

Appendix 1 to Sankar T, Chakravarty MM, Jawa N, et al. Neuroanatomical predictors of response to subcallosal cingulate deep brain stimulation for treatment-resistant depression. *J Psychiatry Neurosci* 2019.

DOI: 10.1503/jpn.180207

© Joule Inc.

Online appendices are unedited and posted as supplied by the authors.

Supplementary Materials

Supplementary Methods

Inclusion and exclusion criteria for patient enrolment

Inclusion criteria required a current major depressive episode (MDE) of at least one year's duration and evidence of treatment resistance. Though treatment resistance is defined variably in the literature, in this study it was considered to be failure to respond to a minimum of four different treatments from at least three different categories, including antidepressant pharmacotherapy of sufficient dose and duration, evidence-based psychotherapy, and electroconvulsive therapy. Patients had to have Hamilton Rating Scale for Depression-17 (HRSD-17)(1) score greater than 20 on at least three separate visits rated by at least two different psychiatrists, with a current depressive episode of at least 1 year. Exclusion criteria included comorbid Axis I psychiatric conditions, a cluster B Axis II diagnosis as determined by the Structured Clinical Interview for DSM-IV Axis II Personality Disorders (SCID-II)(2), suicidal behavior within the past year or a score of 3 or more on the HRSD-17 suicide item, and concurrent neurological or medical conditions with the potential to interfere with DBS therapy as per the judgment of the treating team.

DBS programming

In brief, all patients initially received continuous monopolar stimulation (i.e., pulse

Appendix 1 to Sankar T, Chakravarty MM, Jawa N, et al. Neuroanatomical predictors of response to subcallosal cingulate deep brain stimulation for treatment-resistant depression. *J Psychiatry Neurosci* 2019.

DOI: 10.1503/jpn.180207

© Joule Inc.

Online appendices are unedited and posted as supplied by the authors.

generator case chosen as the positive terminal) through contacts that were found to produce beneficial behavioural effects during intraoperative test stimulation (e.g., calmness, improved mood, increase motivation, etc.). In patients where intraoperative behavioural effects were not observed, monopolar stimulation was started empirically at contacts 1 and 5 respectively (i.e., second-most ventral contact on either side). In all patients, stimulation frequency was 130Hz and pulse width was 90 microseconds. Stimulation amplitude varied from 3-6 V. Adjustments to amplitude were made at follow-up visits depending on clinical response. Patients remained blinded to active stimulation contact and parameters at all times.

Psychiatric follow-up

Psychiatric assessments and stimulator adjustments (if warranted) were performed at 1, 2, and 4 weeks after surgery; biweekly for 3 months; and then monthly for up to 12 months. Responders were defined as patients who achieved a 50% or greater reduction in the severity of depression following 12 months of SCG DBS, as measured by HRSD-17 scores.

Intracranial volume (ICV)

As described in the main body of the manuscript, the VSCALING factor obtained from SIENAX was used as an approximation of ICV. VSCALING factor is inversely

Appendix 1 to Sankar T, Chakravarty MM, Jawa N, et al. Neuroanatomical predictors of response to subcallosal cingulate deep brain stimulation for treatment-resistant depression. *J Psychiatry Neurosci* 2019.

DOI: 10.1503/jpn.180207

© Joule Inc.

Online appendices are unedited and posted as supplied by the authors.

proportional to ICV: a smaller scaling factor implies a larger ICV. Because normalization by VSCALING factor abolished any significant differences between responders and non-responders to SCG DBS, we also compared median VSCALING factor between groups using the Mann-Whitney U-test. Results are shown in supplemental figure 1 below: responders showed significantly smaller scaling factor (i.e., larger ICV) compared to non-responders (U=23.00; p=0.0019).

In order to verify these results, we used an alternate method to compute ICV across all patients. ICV was estimated based on a variant of a previously published method(3). This requires intensity inhomogeneity correction, intensity range normalization(4), and brain extraction using FSL BET, followed by group-wise iterative model creation to align all intracranial cavities into a common space. The intracranial volume is then identified based on a previously derived model and warped back into the native space of each subject, thereby providing a robust estimate of ICV. All image processing was done using the MINC suite of tools (<http://www.bic.mni.mcgill.ca/ServicesSoftware/MINC>) and nonlinear registrations were estimated using ANTs(5).

By this second method, we again found that the ICV was significantly larger in responders compared to non-responders (U=35.00; p=0.0078; supplemental figure 2).

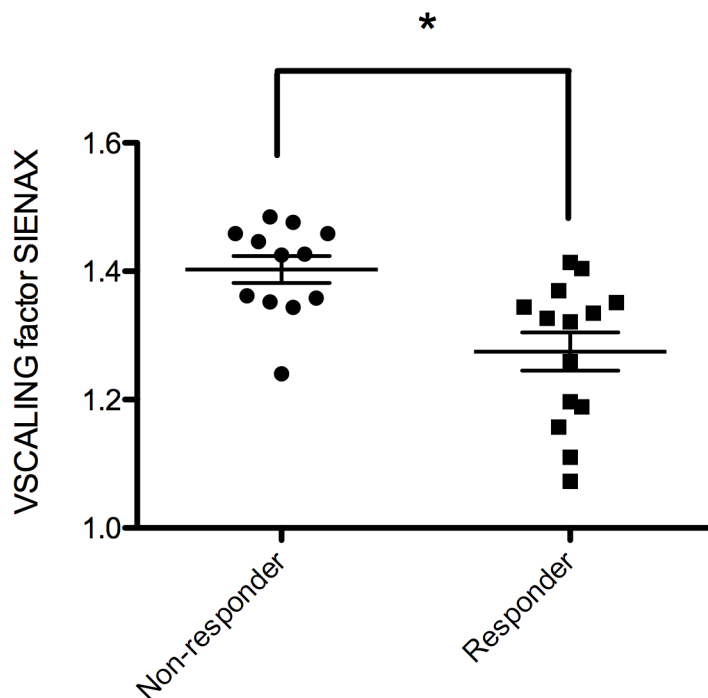
Appendix 1 to Sankar T, Chakravarty MM, Jawa N, et al. Neuroanatomical predictors of response to subcallosal cingulate deep brain stimulation for treatment-resistant depression. *J Psychiatry Neurosci* 2019.

DOI: 10.1503/jpn.180207

© Joule Inc.

Online appendices are unedited and posted as supplied by the authors.

SIENAX VSCALING factors and ICV measurements were highly correlated, increasing confidence in our finding of significantly different head sizes between groups ($R^2=0.75$; $p<0.0001$; supplemental figure 3).



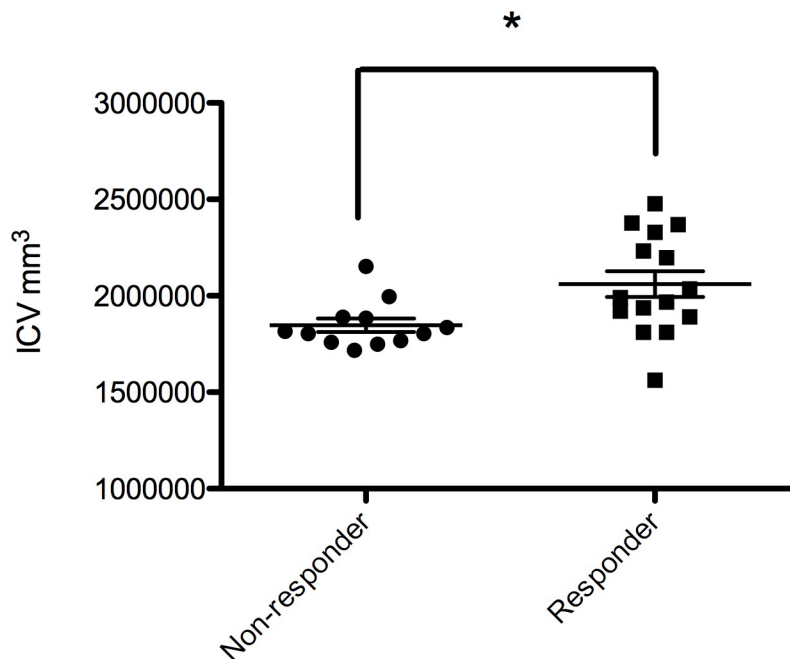
Supplementary figure 1. Comparison of SIENAX VSCALING factor (a surrogate measure of ICV) between responders and non-responders to SCG DBS. * = $p<0.01$.

Appendix 1 to Sankar T, Chakravarty MM, Jawa N, et al. Neuroanatomical predictors of response to subcallosal cingulate deep brain stimulation for treatment-resistant depression. *J Psychiatry Neurosci* 2019.

DOI: 10.1503/jpn.180207

© Joule Inc.

Online appendices are unedited and posted as supplied by the authors.



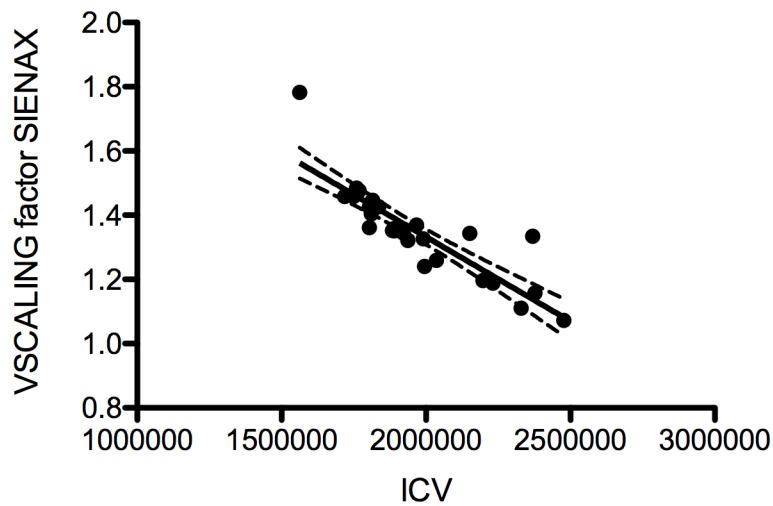
Supplementary figure 2. Comparison of ICV (calculated by alternate method) between responders and non-responders to SCG DBS. * = $p < 0.01$.

Appendix 1 to Sankar T, Chakravarty MM, Jawa N, et al. Neuroanatomical predictors of response to subcallosal cingulate deep brain stimulation for treatment-resistant depression. *J Psychiatry Neurosci* 2019.

DOI: 10.1503/jpn.180207

© Joule Inc.

Online appendices are unedited and posted as supplied by the authors.



Supplementary figure 3. SIENAX VSCALING factor and ICV computed by alternate method are highly correlated. Dotted lines show 95% confidence intervals for line-of-best-fit.

Appendix 1 to Sankar T, Chakravarty MM, Jawa N, et al. Neuroanatomical predictors of response to subcallosal cingulate deep brain stimulation for treatment-resistant depression. *J Psychiatry Neurosci* 2019.

DOI: 10.1503/jpn.180207

© Joule Inc.

Online appendices are unedited and posted as supplied by the authors.

REFERENCES FOR SUPPLEMENTARY MATERIALS

1. Hamilton M. A rating scale for depression. *J Neurol Neurosurg Psychiatry*. 1960;23:56-62. PubMed PMID: 14399272; PMCID: PMC495331.
2. First M, Gibbon M, Spitzer RL, Williams, JBW, Benjamin LS. Structured Clinical Interview for DSM-IV Axis II Personality Disorders, (SCID-II). Washington, D.C.: American Psychiatric Press, Inc.; 1997.
3. Chakravarty MM, Aleong R, Leonard G, Perron M, Pike GB, Richer L, Veillette S, Pausova Z, Paus T. Automated analysis of craniofacial morphology using magnetic resonance images. *PLoS One*. 2011;6(5):e20241. doi: 10.1371/journal.pone.0020241. PubMed PMID: 21655288; PMCID: PMC3105012.
4. Sled JG, Zijdenbos AP, Evans AC. A nonparametric method for automatic correction of intensity nonuniformity in MRI data. *IEEE Trans Med Imaging*. 1998;17(1):87-97. doi: 10.1109/42.668698. PubMed PMID: 9617910.
5. Avants BB, Tustison NJ, Song G, Cook PA, Klein A, Gee JC. A reproducible evaluation of ANTs similarity metric performance in brain image registration. *Neuroimage*. 2011;54(3):2033-44. doi: 10.1016/j.neuroimage.2010.09.025. PubMed PMID: 20851191; PMCID: PMC3065962.