DEEP BRAIN STIMULATION OF THE SUBCALLOSAL CINGULATE GYRUS: FURTHER EVIDENCE IN TREATMENT- RESISTANT MAJOR DEPRESSION

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ABSTRACT

Background: 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 safety of DBS in eight TRD patients. These data correspond to the pre-randomisation period of an ongoing randomised controlled, crossover clinical trial.

Methods: Electrodes were implanted bilaterally in the subgenual cingulate gyrus (SCG; mostly in Broadman areas 24-25) and stimulated at 135 Hz (90-μs pulse width). Voltage and active electrode contacts were adjusted to maximize short-term responses. Clinical assessments included the 17-item Hamilton Depression Raring Scale (HDRS-17; primary measure) and Montgomery-Åsberg (MADRS) scales for depression and the Clinical Global Impression Scale.

Results: In the first week after surgery, 87.5% of the patients reached the response criterion and 50% were in remission (HDRS≤ 7). This was followed by an overall worsening, with a response rate of 37.5% at one moth. From then onwards, patients showed a progressive improvement: 87.5% of patients were classified as responders and 37.5% patients were remitted at six moths whereas the corresponding figures at 1 year were 62.5% and 50%. Clinical effects were seen in all HDRS subscales without a significant incidence of side effects. Surgical procedure and postoperative period were safe for all patients.

Conclusions: 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.

Trial Name**: "**DEEP BRAIN STIMULATION IN TREATMENT RESISTANT MAJOR DEPRESSION. Controlled and Crossed Study on Efficacy and Safety"

Registration number: NCT01268137

INTRODUCTION

Major depressive disorder (MDD) has a lifetime prevalence of around 15-20% (1), and it is one of the leading causes of disability worldwide (2) since is often accompanied by high rates of resistance to treatment. The STAR*D trial reported up to 33% of patients without remission after four sequenced treatments (3), 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 depression (TRD). However, a considerable proportion of patients do not respond, experience frequent relapses, or do not tolerate its adverse effects, mainly memory disturbances (4).

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 the treatment of drug-resistant Parkinson's disease (5). 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 (6). 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 the Brodmann Area 25 (subgenual cingulate gyrus, SCG). Mayberg and colleagues (7,8,9) reported that 60% of TRD

patients subjected to DBS of Cg25 experienced a response (≥50% reduction of the Hamilton Depression Rating Scale –HDRS- score) and 35% fulfilled the criterion for remission (HDRS score ≤ 7) after 6 months of stimulation. The response rates were fairly maintained after 1, 3 and 6 years. Also, 50% of the patients subjected to DBS of NAc responded in a 1-year observation period (10,11). Electrode implantation in the VC/VS also provided response rates of 40% and ~50% at 6 and 24 months, respectively (12).

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 feeds back onto the prefrontal cortex and cingulate cortex, closing a limbic loop. The possibility of modulating a presumable dysfunctional activity of this circuit from the SCG should provide a good chance to bear upon the broad spectrum of depressive symptoms (13, 14), as suggested by the robust antidepressant effects observed in the first sample of TRD patients receiving SCG DBS (7,8, 9).

The current study aims at replicating and extending these findings. Thus, here we describe the short- and long-term clinical outcomes and safety of Cg25 stimulation in a new independent sample of eight patients with TRD.

METHODS AND MATERIALS

We report on the preliminary findings of the pre-randomisation period of a randomised controlled and crossover clinical trial. In this initial phase of the study electrodes were implanted in all patients and chronic stimulation started within the first 48 hours after surgery. The length of this study phase varied depending on the

time required by each patient to achieve clinical stability –i.e., less than 10% variation in HDRS scores along 3 or more consecutive visits after reaching the criterion of response.

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' psychiatrists, an independent psychiatric consultant, a neurologist and a neurosurgeon decided which patients could be enrolled 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). The protocol is registered at http://ClinicalTrials.gov with the identifier NCT01268137.

Inclusion criteria. Individuals 18-70 year-old 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 index (15) and with lack of efficacy of ECT or partial response to maintenance ECT. Admission score on the 17-item HDRS had to be 18 or greater. They 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 safety 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 carried out by means of Structured Clinical Interview for DSM-IV axis I and II (SCID) (16,17). Assessments included HDRS-17 (primary measure) (18), the Montgomery-Åsberg Depression Rating Scale (MADRS)(19), and the Clinical Global Impression Scale (CGI) (20) which were collected to evaluate changes on clinical outcomes. Response was defined as a decrease of 50% or greater of the baseline HDRS-17 score. Remission was defined as a score of 7 or lower in HDRS-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, Atlanta, 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 to calculate the

surgical target. The target subgenual cingulate 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 area 25 [(based on Mayberg et al., (7)]. 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 micro-recordings started 10 mm above the target. Cell activity was amplified and analysed in an oscilloscope and an audio monitor (Leadpoint, Medtronic). Micro-recordings were performed to identify the transition between grey and white matter in area 25 where the electrodes were implanted. DBS electrodes (Medtronic mod. 3387) were implanted bilaterally. Each of the 4 electrode contacts was tested intra-operatively at maximal voltage (9.0 V) to study adverse effects and subjective feelings. During the same surgical act, 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 days after surgery. A high resolution 3D-T1 weighted MRI was obtained using a dedicated protocol on a 1.5T Philips equipment within the first two months after surgery in order to check the electrode localization.

Stimulation settings

In the 1-5 days 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. (8), the first three patients were stimulated as follows: continuous monopolar stimulation at 3.6 V (135 Hz, 90-μs pulse width) using the most ventral electrode contacts. The sequence of changes to maximize the therapeutic effect was 1) to increase voltage amplitude, 2) to increase pulse width, and 3) to change active contacts. Electrode contacts and current stimulation parameters in each patient are shown in Figure 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.

Statistical analysis

Descriptive analyses were performed in order to characterize the sample with parametric and non-parametric tests. To evaluate clinical response, all rating scales were analyzed with ANOVA for repeated measures with time as within-subjects factor (baseline, 1, 2, 4, 6, 9, and 12 months). Post hoc paired comparisons (*t*-test) vs. baseline were calculated for each time point. 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

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

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

At the time of surgery, all patients were being treated with one or two antidepressant from different families that were combined with one or several of the following drugs: a mood-stabilizer (lithium, valproate or lamotrigine), an atypical antipsychotic or an anxiolitic (benzodiazepine or pregabalin). Maintenance ECT (received by four patients, with partial response) was stopped 2 weeks before inclusion in the study. Afterwards, during the follow-up, antidepressant drugs were not changed; benzodiazepines and antipsychotics were reduced in parallel with clinical improvement.

DBS outcomes

87.5% of the patients reached the response criterion and 50% were in remission (HDRS-17≤ 7) in the first week after surgery. This was followed by a general worsening, with an overall response rate of 37.5% at one month. From then onwards, patients showed a progressive improvement: at six months 87.5% of patients were classified as responders and 37.5% patients were remitted whereas the corresponding figures at 1 year were 62.5% and 50%. Notably, 3 of the 4 patients, who fulfilled remission criteria at the end of the 1-year follow-up, were remitted in the third month of chronic stimulation.

HDRS-17 scores were significantly improved by DBS ($F=42.3$; $df=1,6$; $p<0.001$). Figure 2 displays the change of HDRS scores over time. Mood, anxiety, somatic, and sleep subscales of the HDRS-17 were also analysed after 1, 2, 4, 6, 9 and 12 months postsurgery. DBS benefits were seen in all the different subscales of HDRS-17 and associated with global improvement in depressive symptomatology ($F=1.94$; $df=24,168$; $p=0.008$, see Table 3). After the initiation of stimulation, improvements in each of the symptom clusters were progressive until 6 first months, with slight variations from then.

Further, patients were classified as responders and nonresponders after 1 year DBS. There were no differences between responders and nonresponders in age (47.2 *vs.* 47.3, respectively), age at illness onset (23.6 *vs.* 27), duration of illness (5.8 *vs.* 5) or length of the current depressive episode (6.4 *vs.* 6.3). 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

along the follow-up (repeated measures ANOVA, group effect; mood (F=9.72; df=1,6; p=0.02); time x group interaction; mood: F=2.71; df=6,36; p=0.03; anxiety: F=2.67; df=6,36; p=0.03, see Table 3).

CGI and MADRS scores were also significantly improved by DBS (t=–5.8, df=7, p=0.001; t=5.5, df=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. The majority of patients have currently recovered -or even started- leisure activities and social relationships, after having been inactive due to their depressive illness for several years before intervention. Additionally, two patients did not have to require anymore a person for daily support after DBS. These are clear indicators that DBS has also robust effects on psychosocial functioning.

Intraoperative findings and electrode localization

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

Magnetic resonance 1.5T images were co-registered on the 3T 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 Talairach stereotaxic coordinates. Spearman correlation showed a significant relation between electrode localization (nearest gray matter label in table 4) and responders/non-responders at twelve months (rho=0.8, p=0.017). Responders appeared to have electrodes placed mostly in Broadman Area 24, corpus callosum and head of caudate, whereas non-responders had a predominant location near Broadman Area 25.

Incidents and adverse events

Surgical procedure and postoperative period was safe for all patients. Few adverse events were observed: two patients reported cephalalgia, and three of them, pain in the neck at the site of the subdermal cable. In all eight patients there were no other adverse events that have been reported by previous studies, such as wound infection, scalp cellulitis or seizure. One explanation for the lack of infections, already suggested by Mayberg et al. (7), would rely on the fact that all patients had the electrodes and the pulse generator inserted in a single surgery.

One patient, after having displayed an initial clinical improvement, attempted suicide four months after starting DBS, because of which required hospitalization. This patient did not fulfil response criteria at 6- and 12-month 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 –which were on maintenance ECT before DBS– was treated again with 9 sessions of ECT, achieving and maintaining remission criteria from that moment (see ref. 21 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 treatment-resistant depression. These findings represent the second independent series of DBS of the subcallosal cingulate gyrus and confirm that SCG-DBS produces robust improvements in TRD. Indeed, seven patients (87%) responded significantly after six months of chronic stimulation and 50% remitted after one year of DBS Response rates in our study were similar or greater than those reported in prior studies (7-12). In this regard, a recent longitudinal study by Kennedy et al. (9) has reported a response rate of 60% at 1 year of stimulation, which is fairly maintained after three years of DBS. As reported by Lozano et al. (8) the maximal improvement was slightly retarded and progressively consolidated. Interestingly, clinical evolution during the first three months did not predict final outcomes: early worsenings and recurrences were observed even in patients who finally responded. However, those patients who were remitted from the third month, maintained remission criteria until the end of the follow-up.

Regarding intraoperative effects, none of our patients noticed the beginning of DBS. Mayberg et al. (7) reported subjective experiences, but this has not been reported anymore. However, our patients did show a post-surgery improvement within the first two weeks, with a posterior worsening afterwards. This phenomenon could be explained *a priori* by a placebo effect. However, this initial benefit has been partly related to a micro lesion effect either in Parkinson's disease or essential tremor –where transitory clinical improvements can be produced by the solely introduction of electrodes (22,23) – or even in depressive disorder itself (8). DBS of the medial prefrontal cortex in rats indicates that the simple electrode implant evokes antidepressant effects in the forced-swim test (manuscript in preparation), an effect possibly related to inflammatory processes, since the administration of anti-inflammatory drugs prevents the antidepressant benefit. Whatever the reason, this initial benefit was not predictive of the subsequent evolution of our patients.

Indeed, one of the most outstanding question which remains to be answered is why some TRD patients do respond to DBS while others do not. Our results showed up 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- it cannot be completely demonstrated here. Taking into account that ECT is often hard to tolerate in a prolonged maintenance regime, DBS may be an excellent therapeutic alternative for treating TRD without entailing memory loss or cognitive dysfunction. Furthermore, DBS has proven to be safe and compatible with ECT (see 21 for a case report). Furthermore, SCG-DBS might enhance ECT efficacy in patients with

previous partial response to the latter 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 electrophysiologic effects could be claimed for both DBS and ECT, although more research is needed to ascertain it. In any case, the aforementioned comment discloses 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 were different in responders and non-responders, displaying the former a greater improvement in mood and anxiety. Previous studies have also reported the decrement of anxiety (24) and core depressive symptoms (8) as responsible of the general improvement of implanted patients. The present results show that DBS of SGC evokes an overall effect on all HDRS subscales, including anxiety symptoms.

The neurobiological basis of the antidepressant effects of SCG-DBS remains partly 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 depressive patients, a model involving cortical, limbic and thalamic areas has been put forward (14) 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 behavioral therapy) and antidepressant drug treatments (14). 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 25)–, SCG-DBS may normalize a putative monoaminergic hypofunction secondary to abnormal inputs from prefrontal cortex.

Previous studies have concluded that the location of the electrode contacts does not seem to determine outcomes (26). However, our results showed a relationship between response at the end of follow-up period (12 months) and location of electrodes, indicating that the requirement of SCG stimulation, but not necessarily of Cg25. Most responder patients had their electrodes in Cg24 (some also in corpus callosum and head of caudate). An explanation would be consistent with the notion that 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. (26), stimulation within distinctive regions along the SCG should lead to varied outcomes due to the recruitment of different fibber systems, that is to say, more anterior contacts location would probably affect the cingulate bundle, whereas more posterior electrodes would affect a more complete set of projections to and from SCG. Intriguingly, Hamani et al. (26) failed to demonstrate their hypothesis, but our results seem to confirm it. 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 had been applied in the cortical area containing the cell bodies). However, another factor to be taken into account, which also could cast doubt on the significant relation between outcome and electrode location, is that all our patients were

receiving bipolar stimulation, instead of monopolar (used by Mayberg's group). It is possible that monopolar and bipolar stimulation could cause differences of nerve fibber excitation (27) within afferent and efferent connections.

Limitations

Despite the novelty of the present findings (second independent study of SCG-DBS), the study has some limitations. The first one is the limited sample size, which prevents to establish predictors of response to DBS. However, even in this case, 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, which is due to ethical reasons (e.g., dummy DBS in chronic TRD patients). This limitation will be partly solved in the current crossover phase of the present trial. Finally, a weakness of our study in order to understand brain metabolic changes induced by DBS is the lack of functional neuroimaging data.

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 one year of stimulation. Clinical effects were seen in all HDRS-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 BA24, corpus callosum and head of caudate. Likewise, early

responses did not predict the final outcome at 1 year. Finally, all patients with previous partial responses to maintenance ECT showed good responses to DBS.

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Table 1: Clinical and demographic characteristics of the sample.

	Mean (SD)
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 (years)	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)
HDRS-17 pre-DBS	21.3(2.4)

Values represent mean and standard deviation (SD) or otherwise specified. MDD= Major depressive disorder; MADRS= Montogomery-Åsberg Depression Rating Scale; GCI= Global Clinical Impression Scale; HDRS-17= Hamilton Depression Rating Scale of 17 items.

Table 2: Summary of previous treatment tryouts of each included patient, to which they became resistant.

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8
Gender	Female	Female	Female	Female	Male	Female	Female	Male
Pharmacological treatments								
TAD	2	3	3	2	2	1	3	2
MAOIs	2	2	2	2	1	1	1	0
SSRI	2	1	1	3	5	1	2	2
Other	4	4	3	2	2	2	No	No
Dual	2	2	2	2	2	2	2	1
Potentiation	5	2	4	5	3	2	1	2
Stabilizers	3	4	5	2	1	2	2	3
AD Combination	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

Values are the number of drugs of each class intended at adequate dosages and periods
Abbreviations: TAD= tricycle antidepressants (imipramine, clomipramine, amitriptyline, nortriptyline); MAOI =monoamine oxidase inhibitors (phenelzine, tranylcypromine, moclobemide); SSRI= selective serotonin reuptake inhibitors (fluoxetine, fluvoxamine, paroxetine, citalopram, sertraline); Other (mianserine, mirtazapine, reboxetine, trazodone); Dual (venlafaxine, duloxetine); Potentiation= with lithium, methylphenidate, triiodothyronine, pindolol, tryptophan, atypical antipsychotics); Stabilizers (lithium, valproate, lamotrigine, carbamazepine); ECT= electroconvulsive therapy.

Table 3: Effects of DBS on HDRS-17 scores of subscales, MADRS and CGI.

	Pre-DBS	1 month after	2 months after	4 months after	6 months after	9 months after	12 months after
HDRS-17							
Mood	9.5 (2.3)	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)	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)	1.4(1.8)	0.9(1.1)*	0.6(0.9)**	0.1(0.4)**	0.4(1.1)**	0.6(1.2)*
Somatisation	3.5(1.2)	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)

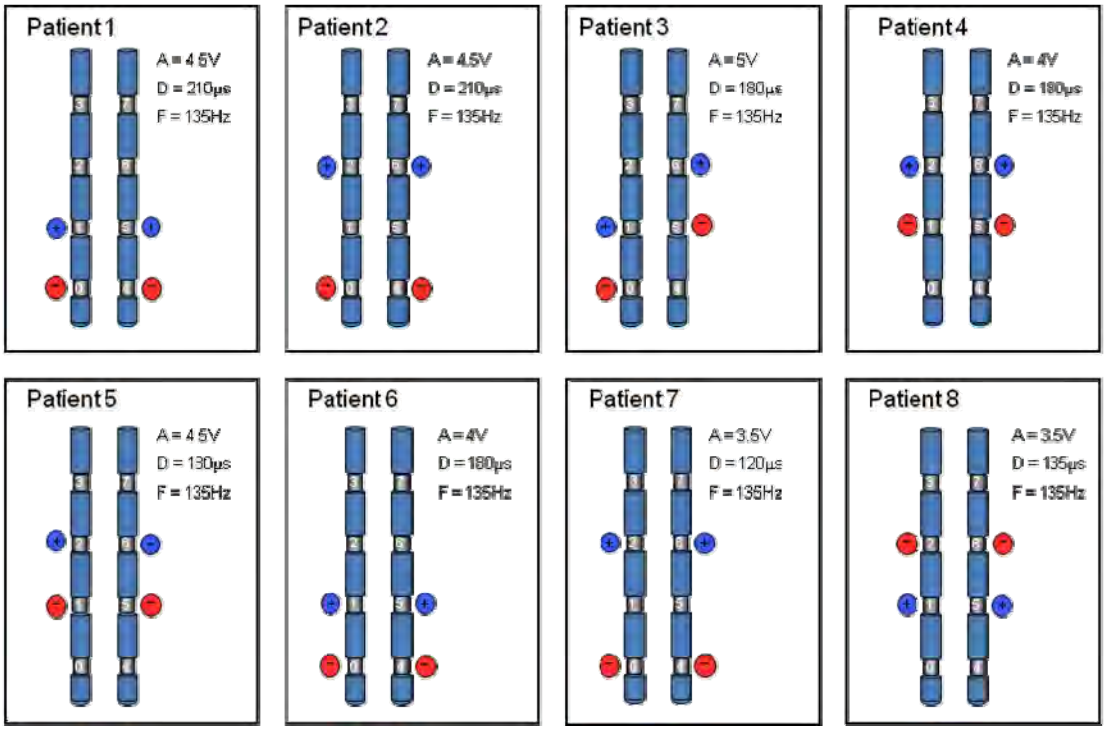
Values represent mean(SD); ** p=0.001,* p=0.01,$^{+}$ p=0.05 for differences from pre-DBS scores.

Table 4: Bilateral single point localization of electrodes in each patient in both MNI and Talairach coordinates. Last column corresponds to nearest gray matter, when the electrode was placed elsewhere.

	MNI	Talairach	Single point	Nearest gray 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

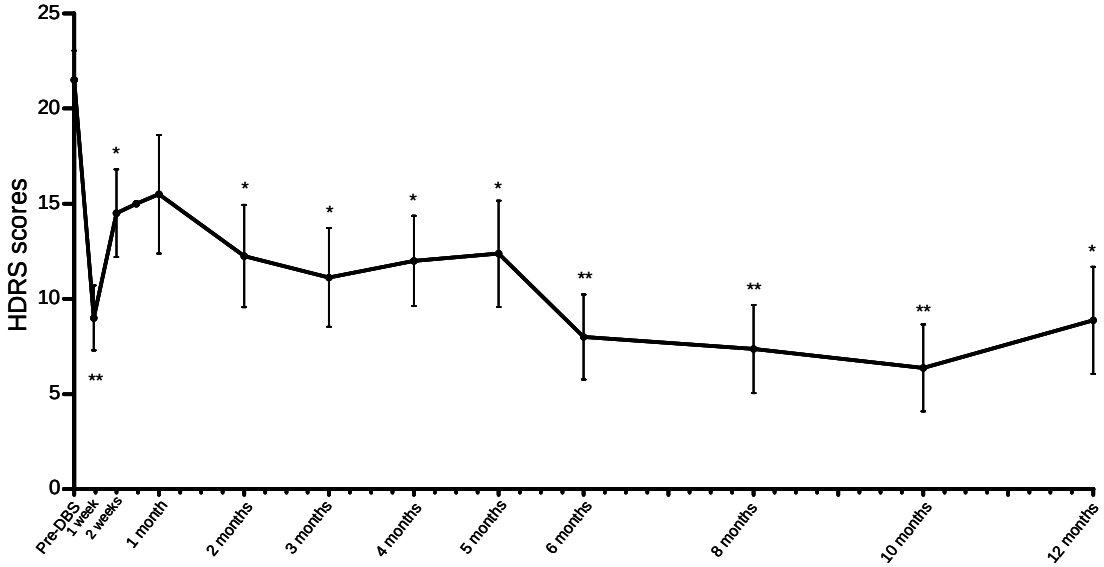
MNI= Montreal Neurological Institute space; WM= white matter; BA= Broadmann Area.

Figure 1: Electrode contacts and current stimulation parameters of every subject.



A = amplitude in volts; D = pulse width in microseconds; F = frequency in hertz.
Red circles represent contact cathode and blue circles, contact anode of electrodes.

Figure 2: HDRS-17 mean scores over time. Bars represent standard errors (SEM).



* p<0.01; ** p<0.001 for differences from Pre-DBS measure.

Figure 3: Location of the electrode contacts on a sagittal view of the cingulate gyrus. Circles are schematic representation of the electrode cathode and anode contacts in patients who responded (green circles) and those who did not respond (red circles) to DBS of the SCG. Numbers correspond to every patient.