See the corresponding editorial in this issue, pp 313–314.

J Neurosurg 116:315–322, 2012

A multicenter pilot study of subcallosal cingulate area deep brain stimulation for treatment-resistant depression

Clinical article

Andres M. Lozano, M.D., Ph.D., F.R.C.S.C.,[1] Peter Giacobbe, M.D., M.Sc., F.R.C.P.C.,[2,8] Clement Hamani, M.D., Ph.D.,[1] Sakina J. Rizvi, H.B.Sc.,[8] Sidney H. Kennedy, M.D., F.R.C.P.C.,[2,8] Theodore T. Kolivakis, M.D., C.M., F.R.C.P.C.,[4] Guy Debonnel, M.D., C.S.P.Q., A.I.H.P.,[4] Abbas F. Sadikot, M.D., Ph.D., F.R.C.S.C.,[3] Raymond W. Lam, M.D., F.R.C.P.C.,[6] Andrew K. Howard, M.D., F.R.C.P.C.,[6] Magda Ilcewicz-Klimek, M.D., F.R.C.P.C.,[6] Christopher R. Honey, M.D., D.Phil.,[5] and Helen S. Mayberg, M.D., F.R.C.P.C.[7]

[1]Division of Neurosurgery and [2]Department of Psychiatry, University of Toronto; Departments of [3]Neurology and Neurosurgery and [4]Psychiatry, McGill University, Montreal; [5]Division of Surgery (Neurosurgery) and [6]Department of Psychiatry, University of British Columbia, Vancouver, Canada; [7]Department of Psychiatry, Emory University, Atlanta, Georgia; and [8]Department of Psychiatry, University Health Network, University of Toronto, Canada

Object. Deep brain stimulation (DBS) has been recently investigated as a treatment for major depression. One of the proposed targets for this application is the subcallosal cingulate gyrus (SCG). To date, promising results after SCG DBS have been reported by a single center. In the present study the authors investigated whether these findings may be replicated at different institutions. They conducted a 3-center prospective open-label trial of SCG DBS for 12 months in patients with treatment-resistant depression.

Methods. Twenty-one patients underwent implantation of bilateral SCG electrodes. The authors examined the reduction in Hamilton Rating Scale for Depression (HRSD-17) score from baseline (RESP50).

Results. Patients treated with SCG DBS had an RESP50 of 57% at 1 month, 48% at 6 months, and 29% at 12 months. The response rate after 12 months of DBS, however, increased to 62% when defined as a reduction in the baseline HRSD-17 of 40% or more. Reductions in depressive symptomatology were associated with amelioration in disease severity in patients who responded to surgery.

Conclusions. Overall, findings from this study corroborate the results of previous reports showing that outcome of SCG DBS may be replicated across centers. *(DOI: 10.3171/2011.10.JNS102122)*

Key Words • deep brain stimulation • depression • mood disorder • psychiatry • cingulate gyrus • subgenual cingulate

Current treatments for major depressive disorder do not result in high remission rates; most studies have reported approximately 30% of patients remit with pharmacotherapy or psychotherapy.[4,9] Given the high level of TRD in major depressive disorder, it is important to explore alternative treatment avenues for this subpopulation.

Several lines of evidence are converging to support the concept that alterations in mood circuitry are involved in the pathogenesis of TRD. A number of structural and functional imaging studies have implicated involvement of the SCG area and connections in the processing of acute sadness.[3,7,20,27,29] Furthermore, TRD is associated with hyperactivity in the SCG.[5,6,13,21] That this hyperactivity is significant in the pathogenesis of depression is supported by the observation that various interventions that alleviate depression produce reductions in the blood flow or metabolic activity in this area.[5,8,11,19–22,24,25,28]

With this rationale, DBS was applied in patients with TRD, as defined by failure of the depression to respond to multiple pharmacological treatments, cognitive behavioral therapy, and electroconvulsive therapy.[17,21] In the origi-

Abbreviations used in this paper: CGI-S = Clinical Global Impression–Severity; DBS = deep brain stimulation; HRSD-17 = 17-item Hamilton Rating Scale for Depression; RESP50 = a minimum 50% reduction in the HRSD-17 score from baseline; SCG = subcallosal cingulate gyrus; TRD = treatment-resistant depression.

This article contains some figures that are displayed in color online but in black and white in the print edition.

nal series of 20 patients, approximately 55% achieved response, defined by a 50% reduction in HRSD-17 scores after 12 months of continuous DBS stimulation.[17] These patients were treated at a single center and with stimulation applied using a pulse generator that delivered constant-voltage stimulation.

The purpose of the present study was to replicate these findings across several centers using the Libra DBS system.

Methods

Patients and HRSD Testing

We conducted a 3-center prospective open-label trial of SCG DBS for 12 months in patients with TRD. The inclusion and exclusion criteria for study entry are shown in Table 1. The study was approved by the institutional review boards of the 3 institutions (University of British Columbia, McGill University, and University Health Network), and written informed consent was obtained from each participant. Each patient underwent 2 baseline psychiatric evaluations 1 month apart, and the depression scores were averaged for the purposes of determining the baseline at study entry. If the second HRSD-17 score was less than 18, a third evaluation was required. If at the third the HRSD score was again less than 18, the case was deemed a "screen failure" and excluded from the study. The demographic information of the patients is shown in Tables 2–4.

Surgery

Surgery was performed as previously described.[17,21] Briefly, a local anesthetic was used and a Leksell stereotactic frame was applied. Patients then underwent brain imaging in which a 3D MR imaging acquisition was used. The reformatted brain images were processed on a workstation, and bilateral targets were chosen within the SCG extending from the lower gray matter bank to the central white matter and to the upper gray matter bank of the gyrus. The surgical procedure was also performed after application of a local anesthetic. Bilateral bur holes were made at the level of the coronal suture, 2 cm from the midline. Libra electrodes (St. Jude Medical) were inserted at the target sites and fixed to the skull. When the frame was removed, general anesthesia was induced and the Libra DBS electrodes were tunneled, using a connector, toward the infraclavicular area where they were connected to a Libra constant-current internal pulse generator (St. Jude Medical). The technical aspects of implanting Libra DBS and Medtronic systems (as used in our previous reports[17,21]) were similar.

Electrode Location

Postoperative T1- and T2-weighted MR images were merged and reformatted along the anterior-posterior commissure line. Deep brain stimulation electrodes were visualized in 3 planes and the sphere-shaped artifacts corresponding to each electrode contact were targeted. We defined as active contacts those being used as the cathodes at 6 months. Because of the variability in the anatomy of the prefrontal cortex and SCG across individuals, coordinates relative to the midcommissural point are less useful. To overcome this, we assessed the location of the active contacts relative to the grid system we have previously published.[10] This system consists of 2 lines, 1 in the anteroposterior and the other in the dorsoventral axis. The anteroposterior line extends from the anterior commissure to the projection of the anterior aspect of the corpus callosum. The dorsoventral line extends from the inferior edge of the corpus callosum to the most ventral aspect of the frontal lobe. Each line was normalized into 100 equal units, and data were converted into percentages, as previously described.[10] In the mediolateral plane we calculated the distance between the center of the active contacts and the edge of the cortical surface. Data from the right and left electrodes were combined for statistical purposes. Statistical analyses were conducted using the ANOVA with significance set at $p \leq 0.05$.

Stimulation Programming Visits

The stimulation parameters were chosen based on our previous experience and on the patients' responses to stimulation over a period of 1–2 weeks. Average stimulation settings on the first visit, at 6 months, and at 12 months are shown in Table 5.

Outcome Measures

The HRSD-17 was the primary outcome measure, and response was defined as a minimum 50% reduction in the HRSD-17 score from baseline (that is, RESP50). The HRSD-17 was administered by the treating psychiatrist at all study visits, including at baseline and at 3, 6, and 12 months after DBS. The CGI-S Scale was a secondary measure.

Results

Twenty-two patients were enrolled in the study, although 1 patient was excluded because of a medical comorbidity, leaving 21 patients who underwent lead implantation. The proportion of patients in the RESP50 group was 57% at 1 month, 48% at 6 months, and 29% at 12 months. The mean decline in HRSD-17 scores in the 21 patients is shown in Fig. 1. At 2 months, there was a decline of 40.3% ± 29.8%. At 6 months the decline was 43.3% ± 31.3%, and at 12 months it was 41.4% ± 23.0%.

The reductions in depressive symptomatology were associated with improvements in disease severity and global improvements in the patients. As shown in Fig. 2, patients shifted from being severely ill to being less ill after surgery, and the majority of the patients improved with surgery. At 12 months none of the 20 patients who remained in treatment were worse than at baseline (Fig. 2).

Position of Active Electrode Contacts

The positions of the DBS contacts used for stimulation are projected onto a brain atlas as shown in Fig. 3. We compared the position of the active electrodes at the 3 study sites. There were no differences in the location of contacts used for stimulation at 6 months across sites when internal landmarks of the medial frontal lobe were

TABLE 1: Inclusion and exclusion criteria for patients with TRD*

inclusion criteria
men & (nonpregnant) women age 30–60 yrs
diagnosed w/ nonpsychotic major depressive disorder, single or recurrent episode by DSM-IV-TR criteria derived from the MINI
1st episode onset before age 35 yrs
chronic illness w/ current episode of ≥24-mo duration &/or recurrent illness w/ at least a total of 4 lifetime episodes (including current episode ≥12 mos) (a new episode starts after a remission of a minimum of 2 mos)
documented resistance to at least 4 depression treatments in a lifetime; cognitive behavioral therapy considered an effective form of treatment
in current episode: documented resistance (i.e., persistence of the major depressive episode) to a minimum of 3 adequate depression treatments from at least 3 different treatment categories (SSRIs, TCAs, other antidepressants, lithium addition, irreversible MAO inhibitor); adequacy of treatments defined by a score of at least 4 (or 3, plus clear evidence that the dose at 4 could not be tolerated) according to the ATHF criteria
in the current episode: documented resistance to ECT (at least 6 sessions [i.e., a minimum score of 3 according to ATHF criteria]) or <6 treatments if there is clear evidence of inability to tolerate more, or refused, or withdrew consent after ECT was recommended
premenopausal women must agree to use acceptable methods of birth control
HRSD-17 score ≥20
Global Assessment of Function Score <50
Modified Mini-Mental State Examination Score ≥27
stable on current antidepressant medication regimen or medication free ≥4 wks
able to give informed consent in accordance w/ institutional policies
able to comply w/ all testing & follow-up requirements defined by the study protocol
other medical conditions must be stable for at least 1 yr (conditions that require intermittent use of steroids or chemotherapy excluded)
confirmed disease state & surgical suitability by independent psychiatric examination
exclusion criteria
diagnosed w/ a bipolar I or bipolar II disorder by DSM-IV-TR criteria derived from the MINI
currently meets the DSM-IV-TR criteria for a major depressive episode w/ atypical symptoms
has alcohol or substance dependence within 12 mos, excluding nicotine; alcohol or substance abuse w/in 6 mos, excluding nicotine
current substantial suicidal risk as defined by a plan or clear immediate intent for self-harm, or made a serious suicide attempt w/in the last year that has required an emergency department visit or hospitalization
has a neurological disease that impairs motor, sensory, or cognitive function or that requires intermittent or chronic medication (e.g., Parkinson disease, migraine, stroke, Huntington disease, head trauma)
clinically relevant abnormality on MRI
has primary or serious (requiring additional treatment) comorbid obsessive compulsive disorder, posttraumatic stress disorder, panic disorder, bulimia, or anorexia in the last year by DSM-IV-TR criteria derived from the MINI
meets criteria for a severe cluster B personality disorder (i.e., borderline, narcissistic, or antisocial) in the last 12 mos by DSM-IV-TR criteria derived from the Structured Clinical Interview for DSM-IV (or the SCID II) borderline personality section
established cardiovascular disease as evidenced by a history of angina, myocardial infarction, or the need for cardiac drugs (w/ the exception of cholesterol-lowering agents)
has cardiac pacemaker/defibrillator or other implanted stimulator
likely to relocate or move to a location distant from study site w/in 1 yr of enrollment
past intracranial neurosurgery
pregnant or has plans to become pregnant in the next 12 mos
has current or lifetime psychosis by DSM-IV criteria

* ATHF = Antidepressant Treatment History Form; ECT = electroconvulsive therapy; MAO = monoamine oxidase; MINI = Mini-International Neuropsychiatric Interview; SSRI = selective serotonin reuptake inhibitor; TCA = tricyclic antidepressant.

TABLE 2: Summary of patient demographics and clinical features*

Factor	University Center			Total
	UBC	McGill	UT	
no. of patients	5	6	10	21
sex (no. of patients)				
female	2	5	6	13
male	3	1	4	8
age in yrs†	43.6 ± 10.0 (35–59)	49.5 ± 3.5 (44–53)	47.9 ± 4.6 (39–55)	47.3 ± 6.1 (35–59)
age at MDD onset†	24 ± 6.2 (19–34)	29.7 ± 10.6 (16–42)	27.5 ± 6.7 (19–39)	27.3 ± 7.7 (16–42)
lifetime episodes†	4 ± 0 (4)	11.5 ± 8.9 (4–25)	6.1 ± 2.8 (4–10)	7.2 ± 5.8 (4–25)
duration of current episode in yrs†	5.2 ± 3.5 (2–9)	2.3 ± 0.5 (2–3)	6.4 ± 4.1 (2–12)	5.0 ± 3.7 (2–12)
past ECT (%)	4 (80)	5 (83)	9 (90)	18 (90)
past psychotherapy (%)	5 (100)	6 (100)	10 (100)	21 (100)
baseline HRSD-17 score†	27.4 ± 6.2 (20–34)	28.6 ± 5.1 (24–37)	26.6 ± 3.5 (18–31)	27.6 ± 4.5 (18–37)
baseline IDS score†	48.4 ± 11.3 (31–60)	41.2 ± 3.77 (37–47)	50 ± 5.42 (37–57)	47.4 ± 5.80 (31–60)
baseline MADRS score†	41.7 ± 5.28 (36–48)	39.4 ± 5.18 (34–47)	40.2 ± 4.13 (34–46)	47.4 ± 5.80 (34–48)
family history of MDD (%)	3 (60)	5 (83)	8 (80)	16 (76)
melancholic feature (%)	4 (80)	5 (83)	9 (90)	18 (90)

* IDS = Inventory of Depressive Symptomatology; MADRS = Montgomery-Åsberg Depression Rating Scale; MDD = major depressive disorder; UBC = University of British Columbia; UT = University of Toronto.
† Data are presented as the mean ± SD with the range in parentheses.

considered (Fig. 3). In the mediolateral plane, contacts at the 3 study institutions were on average between 5–7 mm from the medial cortical surface.

Deep Brain Stimulation Parameters Over Time

The stimulation parameters used in the patients over 12 months are shown in Table 5. In some cases these parameters required adjustments over time. So as not to confound the study, the patients' medications were maintained unchanged from baseline through 6 months.

TABLE 3: Baseline psychotropic medications used by patients*

Medication Type	No. of Patients
benzodiazepine sedative	16
SSRI	12
antipsychotic, atypical	8
mood stabilizer	7
stimulants	5
TCA	4
norepinephrine-dopamine reuptake inhibitor	3
non-benzodiazepine sedative	2
serotonin–norepinephrine reuptake inhibitor	2
antidepressants, other	2
anticonvulsants	2
MAO	2
bupropion	1
antipsychotic, typical	1
noradrenergic & specific serotonergic antidepressant	1
other (tryptophan, synthroid, prednisone, gabapentin)	5

* The mean number of medications that failed was 16 and the mean number of medications at baseline was 3.5 ± 1.3.

Adverse Effects

Suicide was the most serious adverse effect in this study. One patient committed suicide, and another patient attempted suicide. The patient who committed suicide did so at an early stage of the follow-up (after the 8th week). The death was due to an overdose of medications. The patient who attempted suicide was at a different institution. The patient was between the Week 4 and Week 5 follow-up visits. The underlying trigger was thought to be a family matter.

In the current study, nausea and vomiting were recorded in 7 patients. At present, it is unclear whether this represents a side effect of stimulating this region, was a consequence of the interaction between stimulation and medications, or was due to completely unrelated causes.

In another patient, there was a lead extension malfunction immediately after surgery requiring extension replacement. The stimulation was reactivated immediate-

TABLE 4: Variation in medications across study sites

Variable	Baseline Psychotropic Medications by Site		
	McGill	UBC	UT
patient sample size	6	5	10
mean no. of medications	3.2 ± 0.8	4.0 ± 1.6	3.5 ± 1.5
range	2–4	2–6	1–6

TABLE 5: Stimulation parameters in 21 patients over time

Variable	Visit for DBS System (range)		
	Implant	6 mos Postimplant	12 mos Postimplant
mean amplitude in mA	4.2 (2.5–5.0)	4.9 (3.0–7.0)	5.2 (2.5–7.0)
mean pulse width in msec	91 (91)	100.5 (91–182)	93.9 (65–117)
mean frequency in Hz	130.5 (130–140	130 (130)	128.1 (110–130)
mean no. of active contacts on rt	1.3 (1–4)	1.4 (1–4)	1.5 (1–4)
mean no. of active contacts on lt	1.2 (1–3)	1.4 (1–4)	1.4 (1–4)

ly after the revision surgery. One patient had superficial skin erosion at the bur hole site. This appeared 7 weeks after device activation, and the skin incision was revised. The serious and not serious adverse effects are summarized in Table 6.

Discussion

Our results show that using a reduction of 50% in the HRSD-17 score as a criterion, 48% and 29% of TRD patients responded to SCG DBS at 6 and 12 months, respectively. Responses seen at 3 months tend to be maintained at 1 year. The reduction in depression scores is associated with significant clinical global improvements and amelioration of depression severity. The results of this multicenter study suggest that the SCG can be reliably targeted for DBS electrode implantation and that the clinical effects of SCG DBS for TRD are robust and reproducible across centers.

The apparent drop in efficacy from a response rate of 48% at 6 months to 29% at 12 months is potentially worrisome but may be somewhat of an artifact of the data analysis. A proportionately large number of patients are hovering in the range of a 40%–50% reduction in depression scores in the 6–12-month period. While depression scores in 29% of the patients improved by 50% or more at 12 months, in 62% of the patients the scores improved by 40% or more at the same time point. This occurred because 4 of 10 patients dropped from the 50% to the 40% range at 12 months, a small change that is likely noise but which has a large impact when using the 50% cutoff for response in a series with a relatively small number of participants. Our recently reported long-term follow-up in the original 20 patients at 3–6 years after surgery suggests that the benefits of DBS for depression are maintained over time.[12]

Our results raise several questions. A major limitation of this open-label study is that a placebo effect cannot be ruled out. It is not entirely clear why some patients respond and others do not. Several possibilities include disease heterogeneity, individual anatomical variability, differences in stimulation requirements, variable time courses of the effects of stimulation including delay, and carryover effects of stimulation.

Similarly, the choice of target remains an issue. Other than the SCG, it is clear that other brain targets may also be useful for treating TRD, including the nucleus accumbens and the anterior limb of the internal capsule.[1,18] The specific attributes and potential uses of each of these possible therapeutic targets will require much more investigation.

It is not clear whether the constant-current mode of delivery we used offers a significant difference from the previously used clinical DBS systems that have voltage-controlled pulse generators. The use of voltage-controlled stimulation results in voltage distributions in the target neural tissues that depend on the impedance of the electrode-tissue interface.[2,23] The impedance of the DBS electrode–tissue interface has been shown to fluctuate both after implantation and during stimulation.[15] These varying impedance conditions are suspected to produce instability in the voltages produced in the target neural tissues during voltage-controlled DBS, and they may be at least partially responsible for the need to adjust stimulation parameters during the system's initial programming process. Unlike voltage-controlled DBS, current-controlled DBS regulates the current through the electrode-tissue interface. In theory, the voltages generated in the target brain tissues by current-controlled DBS should be fairly independent of the electrode impedance.[14] This increased stability in the extracellular voltages produced from stimulation could, at least in theory, help stabilize the therapeutic efficacy of the stimulation parameters selected. That being said, once scar formation is complete around the electrode, the brain-electrode interface becomes relatively stable. This can be appreciated in other applications of DBS in which changes in stimulation parameters are

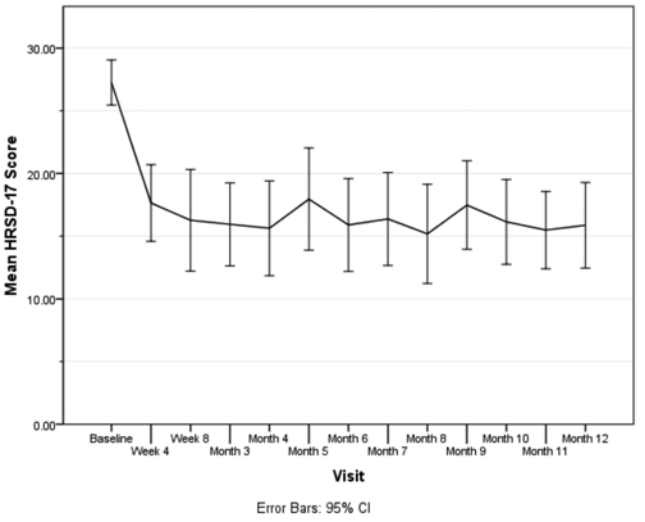

Fig. 1. Graph showing HRSD-17 scores over time in 21 patients receiving DBS.

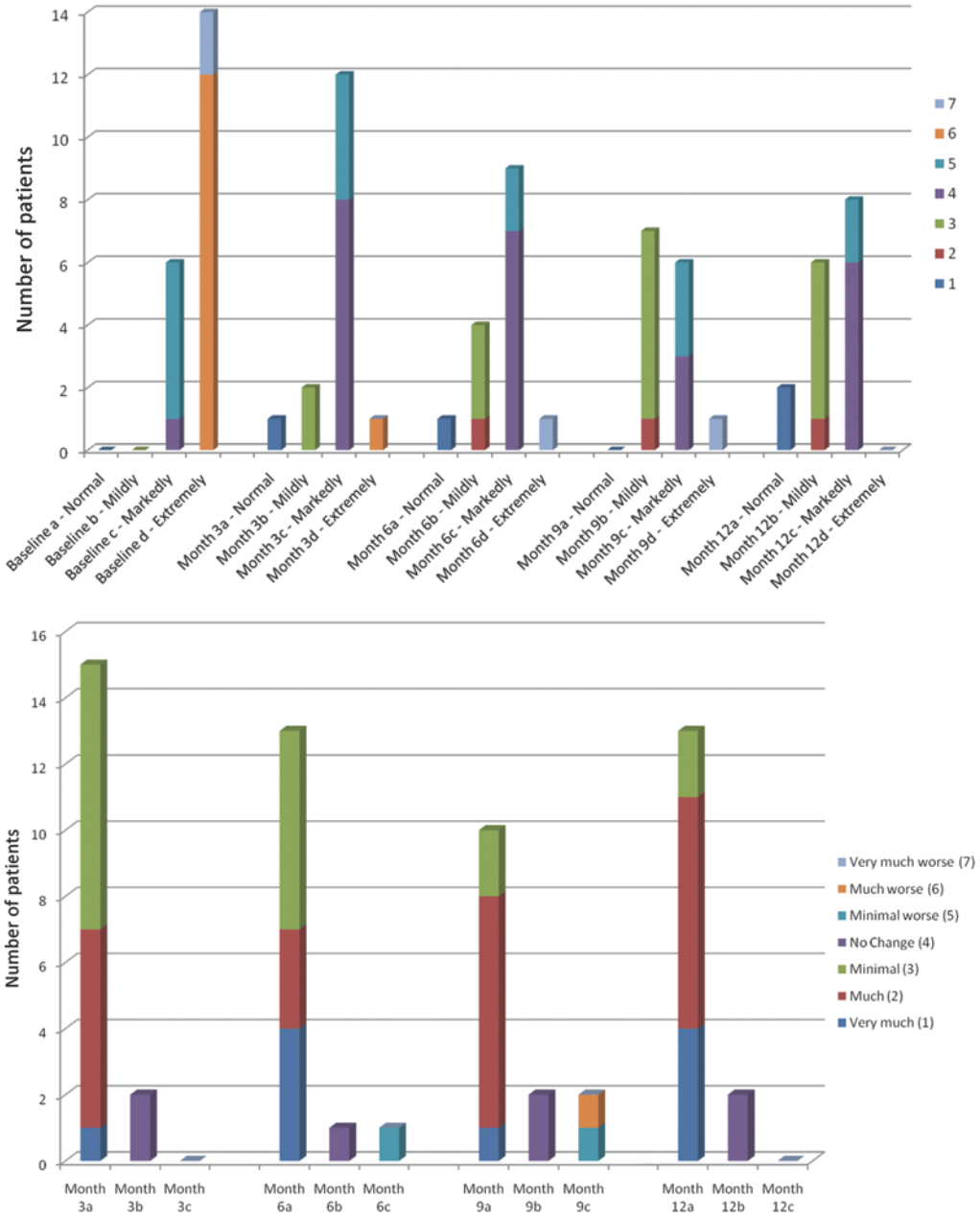

Fig. 2. Upper: Bar graph demonstrating CGI-S scores at baseline and after SCG DBS in 21 patients. The colors represent the categories from 1 to 7 on the CGI-S Scale. The vertical axis is the number of patients at each time point. At baseline, the majority of patients were extremely ill and among the most ill patients (Categories 6 and 7). With time, patients improved, shifting to markedly ill (Categories 4 and 5), mildly ill (Categories 2 and 3), and in some cases normal (Category 1). The CGI-S scores at baseline were available for less than the entire sample of 21 patients. **Lower:** Number of patients who improved (a, Categories 1–3), showed no change (b, Category 4), or worsened (c, Categories 5–7) after SCG DBS, as assessed using the CGI-S improvement scores at 3, 6, 9, or 12 months. With time after DBS, most patients improved. Data were not available for the entire sample of 21 patients. (CGI scale: Considering your total clinical experience with this particular population, how mentally ill is the patient at this time? 0 = not assessed; 1 = normal, not at all ill; 2 = borderline mentally ill; 3 = mildly ill; 4 = moderately ill; 5 = markedly ill; 6 = severely ill; 7 = among the most extremely ill patients.)

not often required after the first weeks or months of treatment. At present, it is unclear whether constant-current systems will have a practical advantage over constant-voltage systems for this indication.

In general the surgical procedure was well tolerated. There were a large number of adverse effects (Table 6). None of the adverse effects was thought to be the result of the stimulation per se. They were likely related to the patient population. No unexpected adverse events were noticed during this trial. One of 21 patients committed suicide 8 weeks into the trial. Treatment resistance is a feature commonly associated with suicidality in individu-

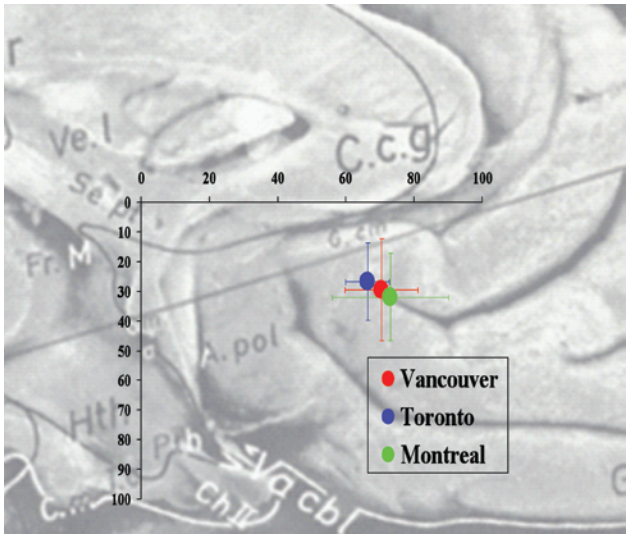

Fig. 3. Mean location of active stimulation contact projected onto the SCG in patients undergoing SCG DBS. The figure is a schematic representation of the average location of the active contacts at 6 months across the 3 centers. The *horizontal scale* normalizes the distance between the anterior commissure and the anterior border of the corpus callosum. The *vertical scale* is the normalized distance between the base of the brain and the inferior-most point of the corpus callosum. No differences were found across centers in the anteroposterior, dorsoventral, and mediolateral axes (the latter not shown). *Central dots* represent the mean location of contacts and the *lines* SDs. Modified and reprinted from Schaltenbrand G, Wahren W: **Atlas for Stereotaxy of the Human Brain.** Stuttgart: Georg Thieme Verlag, 1977. Used with permission from Thieme.

als with depression.[26] In fact, patients with TRD commit twice as many suicides as patients who respond to therapy.[16] Suicides have been reported in other studies of DBS for TRD,[1] highlighting the need for active psychiatric follow-up of this population in the postoperative period.

As a consequence of this work, together with previous experience with DBS at this target in other patients, it is possible to conclude that SCG appears reasonably safe and shows considerable promise in helping patients with TRD. What is now required is a controlled study in a larger number of patients to determine the safety and effectiveness of this approach.

Conclusions

The effects of SCG DBS in patients with TRD were investigated in a 3-center prospective open-label trial. Overall, patients had an RESP50 of 57% at 1 month, 48% at 6 months, and 29% at 12 months. Reductions in depressive symptomatology were associated with amelioration in disease severity in patients who responded to stimulation. Findings from this study corroborate the results of previous reports showing that outcome of SCG DBS may be replicated across centers.

Disclosure

St. Jude Medical provided stimulating devices, data compilation, statistical analysis and financial support for the study. They were not involved in the preparation or submission of the manuscript.

Dr. Lozano holds intellectual property in the field of DBS for depression and is a consultant for St Jude. Dr. Giacobbe has participated in clinical trials or studies from Brain Cells Inc., Clera, GlaxoSmithKline, and St. Jude Medical. He has received honoraria from AstraZeneca and St. Jude Medical. He has research grants from the Canadian Academy of Geriatric Psychiatry, CIHR, Department of Psychiatry–University Health Network, Eli Lilly Canada Inc., and the Michael J. Fox Foundation for Parkinson's Research. He is on the advisory board of Eli Lilly Canada. Dr. Hamani is a consultant for and has received honoraria from St. Jude Medical. He has received research grants from St. Jude Medical and NARSAD. Dr. Kennedy has received research funding or honoraria from AstraZeneca, Biovail, Eli Lilly, GlaxoSmithKline, Janssen-Ortho, Lundbeck, Pfizer, St. Jude Medical, and Servier in the last 3 years. Dr. Kolivakis has received speaker and/or advisory board honoraria from AstraZeneca, Eli Lilly, Lundbeck, Wyeth, Biovail, Novartis, and Janssen Ortho. Dr. Lam has received speaker honoraria from AstraZeneca, Biovail, the Canadian Psychiatric Association, Canadian Network for Mood and Anxiety Treatments, Eli Lilly, Lundbeck, Lundbeck Institute, Servier, and Wyeth. He is part of the advisory Boards of AstraZeneca, Bristol Myers Squibb, Canadian Network for Mood and Anxiety Treatments, Common Drug Review, Eli Lilly, Litebook Company Ltd. (unpaid), Lundbeck, Merck, Servier, and Takeda. He has research Funds (through the University of British Columbia) from Advanced Neuromodulation Systems Inc., AstraZeneca, BrainCells Inc., Canadian Institutes of Health Research, Canadian Psychiatric Research Foundation, Litebook Company Ltd., Lundbeck, Mathematics of Information Technology and Advanced Computing Systems, Michael Smith Foundation for Health Research, and UBC Institute of Mental Health/Coast Capital Savings. Dr. Lam holds the patent/copyright for Lam Employment Absence and Productivity Scale (LEAPS). Dr. Honey has received

TABLE 6: Serious adverse events and other adverse events in 21 patients undergoing DBS

Adverse Event	No. of Occurrences	No. of Patients
serious		
skin erosion	3	1
extension break	2	2
chest pain	1	1
pneumonia	1	1
infection	1	1
suicide attempt	1	1
suicide	1	1
other		
gastrointestinal (nausea, vomiting, diarrhea)	15	9
musculoskeletal (tremor, spasms, stiffness)	12	4
skin (itching, superficial cellulitis, wound drainage)	9	6
headache >1 mo postop	6	6
persistent pain >1 mo postop	4	4
psychiatric changes (agitation, reaction to amplitude increase)	4	3
dizziness	3	3
polyuria	2	2
weight gain	1	1
buzzing in ears	1	1
insomnia	1	1

research funds from Advanced Neuromodulation Systems Inc./St. Jude Medical, B. C. Health Research Foundation, Canadian Institutes of Health Research, Cyberonics Inc., Medical Research Council of Canada, Medtronic of Canada Ltd., QLT PhotoTherapeutics Inc., Titan Pharmaceuticals, Vancouver Coastal Health Authority, and the Vancouver General Hospital/University of B.C. Hospital Foundation. Applications in progress and review pending include Canadian Institutes of Health Research, Michael J. Fox Foundation, National Institutes of Health, and Parkinson's Society of Canada. He has a patent on a method to prevent xenograft rejection. Dr. Mayberg holds intellectual property in the field of DBS for depression and is a consultant for St. Jude.

Author contributions to the study and manuscript preparation include the following. Conception and design: Lozano, Kennedy, Lam, Mayberg. Acquisition of data: all authors. Analysis and interpretation of data: Lozano, Giacobbe, Hamani, Kennedy, Lam, Mayberg. Drafting the article: Lozano, Hamani. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Lozano. Statistical analysis: Lozano. Administrative/technical/material support: Lozano. Study supervision: Lozano.

References

1. Bewernick BH, Hurlemann R, Matusch A, Kayser S, Grubert C, Hadrysiewicz B, et al: Nucleus accumbens deep brain stimulation decreases ratings of depression and anxiety in treatment-resistant depression. **Biol Psychiatry 67:**110–116, 2010
2. Butson CR, Maks CB, McIntyre CC: Sources and effects of electrode impedance during deep brain stimulation. **Clin Neurophysiol 117:**447–454, 2006
3. Damasio AR, Grabowski TJ, Bechara A, Damasio H, Ponto LL, Parvizi J, et al: Subcortical and cortical brain activity during the feeling of self-generated emotions. **Nat Neurosci 3:** 1049–1056, 2000
4. Depression Guideline Panel: **Depression in Primary Care. Volume 2: Treatment of Major Depression. AHCPR Clinical Practice Guidelines, No. 5.2.** Rockville, MD: Agency for Health Care Policy and Research, 1993
5. Dougherty DD, Weiss AP, Cosgrove GR, Alpert NM, Cassem EH, Nierenberg AA, et al: Cerebral metabolic correlates as potential predictors of response to anterior cingulotomy for treatment of major depression. **J Neurosurg 99:**1010–1017, 2003
6. Drevets WC, Price JL, Simpson JR Jr, Todd RD, Reich T, Vannier M, et al: Subgenual prefrontal cortex abnormalities in mood disorders. **Nature 386:**824–827, 1997
7. George MS, Ketter TA, Parekh PI, Horwitz B, Herscovitch P, Post RM: Brain activity during transient sadness and happiness in healthy women. **Am J Psychiatry 152:**341–351, 1995
8. George MS, Stallings LE, Speer AM, Nahas Z, Spicer KM, Vincent DJ, et al: Prefrontal repetitive transcranial magnetic stimulation (rTMS) changes relative perfusion locally and remotely. **Hum Psychopharmacol Clin Exp 14:**161–170, 1999
9. Guze SB, Robins E: Suicide and primary affective disorders. **Br J Psychiatry 117:**437–438, 1970
10. Hamani C, Mayberg H, Snyder B, Giacobbe P, Kennedy S, Lozano AM: 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. **J Neurosurg 111:**1209–1215, 2009
11. Hamani C, Mayberg H, Stone S, Laxton A, Haber S, Lozano AM: The subcallosal cingulate gyrus in the context of major depression. **Biol Psychiatry 69:**301–308, 2011
12. Kennedy SH, Giacobbe P, Rizvi SJ, Placenza FM, Nishikawa Y, Mayberg HS, et al: Deep brain stimulation for treatment-resistant depression: follow-up after 3 to 6 years. **Am J Psychiatry 168:**502–510, 2011
13. Konarski JZ, Kennedy SH, Segal ZV, Lau MA, Bieling PJ, McIntyre RS, et al: Predictors of nonresponse to cognitive behavioural therapy or venlafaxine using glucose metabolism in major depressive disorder. **J Psychiatry Neurosci 34:**175–180, 2009
14. Lempka SF, Johnson MD, Miocinovic S, Vitek JL, McIntyre CC: Current-controlled deep brain stimulation reduces in vivo voltage fluctuations observed during voltage-controlled stimulation. **Clin Neurophysiol 121:**2128–2133, 2010
15. Lempka SF, Miocinovic S, Johnson MD, Vitek JL, McIntyre CC: In vivo impedance spectroscopy of deep brain stimulation electrodes. **J Neural Eng 6:**046001, 2009
16. Leon AC, Keller MB, Warshaw MG, Mueller TI, Solomon DA, Coryell W, et al: Prospective study of fluoxetine treatment and suicidal behavior in affectively ill subjects. **Am J Psychiatry 156:**195–201, 1999
17. Lozano AM, Mayberg HS, Giacobbe P, Hamani C, Craddock RC, Kennedy SH: Subcallosal cingulate gyrus deep brain stimulation for treatment-resistant depression. **Biol Psychiatry 64:**461–467, 2008
18. Malone DA Jr, Dougherty DD, Rezai AR, Carpenter LL, Friehs GM, Eskandar EN, et al: Deep brain stimulation of the ventral capsule/ventral striatum for treatment-resistant depression. **Biol Psychiatry 65:**267–275, 2009
19. Mayberg HS: Modulating dysfunctional limbic-cortical circuits in depression: towards development of brain-based algorithms for diagnosis and optimised treatment. **Br Med Bull 65:**193–207, 2003
20. Mayberg HS, Liotti M, Brannan SK, McGinnis S, Mahurin RK, Jerabek PA, et al: Reciprocal limbic-cortical function and negative mood: converging PET findings in depression and normal sadness. **Am J Psychiatry 156:**675–682, 1999
21. Mayberg HS, Lozano AM, Voon V, McNeely HE, Seminowicz D, Hamani C, et al: Deep brain stimulation for treatment-resistant depression. **Neuron 45:**651–660, 2005
22. Mayberg HS, Silva JA, Brannan SK, Tekell JL, Mahurin RK, McGinnis S, et al: The functional neuroanatomy of the placebo effect. **Am J Psychiatry 159:**728–737, 2002
23. Miocinovic S, Lempka SF, Russo GS, Maks CB, Butson CR, Sakaie KE, et al: Experimental and theoretical characterization of the voltage distribution generated by deep brain stimulation. **Exp Neurol 216:**166–176, 2009
24. Mottaghy FM, Keller CE, Gangitano M, Ly J, Thall M, Parker JA, et al: Correlation of cerebral blood flow and treatment effects of repetitive transcranial magnetic stimulation in depressed patients. **Psychiatry Res 115:**1–14, 2002
25. Nobler MS, Oquendo MA, Kegeles LS, Malone KM, Campbell CC, Sackeim HA, et al: Decreased regional brain metabolism after ECT. **Am J Psychiatry 158:**305–308, 2001
26. Oquendo MA, Currier D, Mann JJ: Prospective studies of suicidal behavior in major depressive and bipolar disorders: what is the evidence for predictive risk factors? **Acta Psychiatr Scand 114:**151–158, 2006
27. Pardo JV, Pardo PJ, Raichle ME: Neural correlates of self-induced dysphoria. **Am J Psychiatry 150:**713–719, 1993
28. Seminowicz DA, Mayberg HS, McIntosh AR, Goldapple K, Kennedy S, Segal Z, et al: Limbic-frontal circuitry in major depression: a path modeling metanalysis. **Neuroimage 22:** 409–418, 2004
29. Talbot PS, Cooper SJ: Anterior cingulate and subgenual prefrontal blood flow changes following tryptophan depletion in healthy males. **Neuropsychopharmacology 31:**1757–1767, 2006

Manuscript submitted December 20, 2010.
Accepted October 3, 2011.
Please include this information when citing this paper: published online November 18, 2011; DOI: 10.3171/2011.10.JNS102122.
Address correspondence to: Andres M. Lozano, M.D., Ph.D., Division of Neurosurgery, Toronto Western Hospital, 399 Bathurst Street, WW 4-447, Toronto, Ontario M5T 2S8, Canada. email: lozano@uhnresearch.ca.