Published in final edited form as:

Biol Psychiatry. 2014 December 15; 76(12): 963–969. doi:10.1016/j.biopsych.2014.03.029.

Defining Critical White Matter Pathways Mediating Successful Subcallosal Cingulate Deep Brain Stimulation for Treatment-Resistant Depression

Patricio Riva-Posse¹, Ki Sueng Choi^{1,2,3}, Paul E. Holtzheimer^{1,4}, Cameron C. McIntyre⁷, Robert E. Gross^{2,5,6}, Ashutosh Chaturvedi⁷, Andrea L. Crowell¹, Steven J. Garlow¹, Justin K. Rajendra¹, and Helen S. Mayberg^{1,5}

¹Department of Psychiatry and Behavioral Sciences, Emory University

²The Wallace H. Coulter Department of Biomedical Engineering, Georgia Institute of Technology and Emory University

³Biomedical Imaging Technology Center, Georgia Institute of Technology and Emory University

⁴Departments of Psychiatry and Surgery, Geisel School of Medicine at Dartmouth

⁵Department of Neurology, Emory University

⁶Department of Neurosurgery, Emory University

⁷Department of Biomedical Engineering, Case Western Reserve University

Abstract

Background—Deep brain stimulation (DBS) of subcallosal cingulate white matter (SCC) is an evolving investigational treatment for major depression. Mechanisms of action are hypothesized to involve modulation of activity within a structurally defined network of brain regions involved in mood regulation. Diffusion tensor imaging (DTI) was used to model white matter connections within this network to identify those critical for successful antidepressant response to SCC DBS.

Methods—Pre-operative high-resolution MRI data, including DTI, were acquired in 16 patients with treatment-resistant depression who then received SCC DBS. Computerized tomography was used post-operatively to locate DBS contacts. The activation volume around the active contacts used for chronic stimulation was modeled for each patient retrospectively. Probabilistic tractography was used to delineate the white matter tracts that traveled through each activation volume. Patient-specific tract maps were calculated using whole-brain analysis. Clinical evaluations of therapeutic outcome from SCC DBS were defined at 6 months and 2 years.

Corresponding author: Patricio Riva-Posse, MD Department of Psychiatry and Behavioral Sciences Emory University School of Medicine 101 Woodruff Circle, suite 4309 Atlanta, GA 30322 phone: (404) 712-1580 privapo@emory.edu.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Financial Disclosures: All other authors report no biomedical financial interests or potential conflicts of interest.

Results—Whole brain activation volume tractography (AVT) demonstrated that all DBS responders at six months (n=6) and 2 years (n=12) shared bilateral pathways from their activation volumes to (1) medial frontal cortex via forceps minor and uncinate fasciculus, (2) rostral and dorsal cingulate cortex via the cingulum bundle, and (3) subcortical nuclei. Non-responders did not consistently show these connections. Specific anatomical coordinates of the active contacts did not discriminate responders from non-responders.

Conclusions—Patient-specific AVT modeling may identify critical tracts that mediate SCC DBS antidepressant response. This suggests a novel method for patient-specific target and stimulation parameter selection.

Keywords

deep brain stimulation; major depressive disorder; bipolar disorder; treatment-resistant depression; subcallosal cingulate; subgenual cingulate; diffusion tensor imaging; tractography; antidepressant response

Introduction

Deep brain stimulation (DBS) is an emerging experimental therapy for treatment-resistant depression (TRD). In the past decade, a number of different stimulation sites have been investigated, including the subcallosal cingulate (SCC) white matter, the ventral capsule/ventral striatum, the nucleus accumbens, the lateral habenula, the inferior thalamic peduncle and the medial forebrain bundle (1-6). Six month response rates across studies range from 41%-66% with sustained and increased response over time. Of the various targets for treating TRD, SCC white matter has been the most studied with published data available for 77 patients implanted at eight separate centers. Within some cohorts, outcome data for patients receiving more than six years of chronic SCC DBS suggest significant and lasting antidepressant efficacy (7-14).

The initial rationale for targeting the SCC white matter was based on converging imaging data demonstrating changes in SCC activity with antidepressant response to a variety of standard treatments (15-19). Selection of this target was further supported by an extensive literature demonstrating monosynaptic connections between the subcallosal cingulate and specific frontal, limbic, subcortical and brain stem sites involved in mood regulation, depression and the antidepressant response (20-26). Placement of the DBS electrodes was guided by local anatomical landmarks with approximate coordinates derived from PET imaging studies localizing the subcallosal cingulate region (Brodmann Area 25) and adjacent white matter, and use of standard neurosurgical atlases (21, 27).

Although SCC DBS is associated with notable antidepressant effects in patients with TRD, the magnitude of the response varies. Initial efforts to define differences in outcome focused on the anatomical location of the active contacts used for chronic stimulation, but these studies did not differentiate responders and non-responders (28). There was no difference in anatomical distribution of the active contacts between responders and non-responders in a second cohort of patients using comparable localization methods (8). Additional PET studies suggested that activity changes in brain regions remote from the site of stimulation, such as

the dorsal cingulate and frontal cortex, were potentially as important to the antidepressant response as activity changes in the vicinity of the SCC DBS target (1). Axonal elements directly modulated by DBS (afferents and efferents projecting to and from the SCC, as well as fibers of passage) may be especially important to the effects of the stimulation (29-32). Characterizing these white matter pathways is therefore seen as a logical next step for optimizing the clinical procedure as well as better delineating mechanisms of action of stimulation.

Fiber tractography techniques have been used in healthy subjects to map the connections of the SCC, identifying midline frontal, cingulate, mesial temporal, striatal, thalamic, hypothalamic and brainstem pathways (33-35). The same pattern of connections had been previously characterized in non-human primates (22, 25, 36). Detailed computational models of the DBS activation volume have additionally been developed and successfully applied to the study of DBS in Parkinson's disease with newest methods incorporating the location of white matter fibers (37-40). This study used individual activation volumes and probabilistic tractography in patients enrolled in a clinical trial of SCC DBS for TRD to define the combination and location of specific white matter tracts mediating clinical response.

Methods and Materials

Participants and clinical protocol

Seventeen chronically depressed, treatment-resistant patients gave written consent to participate in a research protocol at Emory University testing safety and efficacy of SCC DBS in treatment-resistant depression (9) ([clinicaltrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT00367003) NCT00367003). The protocol was approved by Emory University Institutional Review Board and the US Food and Drug Administration under an Investigational Device Exemption (G060028 held by H.S.M.) and was monitored by the Emory University Department of Psychiatry and Behavioral Sciences Data and Safety Monitoring Board.

Patients underwent implantation of bilateral electrodes in the SCC area as previously described by Holtzheimer et al. (9). After a 4-week, single-blind, sham stimulation phase, a 24-week open-label active stimulation phase was conducted. As described in the initial report, after this period during which psychopharmacologic treatment remained unchanged, patients entered a naturalistic long-term follow-up phase. Response was defined here as in the original report of the clinical trial: 50% decrease in 17-item Hamilton Depression Rating Scale (HDRS-17) (41). After 6 months of chronic stimulation there were 7 responders and 10 non-responders (41%). There were no significant differences in demographics or clinical characteristics between responders and non-responders (data available in (9)). At two years of DBS, there were 13 responders and 2 non-responders. Two subjects were explanted before they reached the two year time point. Unfortunately, one of the responders (at six months and two years) was excluded from analysis due to inadequate quality of the presurgical Diffusion Tensor Imaging (DTI) data. Therefore, the imaging analyses were performed in 6 responders and 10 non-responders at 6 months, and 12 responders and 2 non-responders at 2 years.

Magnetic resonance and computer tomography imaging

Multi-sequence structural and diffusion MRI was acquired in a single session one week prior to surgery. T₁-weighted and DTI data were acquired on a 3T Tim Trio MRI scanner with a 12-channel head array coil (Siemens Medical Solutions, Malvern, PA, USA) that permits maximum gradient amplitudes of 40mT/m. Single-shot spin-echo echo-planar imaging (EPI) sequence was used for DTI with generalized auto-calibrating parallel acquisition (GRAPPA) with two-fold acceleration (R=2) (42). DTI parameters were: FOV = 256 × 256; b value = 1000 sec/mm²; voxel resolution = 2×2×2 mm; number of slices = 64; matrix = 128 × 128; 2 averaged; 64 non-collinear directions with one non-diffusion weighted images (b=0); TR/TE = 11300/90 ms. High-resolution T₁ weighted images were collected using a 3D magnetization-prepared rapid gradient-echo (MPRAGE) sequence with the following parameters: TR/TI/TE = 2600/900/3.02 ms; a flip angle of 8°, voxel resolution = 1×1×1 mm; number of slices = 176; matrix = 224×256.

Post-surgical high resolution CT data were acquired on a LightSpeed16 (GE Medical System) with resolution 0.46×0.46×0.65 mm³. These data were used to identify the location of DBS contacts.

DBS Activation Volumes

The DBS contact locations were first identified in native T₁ space based on electrode and contact location in high-resolution CT image that was transferred to native T₁ space using FLIRT (FMRIB's Linear Image Registration Tool). The patient-specific DBS activation volumes were then created by electrical DBS field model based on identified contact location in native T₁ space (see below). For the group shared fiber tract map, individual activation volume in native T₁ space is then transferred to MNI space to perform probabilistic tractography. Figure 1 presents an example of the four contacts visible on one subject's T₁ image with overlapped CT image. There are 4 individual contacts on each DBS lead. Each contact is 1.4 mm in diameter. The contact at the tip of the array is longer than the other 3 (3 mm vs 1.5 mm, respectively), with each separated by a 1.5 mm non-conductive gap (Libra system, St Jude Medical, Plano, TX).

Calculation of the DBS activation volumes required some special considerations given the St. Jude DBS system and the gray/white matter transitions of the SCC region. Therefore, custom activation volumes were created for this study. The detailed methodology for DBS activation volume prediction, described in Chaturvedi et al.(38), relies on artificial neural networks (ANNs) to characterize the spatial extent of directly activated axons as a function of the stimulation parameter settings. These ANNs are trained on the results of thousands of simulations that directly couple DBS electric field models with multi-compartment cable models of axons. In addition, the ANNs used in this study have several unique features: 1) explicit representation of the St. Jude DBS electrode design, 2) use of current-controlled stimulation, and 3) separate ANNs for representing DBS in gray matter or white matter. Gray matter was represented in the DBS electric field model as an isotropic bulk tissue domain, while white matter was represented as an anisotropic bulk tissue domain with the axon models oriented parallel to the orientation of high electrical conductivity (38, 39, 43).

Activation Volume Tractography

A. Pre-processing—Tools from FSL (Oxford Centre for Functional Magnetic Resonance Imaging of the Brain [FMRIB] Software Library, <http://www.fmrib.ox.ac.uk/fsl>) were used for all image registration and tractography processing (44, 45). First, T₁ and DTI data were skull stripped to remove non-brain regions. Diffusion data underwent eddy current correction, and local DTI fitting using FDT (FMRIB's Diffusion Toolbox) (33, 46). T₁ data were segmented into gray matter / white matter / cerebrospinal fluid using FAST (FMRIB's Automated Segmentation Tool) and CSF mask was later used for stop mask to reduce artificial connection errors that caused by probabilistic tractography. T₁ data and CSF mask were normalized to MNI152 template by combination of linear (FLIRT: FMRIB's Linear Image Registration Tool) and nonlinear transformation (FNIRT: FMRIB's Non-linear Image Registration Tool). CT and diffusion images were co-registered to T₁ image by linear transform and then normalized to MNI152 template by applying nonlinear transformation information previously calculated by FNIRT in the nonlinear registration from T₁ to the MNI152 template.

B. Probabilistic Tractography—Whole Brain activation volume probabilistic tractography was performed using FDT (FMRIB's Diffusion Toolbox) (33). Right and left hemisphere tract maps were generated using individually defined activation volumes for each patient using the specific electrode contact and stimulation parameters utilized at the 6-month and 2 year evaluation time points. Five thousand random samples per voxel were sent out from each individual's bilateral activation volumes to whole brain. The whole brain probabilistic tractography map was divided by total number of streamline sent out to compensate seed size difference, and was then binarized (0.001% was used in the present results, but a series of other thresholds were also tested) (47). Each binary map was added to create the common population map of the structural connections for responder and non-responder groups (e.g., *all* subjects in each group share *all* voxels).

Anatomical active stimulation coordinate

Given past attempts using lower resolution MRI data to evaluate anatomical variation in active contact locations in responders and non-responders to SCC DBS (28, 34), a final analysis of the activation volume location in standard stereotaxic space using the high resolution presurgical T₁ images was performed. This analysis would show if structural anatomy alone could explain response to DBS. The activation volume for each subject was transferred to MNI space using a combination of linear and non-linear transformations (FLIRT and FNIRT, see above); the center of mass of the activation volume (x-, y-, z- and Euclidean-distance from MNI center coordinate) was statistically tested.

Results

Probabilistic Whole-Brain Tractography Analysis (Figure 2)

Responder groups—Three bilateral white matter pathways were common to all DBS responders: 1) bilateral forceps minor and medial aspect of the uncinate fasciculus connecting the activation volume to the medial frontal cortex (Brodmann Area 10), 2) the cingulate bundle connecting the activation volume to the rostral and dorsal anterior and mid-

cingulate cortex, and 3) short descending midline fibers connecting the activation volume to subcortical nuclei including the nucleus accumbens, caudate, putamen and anterior thalamus. This particular connectivity pattern was present in the 6 subjects who were responders at six months; a near identical pattern was seen in the expanded group of responders at 2 years (n=12).

Six Month Non-Responder Group—This group (n=10) lacked the connections mentioned above, with shared tracts failing to reach the frontal poles and body of the cingulum bundle and with fewer connections to subcortical areas.

Six Month Non-Responders converted to Responders at 2 years (Figure 3)—Of the 10 subjects in the non-responder group at 6 months, six became responders at two years, two were explanted and two remained non-responders. All subjects had changes in their stimulation location or stimulation parameters, thus changing their individual activation volumes. Confirming the involvement of bilateral forceps minor, cingulum bundle and short subcortical fibers to response, the 6 non-responders at six months who converted to responders at 2 years gained connectivity to these regions. None of the 2 year non-responders (including those explanted) showed this pattern (figure S1 in the supplement).

Anatomical stimulation volume coordinates (Figure 4 and Table 1)

Anatomical location of the active contacts did not discriminate the subgroups. There were no significant differences between responders and non-responders when analyzing either the coordinates of active electrode contacts (activation volumes) or the Euclidean distance from MNI center. (Mann-Whitney U test uncorrected, Left x: $p = 0.32$, y: $p = 0.51$, z: $p = 0.38$, Euclidean distance: $p = 0.58$; Right x: $p = 0.36$, y: $p = 0.63$, z: $p = 0.42$, Euclidean distance: $p = 0.87$) (Table 1 and Figure 4). In addition, there was no lateralized difference in the location of the active contacts in the right and left hemisphere, based on the coordinates of the activation volumes.

Discussion

This study demonstrates that clinical response to SCC DBS is mediated by direct impact on a combination of three distinct fiber bundles passing through the SCC white matter target. These fiber bundles include: (a) bilateral forceps minor of the anterior corpus callosum connecting the right and left medial frontal cortices, (b) the bilateral cingulum bundles connecting ipsilateral subcallosal cingulate to rostral, dorsal anterior and mid-cingulate cortices, and (c) medial branch of the uncinate fasciculus bilaterally connecting subcallosal cingulate and medial frontal cortex rostrally and subcallosal cingulate to the nucleus accumbens, anterior thalamus and other subcortical regions caudally (36). Given the threshold requiring a given voxel in the tractography map to be shared by all responders at any time point, the nearly identical pattern seen in the 6-month (n=6) and 2-year (n=12) responder suggests specificity of the combination of these 3 bundles for clinically effective SCC DBS. Notably, the 2 year non-responder group consistently failed to include medial frontal pathways and if present, they generally did not reach the frontal pole. Critically, contact changes that resulted in the inclusion of all 3 bundles were associated with

conversion of non-responders to responders (figure 3). However, confirmation of these findings will require prospective testing.

These results also reconcile the failure of previous simple measurements of the anatomical location of the active contacts to discriminate responders and non-responders. (28), a finding also confirmed in this cohort (Table 1 and Figure 4). The comparability in the structural location of the active electrode contacts across groups confirms that gray matter variability is not the source of variance; rather it is the variability in the hub location where these 3 fiber bundles intersect. The similarity in the spatial location of the active contacts in responders and non-responders demonstrates that while the surgeon may implant consistently across subjects, the proposed anatomical location does not necessarily coincide with the hub location of the 3 critical white matter bundles for each individual. Overall, the use of patient-specific activation volume tractography (AVT) modeling provides a new strategy for optimizing surgical targeting and stimulation parameter selection for SCC DBS, as well as foundation for evaluating mechanisms mediating DBS effects.

An acknowledged limitation of this study is that the comparison used a qualitative assessment of individual, binarized tract maps. To date, there is no gold standard methodology to reliably quantify the “strength” of connectivity across subjects, an approach that, if available, would allow a more nuanced assessment of the nature of the non-responders. Additionally, alternative diffusion methods (48) may allow detection of more subtle, but equally critical, pathways mediating response to SCC DBS. For example, pathways to the brainstem or medial branches of the uncinate fasciculus, which sits lateral to forceps minor at this axial plane, may also be important to the clinical response (36). While identifying the necessary tracts, these methods do not define the sufficient tracts for response to SCC DBS. Resolution of the diffusion data utilized here does not allow such a level of detail. That said, the method used for this analysis has proven adequate to identify a consistent and specific pattern of tracts and may provide a starting point for refining surgical planning for SCC DBS electrode implantation.

Based on the findings described, it might be postulated that targeting bilateral SCC-Brodmann Area 10 (medial frontal cortex) connections alone might be sufficient to generate the optimal antidepressant effect, as these tracts were most consistently missed in the 6-month non-responders. We have no example of any responder at either time point where medial frontal tracts were impacted in the absence of one or both of the other two bundles, so this hypothesis cannot be tested with the current dataset. The consistent inclusion of the cingulum in both 6-month responders and non-responders further suggests that this bundle is also necessary but definitely not sufficient for response (see pattern in the two long-term non-responders, Figure S1 in the supplement). Future studies using electrodes with the capability for selective steering to each of these individual bundles would allow direct testing of the necessary and sufficient hypothesis (49). Such technological advances would also allow disambiguation of stimulation of the direct SCC-BA10 connections from trans-hemispheric connections through forceps minor and even passing fibers from mF10 to subcortical regions. Given the available data, the most conservative conclusion is that the combination of all 3 pathways is required for reliable clinical response using these methods and devices.

The primary finding from this study is that the antidepressant effect of chronic high frequency DBS likely involves modulation of a distributed, multi-region network in addition to local changes in SCC gray matter. Based on the available evidence, the mechanisms of DBS most likely involve a combination of local effects on neurons and glia which may be directly stimulated by the applied electric field, as well as orthodromic and antidromic effects on fibers of passage (50, 51). Full characterization of the fiber and cell types as well as chronic electrophysiological recordings in multiple brain regions will be required to fully model DBS mechanisms of action, especially considering the complex trans-synaptic effects that result from the stimulation.

From a practical point of view, this network analysis provides a potential new algorithm for target selection for SCC DBS. Instead of a purely anatomical or coordinate-based approach targeting a single region, these findings support a target selection strategy based on network connectivity, i.e., choosing a target to ensure a stimulation field that impacts the critical local regions and the distributed white matter tracts linking the target to other key regions within the network (Figure 5). Prospective testing of presurgical mapping of an individual patient's network structure using probabilistic tractography with lead placement and contact selection targeting the SCC hub will be necessary to test this hypothesis.

Management of non-response to SCC DBS in this context is an important next consideration. While identification of a robust *Responder* pattern was the focus of the analyses in this study, contributors to non-response can include factors beyond ideal electrode placement: unrecognized psychiatric comorbid conditions that affect rating scales, personality characteristics, and psychological or environmental factors that become evident after the implantation. As such, the lack of a full DBS response may be independent of appropriate modulation of the requisite neural pathways. Therefore, we propose that contacts should not be changed prematurely if the individual activation volume connectivity map shows that the tracts match the desired "response fingerprint". This also will require prospective testing and reassessment with a larger patient cohort.

In conclusion, the tractography maps of unambiguous response to chronic SCC DBS define a fiber bundle template involving bilateral forceps minor, cingulum and medial frontal-striatal/subcortical fibers. These pathways can be characterized in individual patients prior to surgery using DBS models coupled to probabilistic tractography. Such an approach provides a new strategy for optimizing electrode implantation and stimulation parameter selection for SCC DBS.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

The authors thank J. Luis Luján and Angela Noecker for assistance with the DBS activation volume calculations and David Gutman and Mary Kelley for discussions regarding tractography analysis strategies.

Paul E. Holtzheimer has received consulting fees from St. Jude Medical Neuromodulation and research funding from Cervel Neurotech and Otsuka. Cameron C. McIntyre received consulting fees from Boston Scientific

Neuromodulation, authored intellectual property now owned by Boston Scientific Neuromodulation, has equity interest in Surgical Information Sciences Inc., Autonomic Technologies Inc., Neuros Medical Inc., and received funding from National Institutes of Health R01 NS059736. Robert E. Gross has received consulting fees from Boston Scientific Neuromodulation, St. Jude Medical Neuromodulation and Medtronic/Lilly. Helen S. Mayberg has received consulting fees from St. Jude Medical Neuromodulation and Eli Lilly, reports intellectual property from St. Jude Medical Neuromodulation and has received funding from Dana Foundation, Woodruff Fund, Stanley Medical Research Institute and the Hope for Depression Foundation.

References

1. Mayberg HS, Lozano AM, Voon V, McNeely HE, Seminowicz D, Hamani C, et al. Deep brain stimulation for treatment-resistant depression. *Neuron*. 2005; 45:651–660. [PubMed: 15748841]
2. 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. *Biological psychiatry*. 2009; 65:267–275. [PubMed: 18842257]
3. Bewernick BH, Hurlmann 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. *Biological psychiatry*. 2010; 67:110–116. [PubMed: 19914605]
4. Sartorius A, Henn FA. Deep brain stimulation of the lateral habenula in treatment resistant major depression. *Medical hypotheses*. 2007; 69:1305–1308. [PubMed: 17498883]
5. Jimenez F, Velasco F, Salin-Pascual R, Hernandez JA, Velasco M, Ciales JL, et al. A patient with a resistant major depression disorder treated with deep brain stimulation in the inferior thalamic peduncle. *Neurosurgery*. 2005; 57:585–593. discussion 585-593. [PubMed: 16145540]
6. Schlaepfer TE, Bewernick BH, Kayser S, Madler B, Coenen VA. Rapid effects of deep brain stimulation for treatment-resistant major depression. *Biological psychiatry*. 2013; 73:1204–1212. [PubMed: 23562618]
7. Lozano AM, Mayberg HS, Giacobbe P, Hamani C, Craddock RC, Kennedy SH. Subcallosal cingulate gyrus deep brain stimulation for treatment-resistant depression. *Biological psychiatry*. 2008; 64:461–467. [PubMed: 18639234]
8. Lozano AM, Giacobbe P, Hamani C, Rizvi SJ, Kennedy SH, Kolivakis TT, et al. A multicenter pilot study of subcallosal cingulate area deep brain stimulation for treatment-resistant depression. *Journal of neurosurgery*. 2012; 116:315–322. [PubMed: 22098195]
9. Holtzheimer PE, Kelley ME, Gross RE, Filkowski MM, Garlow SJ, Barrocas A, et al. Subcallosal cingulate deep brain stimulation for treatment-resistant unipolar and bipolar depression. *Archives of general psychiatry*. 2012; 69:150–158. [PubMed: 22213770]
10. Puigdemont D, Perez-Egea R, Portella MJ, Molet J, de Diego-Adelino J, Gironell A, et al. Deep brain stimulation of the subcallosal cingulate gyrus: further evidence in treatment-resistant major depression. *The international journal of neuropsychopharmacology / official scientific journal of the Collegium Internationale Neuropsychopharmacologicum*. 2011:1–13.
11. Ramasubbu R, Anderson S, Haffenden A, Chavda S, Kiss ZH. Double-blind optimization of subcallosal cingulate deep brain stimulation for treatment-resistant depression: a pilot study. *Journal of psychiatry & neuroscience : JPN*. 2013; 38:120–160.
12. Guinjoan SM, Mayberg HS, Costanzo EY, Fahrner RD, Tenca E, Antico J, et al. Asymmetrical contribution of brain structures to treatment-resistant depression as illustrated by effects of right subgenual cingulum stimulation. *The Journal of neuropsychiatry and clinical neurosciences*. 2010; 22:265–277. [PubMed: 20686133]
13. 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. *The American journal of psychiatry*. 2011; 168:502–510. [PubMed: 21285143]
14. Merkl A, Schneider GH, Schonecker T, Aust S, Kuhl KP, Kupsch A, et al. Antidepressant effects after short-term and chronic stimulation of the subgenual cingulate gyrus in treatment-resistant depression. *Experimental neurology*. 2013; 249:160–168. [PubMed: 24012926]
15. Seminowicz DA, Mayberg HS, McIntosh AR, Goldapple K, Kennedy S, Segal Z, et al. Limbic-frontal circuitry in major depression: a path modeling metaanalysis. *NeuroImage*. 2004; 22:409–418. [PubMed: 15110034]

16. Mayberg HS. Targeted electrode-based modulation of neural circuits for depression. *The Journal of clinical investigation*. 2009; 119:717–725. [PubMed: 19339763]
17. Mayberg HS, Brannan SK, Tekell JL, Silva JA, Mahurin RK, McGinnis S, et al. Regional metabolic effects of fluoxetine in major depression: serial changes and relationship to clinical response. *Biological psychiatry*. 2000; 48:830–843. [PubMed: 11063978]
18. Goldapple K, Segal Z, Garson C, Lau M, Bieling P, Kennedy S, et al. Modulation of cortical-limbic pathways in major depression: treatment-specific effects of cognitive behavior therapy. *Archives of general psychiatry*. 2004; 61:34–41. [PubMed: 14706942]
19. Nobler MS, Oquendo MA, Kegeles LS, Malone KM, Campbell CC, Sackeim HA, et al. Decreased regional brain metabolism after ect. *The American journal of psychiatry*. 2001; 158:305–308. [PubMed: 11156816]
20. Mayberg HS. Limbic-cortical dysregulation: a proposed model of depression. *The Journal of neuropsychiatry and clinical neurosciences*. 1997; 9:471–481. [PubMed: 9276848]
21. 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. *The American journal of psychiatry*. 1999; 156:675–682. [PubMed: 10327898]
22. Freedman LJ, Insel TR, Smith Y. Subcortical projections of area 25 (subgenual cortex) of the macaque monkey. *The Journal of comparative neurology*. 2000; 421:172–188. [PubMed: 10813780]
23. Ongur D, Price JL. The organization of networks within the orbital and medial prefrontal cortex of rats, monkeys and humans. *Cerebral cortex*. 2000; 10:206–219. [PubMed: 10731217]
24. Carmichael ST, Price JL. Connectional networks within the orbital and medial prefrontal cortex of macaque monkeys. *The Journal of comparative neurology*. 1996; 371:179–207. [PubMed: 8835726]
25. Haber SN, Fudge JL, McFarland NR. Striatonigrostriatal pathways in primates form an ascending spiral from the shell to the dorsolateral striatum. *The Journal of neuroscience : the official journal of the Society for Neuroscience*. 2000; 20:2369–2382. [PubMed: 10704511]
26. Ghashghaei HT, Hilgetag CC, Barbas H. Sequence of information processing for emotions based on the anatomic dialogue between prefrontal cortex and amygdala. *NeuroImage*. 2007; 34:905–923. [PubMed: 17126037]
27. Schaltenbrand, GW,W.; Walker, EA. *Atlas for Stereotaxy of the Human Brain*. 2 ed. Thieme; 1998.
28. 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. *Journal of neurosurgery*. 2009; 111:1209–1215. [PubMed: 19480538]
29. Gradinaru V, Mogri M, Thompson KR, Henderson JM, Deisseroth K. Optical deconstruction of parkinsonian neural circuitry. *Science*. 2009; 324:354–359. [PubMed: 19299587]
30. Whitmer D, de Solages C, Hill B, Yu H, Henderson JM, Bronte-Stewart H. High frequency deep brain stimulation attenuates subthalamic and cortical rhythms in Parkinson's disease. *Frontiers in human neuroscience*. 2012; 6:155. [PubMed: 22675296]
31. Lujan JL, Chaturvedi A, Malone DA, Rezai AR, Machado AG, McIntyre CC. Axonal pathways linked to therapeutic and nontherapeutic outcomes during psychiatric deep brain stimulation. *Human brain mapping*. 2012; 33:958–968. [PubMed: 21520343]
32. Miocinovic S, Parent M, Butson CR, Hahn PJ, Russo GS, Vitek JL, et al. Computational analysis of subthalamic nucleus and lenticular fasciculus activation during therapeutic deep brain stimulation. *Journal of neurophysiology*. 2006; 96:1569–1580. [PubMed: 16738214]
33. Behrens TE, Woolrich MW, Jenkinson M, Johansen-Berg H, Nunes RG, Clare S, et al. Characterization and propagation of uncertainty in diffusion-weighted MR imaging. *Magnetic resonance in medicine : official journal of the Society of Magnetic Resonance in Medicine / Society of Magnetic Resonance in Medicine*. 2003; 50:1077–1088.
34. Johansen-Berg H, Gutman DA, Behrens TE, Matthews PM, Rushworth MF, Katz E, et al. Anatomical connectivity of the subgenual cingulate region targeted with deep brain stimulation for treatment-resistant depression. *Cerebral cortex*. 2008; 18:1374–1383. [PubMed: 17928332]

35. Gutman DA, Holtzheimer PE, Behrens TE, Johansen-Berg H, Mayberg HS. A tractography analysis of two deep brain stimulation white matter targets for depression. *Biological psychiatry*. 2009; 65:276–282. [PubMed: 19013554]
36. Lehman JF, Greenberg BD, McIntyre CC, Rasmussen SA, Haber SN. Rules ventral prefrontal cortical axons use to reach their targets: implications for diffusion tensor imaging tractography and deep brain stimulation for psychiatric illness. *The Journal of neuroscience : the official journal of the Society for Neuroscience*. 2011; 31:10392–10402. [PubMed: 21753016]
37. Butson CR, Cooper SE, Henderson JM, McIntyre CC. Patient-specific analysis of the volume of tissue activated during deep brain stimulation. *NeuroImage*. 2007; 34:661–670. [PubMed: 17113789]
38. Chaturvedi A, Lujan J, McIntyre C. Artificial neural network based characterization of the volume of tissue activated during deep brain stimulation. *Journal of Neural Engineering*. 2013; 10:056023. [PubMed: 24060691]
39. Lujan JL, Chaturvedi A, Choi KS, Holtzheimer PE, Gross RE, Mayberg HS, et al. Tractography-Activation Models Applied to Subcallosal Cingulate Deep Brain Stimulation. *Brain stimulation*. 2013; 6:737–739. [PubMed: 23602025]
40. Frankemolle AM, Wu J, Noecker AM, Voelcker-Rehage C, Ho JC, Vitek JL, et al. Reversing cognitive-motor impairments in Parkinson's disease patients using a computational modelling approach to deep brain stimulation programming. *Brain : a journal of neurology*. 2010; 133:746–761. [PubMed: 20061324]
41. Hamilton M. A rating scale for depression. *Journal of neurology, neurosurgery, and psychiatry*. 1960; 23:56–62.
42. Griswold MA, Jakob PM, Heidemann RM, Nittka M, Jellus V, Wang J, et al. Generalized autocalibrating partially parallel acquisitions (GRAPPA). *Magnetic resonance in medicine : official journal of the Society of Magnetic Resonance in Medicine / Society of Magnetic Resonance in Medicine*. 2002; 47:1202–1210.
43. McIntyre CC, Miocinovic S, Butson CR. Computational analysis of deep brain stimulation. *Expert review of medical devices*. 2007; 4:615–622. [PubMed: 17850196]
44. Smith SM, Jenkinson M, Woolrich MW, Beckmann CF, Behrens TE, Johansen-Berg H, et al. Advances in functional and structural MR image analysis and implementation as FSL. *NeuroImage*. 2004; 23(Suppl 1):S208–219. [PubMed: 15501092]
45. Jenkinson M, Beckmann CF, Behrens TE, Woolrich MW, Smith SM. Fsl. *NeuroImage*. 2012; 62:782–790. [PubMed: 21979382]
46. Jenkinson M, Bannister P, Brady M, Smith S. Improved optimization for the robust and accurate linear registration and motion correction of brain images. *NeuroImage*. 2002; 17:825–841. [PubMed: 12377157]
47. Li L, Rilling JK, Preuss TM, Glasser MF, Hu X. The effects of connection reconstruction method on the interregional connectivity of brain networks via diffusion tractography. *Human brain mapping*. 2012; 33:1894–1913. [PubMed: 21928316]
48. Setsompop K, Kimmlingen R, Eberlein E, Witzel T, Cohen-Adad J, McNab JA, et al. Pushing the limits of in vivo diffusion MRI for the Human Connectome Project. *NeuroImage*. 2013; 80:220–233. [PubMed: 23707579]
49. Martens HC, Toader E, Decre MM, Anderson DJ, Vetter R, Kipke DR, et al. Spatial steering of deep brain stimulation volumes using a novel lead design. *Clinical neurophysiology : official journal of the International Federation of Clinical Neurophysiology*. 2011; 122:558–566. [PubMed: 20729143]
50. Tawfik VL, Chang SY, Hitti FL, Roberts DW, Leiter JC, Jovanovic S, et al. Deep brain stimulation results in local glutamate and adenosine release: investigation into the role of astrocytes. *Neurosurgery*. 2010; 67:367–375. [PubMed: 20644423]
51. Hamani C, Nobrega JN. Preclinical studies modeling deep brain stimulation for depression. *Biological psychiatry*. 2012; 72:916–923. [PubMed: 22748616]

Figure 1.

Identification of contact location, A: post-surgical CT image superimposed on the pre-surgical T1 image for one subject. Contacts are numbered inferior to superior, 1 to 4. B: Activation volume using contact 1 and typical parameters for a sample subject (130Hz, 90us, 6mA), C: Probabilistic tractography connections from the calculated activation volume for one subject.

Figure 2.

Whole-brain probabilistic tractography of shared fiber tract maps of SCC DBS target. Left: 6-month responders (n=6); Middle: 6-month non-responders (n=10); 2-year responders (n=12). Responders (6-month and 2-years): Blue. Non-responders (6-month): Green. Based on individual activation volume tract maps: All 6-month responders share bilateral pathways via forceps minor and uncinate fasciculus to medial frontal cortex (BA10); via the cingulum bundle to subgenual, rostral and dorsal anterior and mid-cingulate; and descending subcortical fibers to ventral striatum (nucleus accumbens, ventral pallidum), putamen, hypothalamus and anterior thalamus. 6-month non-responders, while similar in some regions, lack connections to both medial frontal and subcortical regions seen in the responder group. All 2-year responders show a pattern that is nearly identical to the 6-month responder tract map. Abbreviations: mF: medial frontal, vSt: ventral Striatum, Th: thalamus, P: putamen, ACC: anterior cingulate cortex, resp: responder

Figure 3.

Change in tract maps in individuals that were non-responders at 6-months and who converted to responders by 2 years (n=6). Green: 6-month shared tract map. Blue: 2-year shared tract map. Structural connection differences are seen in both forceps minor and descending subcortical connections. Abbreviations: mF: medial frontal, vSt: ventral Striatum, Th: thalamus, P: putamen, ACC: anterior cingulate cortex.

Figure 4. Anatomical locations in MNI space of the DBS activation volumes for responders (Blue) and non-responders (Red) at six months. No statistical difference in anatomical location between the responder and non-responder groups was identified.

Figure 5.

Optimal SCC DBS Fiber Bundle Target Template. Red: Forceps Minor, Blue: Uncinate Fasciculus, Yellow: Cingulate Bundle. Abbreviations: mF10: medial frontal (Brodmann Area 10), Forceps M.: forceps minor, Uncinate F.: uncinat fasciculus, Cingulum B.: cingulum bundle, vSt: ventral Striatum, nAc: nucleus accumbens, Th: thalamus, SCC25: subcallosal cingulate cortex (BA25), Amg: amygdala, ACC: anterior cingulate cortex, MCC: middle cingulate cortex.

Table 1

Coordinates of Activation Volumes in MNI space

	Left hemisphere				Right hemisphere			
	x	y	z	ED	x	y	z	ED
Responder (n=6)	-5.98 (±1.11)	25.61 (±3.02)	-8.11 (±3.69)	27.68 (±2.35)	6.14 (±0.33)	26.21 (±2.12)	-6.04 (±2.21)	27.70 (±1.83)
Non-Responder (n=10)	-6.86 (±1.35)	26.53 (±2.35)	-7.80 (±3.98)	28.77 (±1.73)	5.34 (±1.56)	25.63 (±2.62)	-7.46 (±3.28)	27.48 (±2.20)
Stat. (<i>p</i>)	0.32	0.51	0.38	0.58	0.36	0.63	0.42	0.87

ED: Euclidean distance from MNI center coordinate, Stat.: Statistical analysis (Mann-Whitney U test), *p*: p-value .