct	22	0.28	15	−1.03
	Delayed recall		4	−0.33	3	−0.76
	Recognition hits		28	0.79	27	0.44
	Recognition false positive		0	1.23	0	1.23
	% Retained	Remt_pr	64	0.30	37.50	−0.63
	Recall consistency	Remt_rc	82	0.82	57	−0.52
	Subjective organ	Remt_so	0	−0.83	0	−0.83
Complex	Copy raw	Meg_cop	35	0.28	35	0.57
Figure	Immediate raw	Meg_ir	19	−0.14	20	0.21
	Delay raw	Meg_dr	17	−0.37	19	0.20
JOLO	Raw (30)	Jolo_r	28	0.85	26	0.53
SDMT	Written raw	Writ_r	27		14	
	z-score	Writ_z	−2.12		−3.48	
	Oral raw	Oral_r	30		32	
	z-score	Oral_z	−2.3		−2.11	
Stroop	*z*-score	Stroop	−2.34		94	0.00
Short RMT	Words-raw	Shortwr	25		25	
	Words-%ile		90		> 75th	
	Faces-raw	Shortfr	24		25	

AMIPB, Adult Memory and Information Processing Battery; FIQ, full-scale intelligence quotient; IQ, intelligence quotient; JOLO, Judgment of Line Orientation; MSVT, Medical Symptom Validity Test; NART, National Adult Reading Test; REMT, Repeatable Episodic Memory Test; RMT, Recognition Memory Test; SDMT, Symbol Digit Modalities Test; SPM, Sensory Processing Measure; VIQ, verbal intelligence quotient.

of warmth' associated with a pleasant sensation. His feet felt better almost immediately. The next month, the burning sensation had not returned. Pain was not a problem anymore and the patient requested that he continue with the efficacious DBS settings.

At follow-up, most of the pain and health state assessments were improved. VAS, initially at 6.7/10, was 4.0 (−40%) after 1 year and 3.0 (−55%) after 2 years. The MPQ total score was decreased by 42% (43 to 25) after 2 years of stimulation, and for each domain, except the sensory one (28 to 25), the score was 0 at follow-up (affective: 1 to 0, evaluative: 4 to 0 and miscellaneous: 10 to 0). The SF-36 total score improved slightly at follow-up (+2.1% at 2 years; 242–247), with improved subscores of Bodily Pain, Vitality and Mental Health (+13%, +5% and +14% respectively), Physical Functioning, Role – Physical, Social Functioning and Role – Emotional remaining unchanged and General Health decreased by 29% (28 to 20). The first section of the EQ-5D score was not modified by the DBS, but the Health VAS was considerably increased (+150%; 20–50) (Table 1).

Two years after surgery, the neuropsychological assessment showed no significant change in test performance apart from (a) selective improvement on the Stroop Task (50th centile) and (b) self and carer rating of executive functioning showed significant increases in scores on both apathy (Pre-op: 56, self; 85, wife – Post-op: 73, self; 102, wife) and executive dysfunction (Pre-op: 65, self; 91, wife – Post-op: 77, self; 105, wife) scales on the FrSBE (Tables 2 and 3). No change was evident in cognitive processing speed, with scores falling at the first percentile on both written and oral components of the Symbol Digit Modality Test.

Discussion

This is the first report to show that bilateral ACC DBS alone can significantly alleviate the suffering of treatment-resistant chronic pain. It provides a promising avenue for patients for whom other treatments including PAG and sensory thalamus DBS are ineffective [3]. Chronic pain is a complex experience, comprising cognitive, affective and sensory-discriminative aspects, and medial brain regions including the ACC have been shown to be involved in the affective aspects of pain [5]. Suffering lies at the core of the experience of pain and has widespread effects on mood, disability and employment.

The first neurosurgical dissociation of nociception from the suffering of pain was noted by surgeons practising surgery for psychiatric disorders. As well as Cairns' cingulotomies, Watts and Freeman [12] observed that frontal lobotomy rendered patients 'not bothered' by their pain. In 1962, Foltz and White [13] in Massachusetts performed cingulotomy by electrocoagulation, decreasing the unpleasantness of pain without affecting the patient's ability to discern pain intensity. Cingulotomy has been reported to induce indifference to pain [14] and apathy [15]. In our case, both the patient and his wife reported a significant increase in apathy and problems with executive function using the FrSBE and this could potentially be unwanted side-effects of this type of surgery. This is being investigated further in a larger cohort of ACC-DBS patients. Chronic limbic stimulation for pain could therefore lead to some psychological consequences but these do not appear to be a significant barrier to functional improvement.

Interestingly, some studies showed activity in the rostral and dorsal ACC during DBS of the thalamus in five patients with chronic pain [16,17], as did single photon emission tomography and magneto encephalography studies with human participants receiving PAG DBS [16,18,19]. A recent magneto encephalography study from our group has shown the complementary finding of PAG activation with ACC DBS in addition to long-term changes in ACC activity with ACC DBS [20].

The rationale for targeting the ACC derives largely from successful case series of dorsal cingulotomy to relieve cancer pain [8]. A comprehensive review suggested that the procedure was useful in 80 (52%), but not in 73 patients (48%) [21]. Historically, the first bilateral cingulotomies for cancer pain were performed by Foltz and White [22], reporting good or excellent relief in nine of 11 patients. The largest reported case series of 35 patients with cancer pain reported 20 (57%), with satisfactory pain relief 3 months after surgery [23]. The first cingulate cortex DBS was reported by Spooner *et al.* [24] in a patient with cervical spinal cord injury and whole-body pain who showed greater improvements in pain and mood with bilateral ACC DBS [24]. However, this study is a short-term one, with 4 months of postoperative follow-up, and the electrode locations remain unclear.

In this study, electrodes were implanted into 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 (Fig. 1). Interestingly, during the trial week before the implantation of the generator, the settings preferred by the patient appeared to be stimulation with the deepest contacts as active. The data suggest that the corpus callosum could play an important role in the relief of neuropathic pain. As the upper part of the corpus callosum contains fibres interconnecting both the cingulate cortices [25], DBS of this area could stimulate all the structures of the cingulum concurrently, potentially augmenting analgesia.

This case study shows that DBS of the ACC can significantly alleviate the suffering of treatment-resistant chronic pain. This provides a promising avenue for patients for whom other treatments including PAG and sensory thalamus DBS are ineffective.

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Conflicts of interest

There are no conflicts of interest.

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