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ARTICLE

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Deep brain stimulation of the subcallosal cingulate gyrus: further evidence in treatment-resistant major depression

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Abstract

Deep brain stimulation (DBS) is currently tested as an experimental therapy for patients with treatment-resistant depression (TRD). Here we report on the short- and long-term (1 yr) clinical outcomes and tolerance of DBS in eight TRD patients. Electrodes were implanted bilaterally in the subgenual cingulate gyrus (SCG; Broadman areas 24–25), and stimulated at 135 Hz (90-μs pulsewidth). Voltage and active electrode contacts were adjusted to maximize short-term responses. Clinical assessments included the 17-item Hamilton Depression Rating Scale ($HAMD_{17}$; primary measure), the Montgomery–Åsberg Depression Rating Scale (MADRS) and the Clinical Global Impression (CGI) Scale. In the first week after surgery, response and remission (HAMD $\leqslant$7) rates were, respectively 87.5% and 50%. These early responses were followed by an overall worsening, with a response and remission rates of 37.5% (3/8) at 1 month. From then onwards, patients showed a progressive improvement, with response and remission rates of 87.5% and 37.5%, respectively, at 6 months. The corresponding figures at 1 yr were 62.5% and 50%, respectively. Clinical effects were seen in all HAMD subscales without a significant incidence of side-effects. Surgical procedure and post-operative period were well-tolerated for all patients. This is the second independent study on the use of DBS of the SCG to treat chronic depression resistant to current therapeutic strategies. DBS fully remitted 50% of the patients at 1 yr, supporting its validity as a new therapeutic strategy for TRD.

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Introduction

Major depressive disorder (MDD) has a lifetime prevalence of ~15–20% (Kessler *et al.* 2005), and it is one of the leading causes of disability worldwide (Giacobbe *et al.* 2009) as is often accompanied by high rates of resistance to treatment. The STAR*D trial reported that up to 33% of patients do not reach remission criteria after four sequenced treatments (Rush *et al.* 2006), leaving clinicians with few therapeutic options to alleviate the sadness, hopelessness, lack of pleasure and suicidal thoughts in chronic depressive patients.

Electroconvulsive therapy (ECT) is a long-established alternative strategy for treatment-resistant

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depression (TRD). However, a considerable proportion of patients do not respond, experience frequent relapses, or do not tolerate its adverse effects, mainly memory disturbances (Kellner *et al.* 2006). Other non-invasive methods, such as transcranial magnetic stimulation (TMS) raised interest for the treatment of drug-resistant depression. However, this technique shows highly heterogeneous results (Avery *et al.* 2006; Burt *et al.* 2002; Fregni *et al.* 2005).

On the other hand, deep brain stimulation (DBS) is currently tested as an experimental therapy for patients with TRD. DBS involves the high-frequency electrical stimulation of stereotaxically implanted electrodes in certain brain regions, such as the subthalamic nucleus for drug-resistant Parkinson's disease (Limousin *et al.* 1998). DBS has shown promising results in TRD so far, and may become a new therapeutic opportunity for chronic, treatment-refractory patients, with few adverse effects. DBS may modulate nerve transmission in cortico-striatal-thalamo-cortical loops in a reversible and adjustable manner (Mayberg, 2009). Various target areas have been examined for DBS to modulate cortico-limbic circuits, including the anterior limb of the internal capsule, the ventral capsule/ventral striatum (VC/VS), the nucleus accumbens (NAc), and Brodmann area (BA) 25 [subgenual cingulate gyrus (SCG)]. Mayberg and colleagues (Kennedy *et al.* 2011; Lozano *et al.* 2008; Mayberg *et al.* 2005) reported that 60% of TRD patients subjected to DBS of the subgenual cingulate (Cg25) experienced a response [$\geqslant$50% reduction of Hamilton Depression Rating Scale (HAMD) score] and 35% fulfilled the criterion for remission (HAMD score $\leqslant$7) after 6 months of stimulation. The response rates were reasonably maintained after 1, 3 and 6 yr. Moreover, 50% of the patients subjected to DBS of NAc responded in a 1-yr observation period (Bewernick *et al.* 2010; Schlaepfer *et al.* 2008). Electrode implantation in the VC/VS also provided response rates of 40% and $\sim$50% at 6 and 24 months, respectively (Malone *et al.* 2009).

Cg25 may play a key role in the control of cortico-limbic circuits given its connectivity with brain structures involved in affective disorders, namely the anterior cingulate cortex, the amygdala, the caudate nucleus and the thalamus, which feed back onto the prefrontal cortex and cingulate cortex, closing a limbic loop. The possibility of modulating a presumably dysfunctional activity of this circuit from the SCG should provide a good opportunity to bear upon the broad spectrum of depressive symptoms (Phillips *et al.* 2003; Seminowicz *et al.* 2004), as suggested by the robust antidepressant effects observed in the first sample of TRD patients receiving SCG DBS (Kennedy *et al.* 2011; Lozano *et al.* 2008; Mayberg *et al.* 2005).

The current study aims at replicating and extending the latter findings. Thus, we describe here the short- and long-term clinical outcomes and tolerance of SCG stimulation in a new independent sample of eight patients with TRD.

Methods and materials

We report on the preliminary findings of the pre-randomization period of a randomized controlled and cross-over clinical trial. In this initial phase of the study electrodes were implanted in all patients and chronic stimulation started within the first 48 h after surgery. The length of this study phase varied depending on the time required by each patient to achieve clinical stability, i.e. <10% variation in HAMD scores in $\geqslant$3 consecutive visits after reaching the criterion of response, thus more than the 9-month period we initially anticipated. Here we report the findings of 1 yr follow-up.

Patient selection

Eight patients with TRD were included in the study. They were recruited from the Hospital de la Santa Creu i Sant Pau from January 2008 to December 2009. A committee composed of the patients' psychiatrist, an independent psychiatric consultant, a neurologist and a neurosurgeon decided which patients could be enrolled in the study, by pre-selecting subjects among the most treatment-resistant patients. All selected patients agreed to be included in the study. All patients were properly informed of the aims and risks of the study and signed an informed consent form after meeting with both the psychiatrist and neurosurgeon. The study was approved by the hospital ethical committee and the Agencia Española de Medicamentos y Productos Sanitarios (Spanish regulatory drug agency).

Inclusion criteria

Individuals aged 18–70 yr diagnosed as having a major depressive episode according to DSM-IV-TR criteria, resistant to pharmacological treatment, at least in stage IV of the Thase–Rush scale (Thase & Rush, 1997) and with lack of efficacy of ECT or partial response to maintenance ECT. Admission score on the 17-item HAMD ($HAMD_{17}$) had to be $\geqslant$18. Patients should have not modified their antidepressant treatment in the previous month prior to study inclusion.

Exclusion criteria

Acute, serious or unstable comorbid neurological or medical illness, current or past non-affective psychotic disorder, severe personality disorder that could impact tolerance or compliance during the study, current substance abuse or dependence (except nicotine), surgical contraindications to undergoing DBS and pregnancy.

Clinical assessments

Demographics were collected from all patients. Blood samples were obtained in order to determine presurgical conditions and antidepressant plasma levels. A psychiatric screening was performed by means of Structured Clinical Interview for DSM-IV Axis I and II (SCID; First *et al*. 1997, 2002). Assessments included $HAMD_{17}$ (primary measure) (Hamilton, 1967), the Montgomery–Åsberg Depression Rating Scale (MADRS; Montgomery & Åsberg, 1979), and the Clinical Global Impression Scale (CGI; Ikadouri *et al.* 2007) which were collected to evaluate changes on clinical outcomes. Response was defined as a decrease of $\geqslant 50\%$ of baseline $HAMD_{17}$ score. Remission was defined as a score of $\leqslant 7$ in $HAMD_{17}$. Patients were visited at least twice a month throughout this study period (12 months) to assess efficacy.

Cognitive functioning was assessed at baseline and after clinical stabilization by means of a comprehensive neuropsychological battery (general intellectual ability, learning, memory, executive function, language and processing speed).

Surgical procedure

Surgical electrode implantation was performed in the white matter adjacent to the Cg25 region and the DBS pulse-generating device was implanted abdominally. Prior to surgery, a Leksell G stereotactic frame (Elekta Instruments, USA) was fitted to the patient's head. Using the neuronavigator (BrainLab model 1.19) the CT scan with the stereotactic frame was fused to the MRI image to calculate the surgical target. The target SCG white matter was delimited as follows: in a midline T2 sagittal image the cingulate gyrus below the genu of the corpus callosum was identified; next, a line was traced from this point of the corpus callosum to the anterior commissure and the mid-point was identified; an image was then taken of the T2 coronal section corresponding to the plane of the mid-point and the definitive coordinates were calculated for the transition area between the white and grey matter for BA 25 (based on Mayberg *et al.* 2005). In the operating room, with the patient under local anaesthesia, a burr hole was drilled 2 cm from the midline in front of the coronal suture.

Intra-operative neurophysiological extracellular recordings started 10 mm above the target. Cell activity was amplified and analysed in an oscilloscope and an audio monitor (Leadpoint, Medtronic, USA). Extracellular recordings were performed to identify the transition between grey and white matter in BA 25 where the electrodes were implanted. DBS electrodes (Medtronic model 3387) were implanted bilaterally. Each of the four electrode contacts was tested intra-operatively at maximal voltage (9.0 V) to study adverse effects and subjective feelings. During the same surgical procedure, a programmable internal pulse generator (Kinetra, Medtronic) was implanted subcutaneously under general anaesthesia in the tissue of the abdominal wall.

Patients were discharged 4–8 d after surgery. A high-resolution 3D T1-weighted MRI was obtained using a dedicated protocol on 1.5 T Philips equipment within the first 2 months after surgery in order to check the electrode localization.

Stimulation settings

In the 1–5 d after surgery, stimulation parameters (voltage, frequency, etc.) were adjusted prior to starting chronic stimulation. Acute changes observed during single-blind sequential stimulation (e.g. patients were unaware whether DBS was being performed or not) were recorded. Based on the parameters used for Parkinson's disease and on previous work by Lozano *et al.* (2008), the first three patients were stimulated as follows: continuous monopolar stimulation at 3.6 V (135 Hz, 90-μs pulsewidth) using the most ventral electrode contacts. The sequence of changes to maximize the therapeutic effect was (1) to increase voltage, (2) to increase pulsewidth, and (3) to change active contacts. Electrode contacts and current stimulation parameters in each patient are shown in Fig. 1. In the first three patients, bipolar stimulation was required for better clinical effects. Subsequently, bipolar stimulation was used in the rest of patients using similar stimulation parameters. Mean voltage was 4.2 V (range 3.5–5 V).

Statistical analysis

Sample descriptive analyses were performed with parametric and non-parametric tests. To evaluate clinical response, data from all rating scales were analysed with ANOVA for repeated measures with time as within-subjects factor (baseline, 1, 2, 4, 6, 9, 12

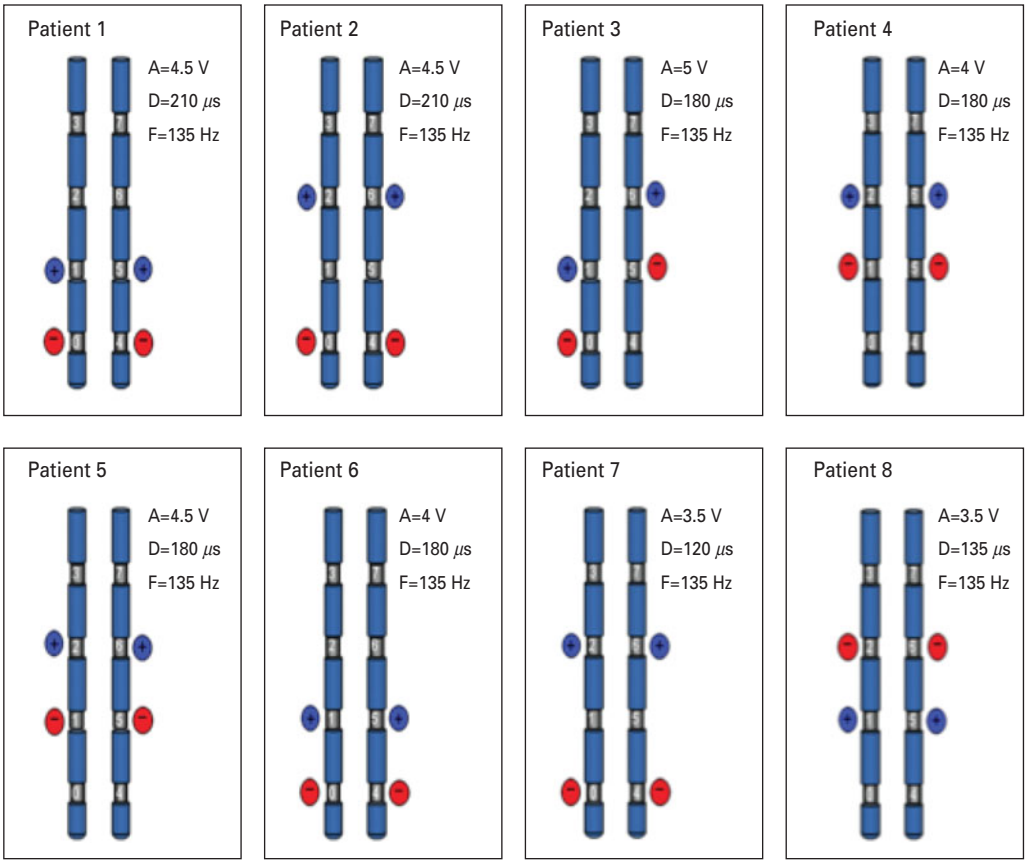

Fig. 1. Electrode contacts and current stimulation parameters in every patient. A, Amplitude in volts; D, pulsewidth in microseconds; F, frequency in Hertz. Red circles represent contact cathode and blue circles, contact anode of electrodes.

months) followed by *post-hoc t* tests *vs*. baseline. Additional analyses were performed using *t* tests or ANOVA, as appropriate. Significance level was set at 5% (two-tailed). Last observation carried forward analysis was applied for missing data.

Results

Patients' characteristics

Subjects' clinical and demographic characteristics are shown in Table 1. The $HAMD_{17}$ mean score was 21.3 (S.D. = 2.4) at entry. The mean age at onset of disease was 24.9 (S.D. = 5.3) yr and the mean age at electrode implant was 47.4 (S.D. = 11.3) yr. Duration of the current episode was 6.3 (S.D. = 1.8) yr. The length of follow-up period was 1 yr.

All patients had failed in multiple trials of pharmacotherapy and six of them also failed in adequate individual psychotherapy. Included patients had shown good treatment responses in the early stages of the disorder, and they became treatment-resistant over the course of the illness (see Table 2*a* for a summary of treatment history of each patient). In this regard, all patients had received ECT, four of which showed partial response to maintenance ECT before DBS.

At the time of surgery, all patients were being treated with one or two antidepressant drugs from different families, combined with one or several of the following drugs: a mood stabilizer (lithium, valproate, lamotrigine), an atypical antipsychotic or an anxiolytic (benzodiazepine or pregabalin). Maintenance ECT (received by four patients, with partial response) was stopped 2 wk before inclusion in the study. Antidepressant drugs were not changed during the follow-up period; benzodiazepines and antipsychotic drugs were reduced in parallel with clinical improvement. Patient 4 suffered tricyclic antidepressant intoxication due to drug interaction within the first month after intervention, so the antidepressant drug had to be changed to a SSRI; this patient did not respond to DBS at the end of follow-up. A detailed description of baseline and 1-yr follow-up pharmacological treatment is given in Table 2*b*.

Table 1. Clinical and demographic characteristics of the sample

	Mean (S.D.)
Gender (female/male)	6/2
Marital status	
Single (*n*)	4
Married (*n*)	4
Years of education	12.5 (3.9)
Age at surgery	47.4 (11.3)
Age at MDD onset	24.9 (5.3)
Length of current episode (yr)	6.3 (1.8)
Previous suicidal attempts (*n*)	8
Family history of affective disorders (*n*)	7
Number of previous episodes	5.5 (3.7)
Number of previous hospitalizations	7.5 (5.5)
Patients with melancholic characteristics (*n*)	6
MADRS	
Pre-DBS	28.5 (6.3)
GCI	
Pre-DBS	5.1 (0.8)
$HAMD_{17}$	
Pre-DBS	21.3 (2.4)

DBS, Deep brain stimulation; MDD, major depressive disorder; MADRS, Montgomery–Åsberg Depression Rating Scale; GCI, Clinical Global Impression scale; $HAMD_{17}$, Hamilton 17-item Depression Rating Scale.
Values represent mean and standard deviation (S.D.) unless specified otherwise.

DBS outcomes

Seven (87.5%) out of eight patients reached the response criterion and four (50%) of eight were in remission ($HAMD_{17} \leqslant 7$) in the first week after surgery. This was followed by a general worsening, with an overall response rate of 37.5% (3/8 patients) at 1 month. From then onwards, patients showed a progressive improvement: at 6 months, response and remission rates were, respectively, 87.5% (7/8) and 37.5% (3/8), whereas the corresponding figures at 1 yr were 62.5% (5/8) and 50% (4/8). Notably, 3/4 patients, who fulfilled remission criteria at the end of the 1-yr follow-up, had already remitted after 3 months of DBS.

$HAMD_{17}$ scores were significantly improved by DBS ($F = 42.3$, d.f. = 1, 6, $p < 0.001$). Figure 2 displays the mean and individual changes of HAMD scores over time. Mood, anxiety, somatic, and sleep subscales of the $HAMD_{17}$ were also analysed after 1, 2, 4, 6, 9 and 12 months post-surgery. DBS was effective in all subscales as well as in the global depressive symptoms ($F = 1.94$, d.f. = 24,168, $p = 0.008$, see Table 3).

Further, patients were classified as responders and non-responders after 1 yr DBS. There were no differences between responders and non-responders in age (47.2 *vs.* 47.3 yr, respectively), onset of illness (23.6 *vs.* 27 yr), duration of illness (5.8 *vs.* 5 yr) or length of the current depressive episode (6.4 *vs.* 6.3 yr). Interestingly, four out of the five patients who responded to DBS had partially responded to maintenance ECT before surgery ($\chi^2 = 4.8$, $p = 0.03$). As expected, responders showed a more marked reduction of mood and anxiety clusters scores at follow-up (repeated-measures ANOVA), group effect (mood: $F = 9.72$, d.f. = 1, 6, $p = 0.02$); time × group interaction (mood: $F = 2.71$, d.f. = 6, 36; $p = 0.03$; anxiety: $F = 2.67$, d.f. = 6, 36, $p = 0.03$, see Table 3).

CGI and MADRS scores were also significantly improved by DBS ($t = -5.8$, d.f. = 7, $p = 0.001$; $t = 5.5$, d.f. = 7, $p = 0.001$, respectively; Table 3). Neuropsychological performance at the time of clinical stabilization (5.8 months on average) was unaffected by DBS. However, all patients reported a better impression about their performance than before DBS when asked. At the time of writing, the majority of patients have recovered, or even started leisure activities and social relationships, after having been inactive due to their depressive illness for several years prior to intervention. Additionally, two patients no longer require daily support. These are indicators that DBS would also enhance the psychosocial functioning.

Intra-operative findings and electrode localization

None of the patients reported acute behavioural or cognitive effects spontaneously, or after answering intra-operative stimulation test items. Similarly, no adverse effect was reported by any patient at a stimulation intensity of 9.0 V in any electrode contact.

Magnetic resonance 1.5 T images were co-registered on the 3 T images (obtained just before surgery) to determine localization on the highest quality images. DBS electrodes were visualized in coronal, axial and sagittal planes. The tip to be targeted was the single electrode (16.6 mm long) which included the two active contacts (cathode and anode) since all patients were already receiving bipolar stimulation. Thereafter, all images where normalized to MNI (Montreal Neurological Institute) space and coordinates were defined. The location of the electrodes was set by using the labels of the nearest grey matter delivered by the Talairach atlas. Figure 3 shows the approximate location of electrodes in each patient, obtained after normalization to a single MNI space. Table 4 shows the exact location of electrodes according to MNI and

Table 2*a*. Summary of previous treatments to which patients developed resistance

	Patient 1 (female)	Patient 2 (female)	Patient 3 (female)	Patient 4 (female)	Patient 5 (female)	Patient 6 (female)	Patient 7 (female)	Patient 8 (female)
Pharmacological treatments								
TCAs	2	3	3	2	2	1	3	2
MAOIs	2	2	2	2	1	1	1	0
SSRIs	2	1	1	3	5	1	2	2
SNRIs	2	2	2	2	2	2	2	1
Others	4	4	3	2	2	2	No	No
Potentiation	5	2	4	5	3	2	1	2
Mood stabilizers	3	4	5	2	1	2	2	3
Drug combinations	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
ECT	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Psychotherapy	No	Yes	Yes	Yes	Yes	Yes	No	Yes

TCAs, Tricyclic antidepressants (imipramine, clomipramine, amitriptyline, nortriptyline); MAOIs, monoamine oxidase inhibitors (phenelzine, tranylcypromine, moclobemide); SSRIs, selective serotonin reuptake inhibitors (fluoxetine, fluvoxamine, paroxetine, citalopram, sertraline); SNRIs, venlafaxine, duloxetine; Others, mianserine, mirtazapine, reboxetine, trazodone; Potentiation: with lithium, methylphenidate, triiodothyronine, pindolol, tryptophan, atypical antipsychotics; Mood stabilizers: lithium, valproate, lamotrigine, carbamazepine; ECT, electroconvulsive therapy.
Values are the number of drugs of each class attempted at adequate dosages and periods.

Talairach stereotaxic coordinates. Spearman's correlation showed a significant relationship between electrode localization (nearest grey matter label in Table 4) and responders/non-responders at 12 months ($\rho = 0.8$, $p = 0.017$). Responders appeared to have electrodes placed mostly in BA 24, corpus callosum and head of caudate, whereas non-responders had a predominant location near BA 25.

Incidents and adverse events

Surgical procedure and post-operative period was well-tolerated for all patients. Few adverse events were observed: two patients reported cephalalgia, and three reported pain in the neck at the site of the subdermal cable. In all eight patients there were no other adverse events reported by previous studies, such as wound infection, scalp cellulitis or seizures. One explanation for the lack of infections, already suggested by Mayberg *et al.* (2005), relies on the fact that all patients had the electrodes and the pulse generator inserted in a single surgical intervention.

One patient, after having displayed an initial clinical improvement, attempted suicide 4 months after starting DBS, which required hospitalization. This patient did not fulfil response criteria at 6 and 12 months' post-surgery, although she still achieved a certain improvement in her psychosocial functioning. On the other hand, two of the five final responders displayed a severe depressive recurrence during the first 3–4 months after starting DBS. One of them, who was on maintenance ECT before DBS, was treated again with nine sessions of ECT, achieving and maintaining remission criteria since then (see Puigdemont *et al.* 2009 for more details).

Discussion

The present study confirms and extends previous observations on the usefulness of DBS to treat depressive symptoms in patients suffering from severe TRD. These findings represent the second independent series of DBS of the subgenual cingulate gyrus (SCG) and confirm that SCG-DBS produces robust improvements in TRD. Indeed, seven (87%) patients responded significantly after 6 months of chronic stimulation and 50% remitted after 1 yr of DBS. Response rates in our study are similar or greater than those reported in previous studies (Bewernick *et al.* 2010; Kennedy *et al.* 2011; Lozano *et al.* 2008; Malone *et al.* 2009; Mayberg *et al.* 2005; Schlaepfer *et al.* 2008). In this regard, a recent longitudinal study by Kennedy *et al.* (2011) has reported a response rate of 60% after 1 yr of stimulation, which is reasonably maintained after 3 yr of DBS. As reported by Lozano *et al.* (2008) the maximal clinical improvement was observed after several months of chronic stimulation reaching a plateau after 6 months. Interestingly, clinical evolution during the first 3 months did not predict final outcomes: early worsening and recurrences were observed even in

Table 2*b*. Detailed description of pre-DBS and 1-yr follow-up pharmacological treatment per each patient

	Pharmacological treatment pre-DBS	Pharmacological treatment 1-yr follow-up
Patient 1	Duloxetine (300 mg/d)	Duloxetine (300 mg/d)
	Mianserine (60 mg/d)	Mianserine (60 mg/d)
	Pregabaline (900 mg/d)	Pregabaline (600 mg/d)
	Lithium (600 mg/d)	Lithium (400 mg/d)
	Quetiapine (400 mg/d)	Quetiapine (400 mg/d)
	Clonazepam (2 mg/d)	Clonazepam (1.5 mg/d)
Patient 2	Duloxetine (120 mg/d)	Duloxetine (120 mg/d)
	Olanzapine (20 mg/d)	Quetiapine (1000 mg/d)
		Lorazepam (2 mg/d)
Patient 3	Venlafaxine (300 mg/d)	Venlafaxine (300 mg/d)
	Mirtazapine (60 mg/d)	Mirtazapine (60 mg/d)
	Lithium 400 mg/d	Lithium (400 mg/d)
	Diazepam (30 mg/d)	Diazepam (30 mg/d)
	Quetiapine (150 mg/d)	Quetiapine (150 mg/d)
	Ziprasidone 80 mg/d	
Patient 4	Fluvoxamine (200 mg/d)	**Escitalopram (40 mg/d)**
	Clomipramine (100 mg/d)	**Mianserine (60 mg/d)**
	Pregabaline (150 mg/d)	Pregabaline (150 mg/d)
	Flunitrazepam (1 mg/d)	**Diazepam (25 mg/d)**
		Quetiapine (50 mg/d)
Patient 5	Duloxetine (90 mg/d)	Duloxetine (90 mg/d)
	Mirtazapine (30 g/d)	Mirtazapine (30 mg/d)
	Olanzapine (15 mg/d)	Olanzapine (5 mg/d)
	Diazepam (62.5 mg/d)	Diazepam (50 mg/d)
	Alprazolam (6 mg/d)	Alprazolam (6 mg/d)
	Zolpidem (10 mg/d)	Zolpidem (10 mg/d)
	Levomepromazine (50 mg/d)	Levomepromazine (50 mg/d)
		Pregabaline (300 mg/d)
Patient 6	Duloxetine (120 mg/d)	Duloxetine (120 mg/d)
	Mirtazapine (60 mg/d)	Mirtazapine (60 mg/d)
	Valproate (1500 mg/d)	Valproate (1500 mg/d)
	Levomepromazine (100 mg/d)	Trazodone (200 mg/d)
	Trazodone (200 mg/d)	Lorazepam (5 mg/d)
	Lorazepam (5 mg/d)	Midazolam (7.5 mg/d)
	Midazolam (7.5 mg/d)	
	Alprazolam (1.5 mg/d)	
Patient 7	Imipramine (150 mg/d)	Imipramine (150 mg/d)
	Zolpidem (10 mg/d)	Medazepam (10 mg/d)
	Medazepam (10 mg/d)	
Patient 8	Clomipramine (250 mg/d)	Clomipramine (250 mg/d)
	Lamotrigine (400 mg/d)	Lamotrigine (400 mg/d)
	Quetiapine (50 mg/d)	Quetiapine (50 mg/d)
	Clorazepate (30 mg/d)	Clorazepate (10 mg/d)
	Lormetazepam (1 mg/d)	

Drugs that were ruled out or diminished after 1 yr are underlined. Drugs that have been changed or introduced after 1 yr are in bold.

patients who finally responded. However, patients remitted at 3 months maintained remission criteria until the end of the 1 yr follow-up.

Regarding intra-operative effects, none of our patients noticed the initiation of electrode stimulation. Mayberg *et al.* (2005) reported subjective experiences,

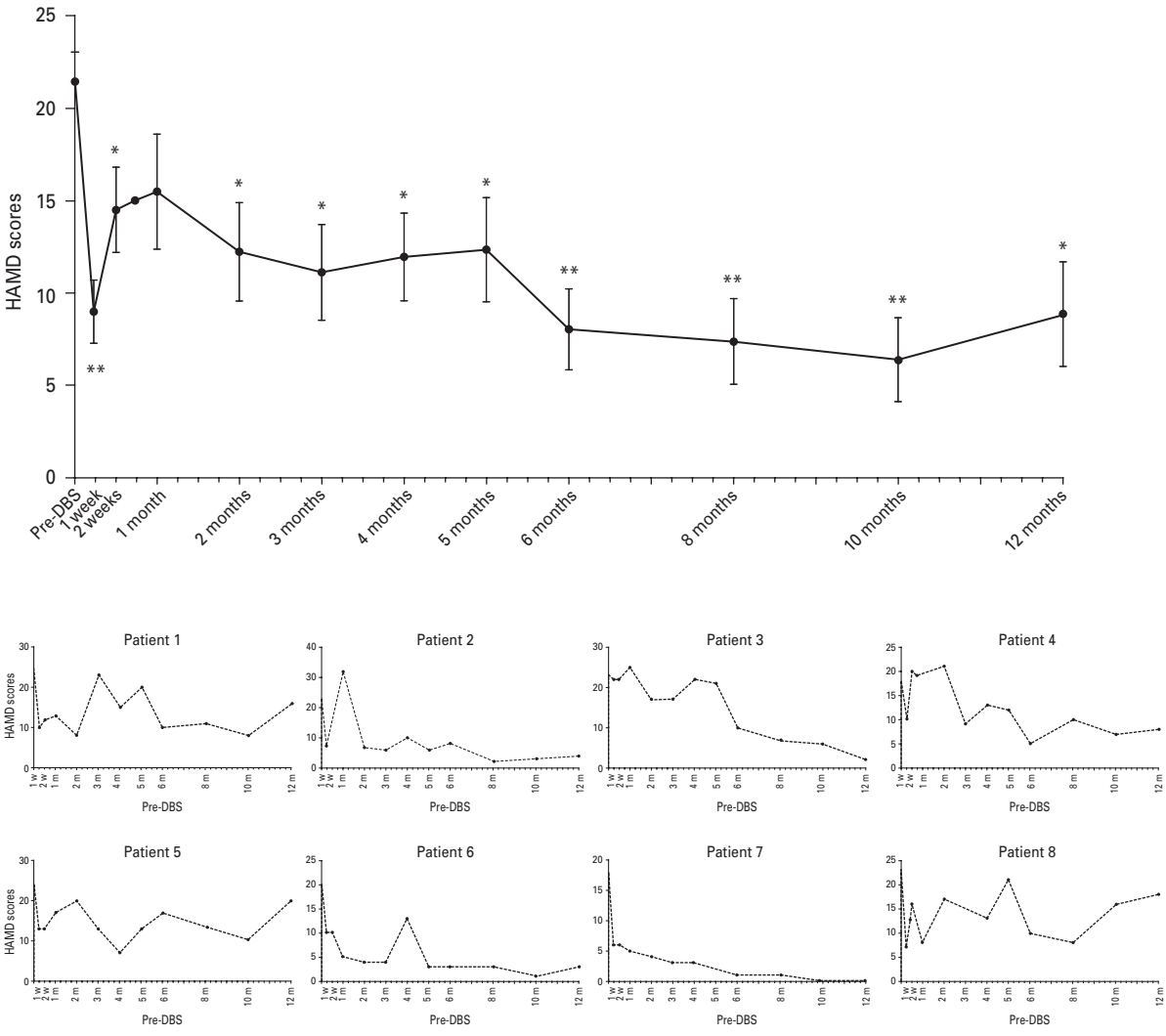

Fig. 2. Effect of deep brain stimulation (DBS) of the subcallosal gyrus (SCG) on the 17-item Hamilton Depression Rating Scale ($HAMD_{17}$). *Upper panel*: Mean ± S.D. change of $HAMD_{17}$ for all patients in the study. *Lower panels*: Individual changes of $HAMD_{17}$ (w, week; m, month). * $p<0.01$, ** $p<0.001$ *vs.* inclusion.

but this has not been further reported. However, our patients did show a post-surgery improvement within the first 2 wk, with a subsequent transient worsening. This phenomenon could be explained *a priori* by a placebo effect although it has been partly related to a micro lesion in the treatment of Parkinson's disease and essential tremor, where transient clinical improvements can be evoked solely by the introduction of electrodes (Maltête *et al.* 2009; Morishita *et al.* 2010). A similar effect could also occur in the treatment of chronic major depression (Lozano *et al.* 2008). In our case, this initial benefit did not predict the subsequent evolution of patients.

Indeed, one of the most intriguing questions in DBS is why some TRD patients do respond to DBS while others do not. Our results demonstrated a relationship between previous partial responses to ECT and response to DBS. This observation suggests that previous response to ECT is a predictor of DBS outcomes, although – due to the small sample size – this cannot be fully clarified. Taking into account the limitations and side-effects of ECT in prolonged maintenance regimens, DBS may be an excellent therapeutic alternative for treating TRD without entailing memory loss or cognitive dysfunction. Moreover, DBS has proven to be well-tolerated and compatible with ECT (see Puigdemont *et al.* 2009 for a case report).

Furthermore, SCG-DBS might enhance ECT efficacy in patients with previous partial response to the latter

Table 3. Effects of DBS on $HAMD_{17}$ subscales, MADRS and CGI scores

	Pre-DBS	1 wk after	2 wk after	1 month after	2 months after	4 months after	6 months after	9 months after	12 months after
$HAMD_{17}$									
Mood	9.5 (2.3)	4.7 (2.8)*	6.3 (2.4)*	6 (3.7)$^{+}$	4.6 (3.7)*	4.8 (2.9)*	3.5 (2.6)**	2.4 (2.4)**	3.9 (4.6)*
Anxiety	5.8 (1.5)	2.3 (1.7)**	3.9 (2.6)	4.8 (3.1)	3.6 (2.6)$^{+}$	3.3 (2.1)*	1.9 (1.7)**	2.1 (1.6)**	2.8 (1.9)*
Insomnia	2.3 (1.4)	1 (0.9)*	1.1 (1.5)	1.4 (1.8)	0.9 (1.1)*	0.6 (0.9)**	0.1 (0.4)**	0.4 (1.1)**	0.6 (1.2)*
Somatization	3.5 (1.2)	2.4 (1.2)$^{+}$	2.8 (1)	2.9 (1.4)	3 (1.4)	2.6 (0.7)$^{+}$	2.4 (1.1)$^{+}$	1.8 (0.9)**	1.6 (0.9)**
MADRS	28.5 (6.3)								10.8 (11.3)
CGI	5.1 (0.8)								2.1 (1.4)

$HAMD_{17}$, Hamilton 17-item Depression Rating Scale; MADRS, Montgomery–Åsberg Depression Rating Scale; GCI, Clinical Global Impression scale.
Values represent mean (S.D.).
$^{**}p = 0.001$, $^{*}p = 0.01$, $^{+}p = 0.05$ for differences from pre-DBS scores.

treatment, given that, when a relapse occurs after the implantation of the neurostimulator, ECT yielded a better sustained response. A common mechanism of action in terms of the electrophysiological effects could be claimed for both DBS and ECT, although more research is required. In any case, the above data indicate that DBS is not an endpoint for the treatment of implanted patients, but a strategy that can allow new intentions of previously ineffective antidepressant treatments if these patients suffer a relapse.

Interestingly, changes in clinical symptoms, as measured with the HAMD subscales, were different in responders and non-responders, where those patients who responded displayed a greater improvement in mood and anxiety. Previous studies have also reported the decrease in anxiety (Bewernick *et al.* 2010) and core depressive symptoms (Lozano *et al.* 2008) as being responsible of the general improvement of implanted patients. The present results show that DBS of SCG evokes an overall effect on all HAMD subscales, including anxiety symptoms.

The neurobiological basis of the antidepressant effects of SCG-DBS is presently unknown, due to the poor knowledge of brain circuits involved in the pathophysiology and treatment of major depression. Based on alterations of brain energy metabolism in depressed patients, a model involving cortical, limbic and thalamic areas has been put forward (Seminowicz *et al.* 2004) in which SCG areas play key roles. The enhanced activity of some of these areas (including Cg25) seen in untreated depressed patients decreases after psychological (cognitive behavioural therapy) and antidepressant drug treatments (Seminowicz *et al.* 2004). Thus, DBS may normalize an altered function of cortico-limbic and cortico-thalamic networks by removing an altered input from SCG onto other frontal areas. Further, given the strong reciprocal connectivity between the prefrontal cortex and the brainstem monoaminergic nuclei, where the cell bodies of ascending serotonergic, noradrenergic and dopaminergic neurons are located (see for review Groenewegen & Uylings, 2000), SCG-DBS may normalize a putative monoaminergic hypofunction secondary to abnormal inputs from prefrontal cortex.

Previous studies failed to find a relationship between the location of active electrode contacts and treatment outcome (Hamani *et al.* 2009). However, our results show a relationship between long-term response (1 yr) and electrode location, indicating the requirement of SCG stimulation, but not necessarily of Cg25. Unlike in Mayberg's studies, stimulating Cg25 (Hamani *et al.* 2009; Lozano *et al.* 2008; Mayberg *et al.* 2005), most responder patients in the present study had their electrodes in Cg24 (some also in corpus callosum and head of caudate). This difference may be due to several factors. On the one hand, we used bipolar stimulation in our patients whereas previous studies in the SCG by Mayberg's group have used monopolar stimulation. Indeed, both procedures result in different excitation of nerve fibres (Yokoyama *et al.* 2001) probably affecting different afferent and efferent areas to the stimulation site. On the other hand, DBS drives focal activity at the immediate target, which, in turn, leads to inhibition or excitation in adjacent and remote areas to which it is connected. As hypothesized by Hamani *et al.* (2009), stimulation

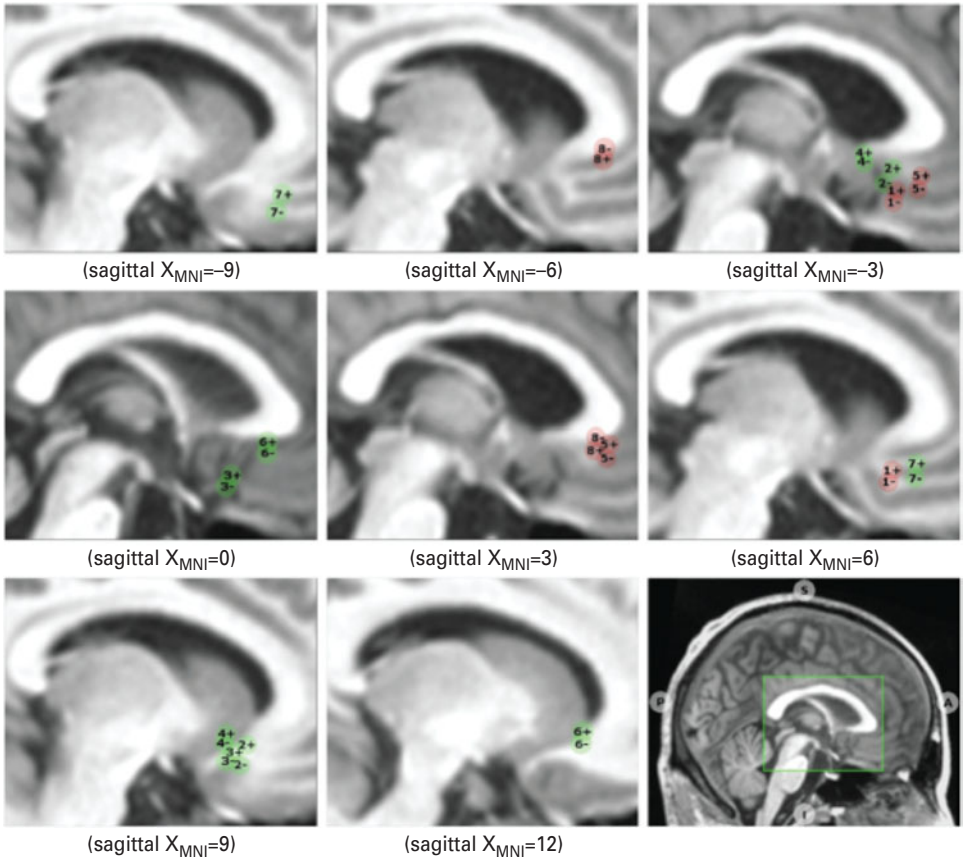

Fig. 3. Location of the electrode contacts on a sagittal view of the cingulate gyrus. Circles are schematic representations of the electrode contacts in patients responding (green circles) and not responding (red circles) to DBS of the SCG. Numbers correspond to every patient. More detailed information is given in Table 4.

within distinctive regions along the SCG should lead to varied outcomes due to the recruitment of different fibre systems, i.e. more anterior contact location would probably affect the cingulate bundle, whereas more posterior active contacts would affect a more complete set of projections to and from SCG. Intriguingly, unlike in Hamani *et al.* (2009), our results appear to confirm this view. This difference may be explained by the putative involvement of the areas in which our patients had the electrodes implanted (e.g. corpus callosum stimulation will evoke an immediate depolarization blockade of stimulated axons, as if DBS were applied in the cortical area containing the cell bodies).

Limitations

Despite the novelty of the present findings (second independent study of SCG-DBS), the study has some limitations. First is the limited sample size, which prevented us establishing predictors of response to DBS. However, reporting the present results can help to establish DBS as a therapeutic tool in the treatment of resistant depression. A second limitation, in common with previous DBS studies in depression, is the lack of a control group, due to ethical reasons (e.g. dummy DBS in chronic TRD patients). This limitation will be partly solved in the current cross-over phase of the present trial. Last, a weakness of our study is the lack of functional neuroimaging data in order to understand brain metabolic changes induced by DBS.

Conclusions

These findings report the second independent study on the use of DBS of the SCG to treat depression resistant to current therapeutic strategies. DBS of the SCG was able to induce a full remission in four out of the eight patients included after 1 yr

Table 4. Bilateral single point localization of electrodes in each patient in both MNI and Talairach coordinates

	MNI	Talairach	Single point	Nearest grey matter
Patient 1				
Left negative	−2, 20, −18	−3, 18, −10	Left anterior cingulate	Left anterior cingulate BA 25
Left positive	−2, 20, −15	−3, 18, −8	Left anterior cingulate	Left anterior cingulate BA 25
Right negative	5, 19, −16	4, 17, −8	Right anterior cingulate	Right anterior cingulate BA 25
Right positive	5, 19, −13	4, 17, −6	Right anterior cingulate BA 25	Right anterior cingulate BA 25
Patient 2				
Left negative	−3, 17, −14	−4, 15, −7	Left anterior cingulate BA 25	Left anterior cingulate BA 25
Left positive	−4, 19, −9	−5, 17, −2	Left extra-nuclear WM	Left caudate head
Right negative	9, 16, −15	8, 14, −8	Right anterior cingulate WM	Right caudate head
Right positive	8, 18, −10	7, 16, −3	Right extra-nuclear WM	Right caudate head
Patient 3				
Left negative	−0, 13, −17	−1, 12, −10	Left anterior cingulate	Left anterior cingulate BA 25
Left positive	−0, 14, −14	−1, 13, −7	Left anterior cingulate	Left anterior cingulate BA 25
Right negative	9, 14, −14	8, 12, −7	Right anterior cingulate WM	Right caudate head
Right positive	10, 15, −12	8, 13, −5	Right caudate head	Right caudate head
Patient 4				
Left negative	−2, 10, −7	−3, 8, −1	Left extra-nuclear WM	Left caudate head
Left positive	−2, 11, −5	−3, 9, 1	Left lateral ventricle	Left caudate head
Right negative	8, 12, −9	7, 10, −3	Right caudate head	Right caudate head
Right positive	8, 13, −7	7, 11, −1	Right caudate head	Right caudate head
Patient 5				
Left negative	−3, 26, −13	−4, 24, −5	Left anterior cingulate BA 24	Left anterior cingulate BA 24
Left positive	−3, 26, −11	−4, 23, −3	Left anterior cingulate BA 24	Left anterior cingulate BA 24
Right negative	4, 27, −9	3, 24, −1	Right corpus callosum	Right anterior cingulate BA 24
Right positive	4, 28, −6	3, 25, 1	Right corpus callosum	Right anterior cingulate BA 24
Patient 6				
Left negative	−0, 24, −8	−1, 21, −1	Inter-hemispheric	Left anterior cingulate BA 24
Left positive	−0, 24, −5	−1, 21, 2	Inter-hemispheric	Left anterior cingulate BA 24
Right negative	13, 22, −9	11, 19, −2	Right caudate head	Right caudate head
Right positive	13, 22, −6	11, 19, 1	Right caudate head	Right caudate head
Patient 7				
Left negative	−9, 27, −20	−9, 25, −12	Left medial frontal gyrus WM	Left medial frontal gyrus BA 11
Left positive	−9, 29, −15	−9, 27, −7	Left anterior cingulate WM	Left anterior cingulate BA 24
Right negative	5, 26, −14	4, 24, −6	Right anterior cingulate BA 24	Right anterior cingulate BA 24
Right positive	5, 26, −9	4, 23, −2	Right corpus callosum	Right anterior cingulate BA 24
Patient 8				
Left negative	−6, 29, −3	−6, 26, 4	Left corpus callosum	Left caudate head
Left positive	−6, 29, −5	−6, 26, 2	Left corpus callosum	Left anterior cingulate BA 24
Right negative	3, 28, −4	2, 25, 3	Right corpus callosum	Right anterior cingulate BA 24
Right positive	4, 28, −6	3, 25, 1	Right corpus callosum	Right anterior cingulate BA 24

MNI, Montreal Neurological Institute space; WM, white matter; BA, Brodmann area.
Last column corresponds to nearest grey matter, when the electrode was placed elsewhere.

of stimulation. Clinical effects were seen in all $HAMD_{17}$ subscales without a significant incidence of side-effects. On the other hand, responses appear to depend on electrode localization, with most responder patients having electrodes localized in BA 24, corpus callosum and head of caudate. Similarly, early responses did not predict the final outcome at 1 yr. Finally, all patients with previous partial responses to maintenance ECT showed good responses to DBS.

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Statement of Interest

Dr Enric Alvarez has received consulting and educational honoraria from several pharmaceutical companies including Eli Lilly, Sanofi-Aventis, Lundbeck and Pfizer, and he has participated as main local investigator in clinical trials for Eli Lilly, Bristol–Myers and Sanofi-Aventis and also as national coordinator of clinical trials for Servier and Lundbeck. Dr Víctor Pérez has received educational honoraria from the following pharmaceutical companies: Sanofi-Aventis, Lundbeck, Pfizer and Eli Lilly. Dr Francesc Artigas has received consulting and educational honoraria from Boehringer-Ingelheim, Eli Lilly, Lundbeck, Elan and Pierre Fabre.

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