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**Stanford Brain Stimulation Laboratory**

Department of Psychiatry & Behavioral Sciences

401 Quarry Road

Stanford, CA 94305

MailCode: 5717

nolanw@stanford.edu

Dear Alisha DSouza:

We hope this letter finds you well. We are contacting you with regard to our manuscript [JoVE56043] previously entitled “Bilateral epidural prefrontal cortical stimulation for treatment-resistant depression." We thank you for the kind words on our manuscript, and we are delighted that you found it potentially worthy of publication in *JoVE*. We have edited the manuscript to address all of the insightful points raised by reviewers, and these edits are listed below with the corresponding point that each addresses. We hope that you find these edits satisfactory, and we remain open to further suggestions as you see fit.

**JoVE Scientific Review Editor:**

The manuscript titles appears to match an existing publication, please edit the title. Please ensure that the manuscript title best reflects the filmable content (i.e. the portions you highlight).  
Response: We have edited the title accordingly.

Abstracts: Your Short Abstract exceeds our 50-word limit. Please revise the Short Abstract so that it clearly states the goal of the protocol within 50 words. Please re-word the Long Abstract to more clearly state the goal of the protocol.  
Response**:** We have edited the short abstract to 40 words and have reworded the long abstract to more clearly state the goal of the protocol.

Protocol Language: Please ensure that all text in the protocol section is written in the imperative tense as if you are telling someone how to do the technique  
Response: We have changed all statements in the protocol section to imperative tense.

Protocol Detail: Please add more details to the following protocol steps (15 steps indicated).Response: We have added detail to the steps indicated.

Protocol Highlights: please highlight ~2.5 pages or less of text (which includes headings and spaces) in yellow, to identify which steps should be visualized to tell the most cohesive story of your protocol steps  
Response: The steps that should be visualized are highlighted for filming.

Discussion: JoVE articles are focused on the methods and the protocol, thus the discussion should be similarly focused. Please ensure that the discussion covers the following in detail and in paragraph form: 1) modifications and troubleshooting, 2) limitations of the technique, 3) significance with respect to existing methods, 4) future applications and 5) critical steps within the protocol.  
Response**:** The discussion has been reformatted to focus on these areas.

Figure/table legends: Each figure or table must have an accompanying legend including a short title, followed by a short description of each panel and/or a general description. Please place the legends at the end of the results section.  
Response: A legend as described has been added for each figure/table.

References: Please make sure that your references comply with JoVE instructions for authors.  
Response**:** We have updated the manuscript to use the JoVE EndNote template.

Commercial language: Locate and replace all commercial sounding language in your manuscript with generic names. Figure: Since this is an image of a commercial instrument without a clear view of the settings, it may be preferable to remove it or edit to block out the commercial name “n’vision”.Response: We have removed commercial sounding language. We have also removed the referenced image from the manuscript as it does not provide accurate a clear view of the settings.

Table of Materials: Please revise the table of the essential supplies, reagents, and equipment. The table should include the name, company, and catalog number of all relevant materials/software in separate columns in an xls/xlsx file. Please include items such as surgical tools. Instruments, imaging instruments, neuronavigation system.Response: Such a table has been created and added as Table 5.0. It is included in our updated manuscript as an xlsx file.

Other comments: Please define abbreviations. Please use standard abbreviations and symbols for Si units.   
Response**:** Abbreviations have been standardized and defined.

Please add a Disclosures section.   
Response**:** Disclosures section is now included following Acknowledgements.

If you are re-using figures/data/tables from a previous publication, you must obtain explicit permission to re-use the figure from the previous publisher (this can be in the form of a letter from an editor or a link to the editorial policies that allows you to re-publish the figure). Please upload the text of the re-print permission (may be copied and pasted from an email/website) as a Word document to the Editorial Manager site in the "Supplemental files (as requested by JoVE)" section.   
Response: Permission was obtained from Elsevier, the publisher of the journal Brain Stimulation, using their online Copyright Clerance Center’s RightsLink program. This re-print permission has been included as a Word document.

Please also cite the figure appropriately in the figure legend, i.e. "This figure has been modified from [citation]."   
Response: A statement to this effect has been added to the relevant tables.

**Reviewer #1:**

Discussion: In general, not very focused and highly speculative. Would consider just summarizing the results and addressing the major outstanding questions not answered/raised by this study.  
Response: As suggested by the Editor and Reviewers, the Discussion has been reformatted with subheadings to help focus the content and guide the reader. Speculative sections have been removed. A brief summary appears at the start of the Discussion, and major outstanding questions not answered/raised by this study appear in the *Future applications* subsection.

Discussion: …the fact that with EpCS over these locations, none of the neuropsych measures changed, should be emphasized more.   
Response: We agree. This is now emphasized in the summary of results at the start of the Discussion as well as in the *Significance with respect to existing methods* section.

Discussion: I think you could reduce discussion to three very focused paragraphs, with the third being the 'Limitation's section. In the limitations section, make sure to emphasize that the results must be cautiously interpreted given that 1) only 5 patients are included, 2) this is an open label trial and 3) no comparison group is included.  
Response: The Discussion has been significantly reduced; however, three paragraphs would not allow for the use of the subheadings recommended by the Editor and Reviewer 2. The limitations, including the above suggestions, are now under the *Limitations of the Technique* subheading.

Discussion: Consider discussing differences between MDD and BP Type I and whether these would be predicted to respond to EpCS similarly or not.  
Response: We included patients with unipolar and bipolar depression. This was not associated with efficacy, but there were too few participants to draw any meaningful information beyond that this technique seems to work in both.

Discussion: Are there any other studies that provide evidence of synergistic effect of VNS and EpCS?  
Response: We are not aware of any other studies that provide evidence of a potential synergistic effect of VNS and EpCS. Our study did not provide evidence of synergy, nor was it structured to assess synergy. Discussion comments about VNS have been removed to maintain focus as suggested by all Reviewers.

Discussion: Which subject had the cortical atrophy? Please indicate.  
Response: Subject 3. The Discussion now includes references to specific subjects where relevant.

In 5.3.2, no explanation is given as to why 36,000 stimuli per day is superior to 345,600 stimuli per day.

Response: Intermittent stimulation is chosen to attempt to optimize durable long-term change that does not relapse with cessation of treatment (i.e. when the battery expires). In some applications (e.g., DBS for tremor), the clinical changes occur immediately after switching the stimulator on or off. This argues for stimulus-locked activation or inhibition of neural cells or modification of a pattern of desynchronization within specific neural pathways or loops (62). In contrast, other applications (e.g., DBS for dystonia or depression, ECS for chronic pain, or the unilateral EpCS study listed earlier) show delayed and gradual clinical improvements. In these cases, time-consuming processes are needed to alter synaptic plasticity critical for long-term treatment of major depression. Similarly, we have observed longer antidepressant onset with VNS applied intermittently with on/off duty cycles. This has ben included in the manuscript.

In 5.4, how the parameters were adjusted (reasoning, interval selection, etc) is not addressed.

Response**:** Further detail has been added to sections 5 and 6 detailing the adjustment of the stimulation parameters. Not all parameters need be adjusted, and we realize this was not clear in the initial draft of the manuscript. Recommended frequency and pulse width settings are now stated in these sections, and cite previous 5-year follow-up data in which these settings were refined. The setting that may need adjustment is voltage, and this setting is therefore stated as a possible range (4.5-6.5V).

No example imaging from the study is included to be able to evaluate exactly where each contact is located, which some might find useful.

Response**:** Unfortunately no example imaging from the original study is available, however we will make every effort to include exact contact placement in the video to be filmed for this publication.

Minor concerns: grammatical corrections noted.   
Response: The grammatical corrections listed under Minor Concerns have been included.

Not clear what 'unsuccessful clinical treatments' means.

Response: It refers to various psychopharmacological interventions prescribed by their physician, including ECT, TMS, VNS. This has been included in the manuscript.

Is the difference between 6 and 4.4 psychotropic drugs significant?

Response: This was a non-significant difference and has been noted as such in the manuscript.

Intraoperative Testing: If many of these are not significant, consider leaving them out and simply describe in text.

Response: For clarity we have followed this recommendation and altered table 3 to focus on the most important findings, all other findings are described in text.

Intraoperative Testing: for p-values, please provide n and type of test.

Response: N and type of test has been included in the column headings for table 3 and in table legend for table 4.

Intraoperative Testing: Not familiar with most of these assessments, does higher or lower mean improvement? Should indicate this for each test in table legend.

Response: We have indicated if higher or lower means improvement for the clinical assessment tools described in table 3.

Intraoperative Testing: Why are some test results blank? Why are some test results 0? What does zero vs blank mean?

Response: Some test results are blank because they were not performed at the indicated time point. Test results are 0 are only associated with the Medical Outcomes Study 36 Item Short Form Survey (MOS-SF36), where a score of 0 indicates maximum disability and a score of 100 indicates no disability. This has been clarified in the table legend.

Consider listing the parameter settings for each patient at preop, 2 weeks, 4 months, 7 months, and 5 years.   
Response: For clarity, and given the methods focus on this paper, we have included our recommended parameter settings that were developed over our previous 5-year study period. We believe our final parameter settings are most appropriate for future studies using this methodology, given that they were extensively fine-tuned during this period. However, we do include references to past publications that detail how settings changed from the 2 week to 5 year period.

**Reviewer #2:**

Discussion: This section requires significant revision and reduction. One approach would be the use of subheadings to guide the reader regarding which topic is being addressed, and to help them understand the context of the techniques and associated findings.   
Response: As suggested by the Editor and Reviewers, the discussion has been reformatted with subheadings to help focus the content and guide the reader.

In general, the Discussion is very lengthy, and most of it is speculative. I would strongly suggest the authors trim this section and focus on the lessons learned from their EpCS work and not venture into speculation.   
Response: The Discussion has been significantly reduced in length. Speculative sections have been removed with exception of the *Future applications* subsection, which is inherently speculative.

Furthermore, the Discussion section must include the authors' reflection and interpretation of the serious adverse events.  
Response: The adverse events can be found under the *Limitations of the technique* subsection. This section has been expanded.

I was surprised to discussion of these results and how they compare to other forms of invasive stimulation (e.g., sgACC DBS, VC/VS DBS, DBS to the MFB) occurred very briefly and only at the end of this section.  
Response: This content can now be found under the *Significance with respect to existing methods* subsection. As the content of the Discussion has been significantly reduced, the relative size of this content is now balanced with the other subsections; thus, little has been added to this subsection.

Discussion, Page 3, middle paragraph: The section on connectivity-based optimization is very speculative for EpCS, and should be deleted. TMS focality (or lack thereof) would not be sufficient to inform EpCS electrode use/placement.   
Response: The content on connectivity-based optimization appears now exclusively under *Future applications* and in a reduced form. We feel strongly that this is the next logical step in optimizing EpCS; hence, we continue to include a small discussion on this topic in this relevant subsection. Comments concerning how TMS relates to this work have been removed.

Furthermore, the manuscript appears to make claims about accelerated TBS that are not substantiated. Reference 94 showed very modest antidepressant effects, and reference 95 reported reduction in suicidality was unrelated to active or sham status. Discussion, Page 3, last paragraph: The sentence regarding TBS is confusing; do the authors expect that EpCS will be used to calibrate later use of TBS, in the same patient? Is EpCS safe in combination with TBS?  
Response: Comments regarding TBS have been removed.

Abstract - statements that EpCS may be more promising than noninvasive stimulation should be deleted.  
Response: The statement to this effect has been removed.

Abstract - functional Connectivity is addressed at the end, but is otherwise not introduced nor explained. This should also be deleted or paraphrased to omit this technical term.

Response: Reference to functional connectivity has been deleted.

Short Abstract - the description of pulse generators is unnecessary in this section. This would be very confusing for those not familiar with the issue. It is appropriately included later in the manuscript body.

Response: Description of pulse generators has been deleted.

Introduction, first page, last paragraph - the manuscript states that EpCS allows more direct stimulation than noninvasive methods/ECT, creating a false dichotomy. This is not technically correct; in tCS and ECT, current flows through the tissue and in TMS current is induced.

Response: This statement has been removed.

Protocol, 1.2.1 - Please clarify that medication dose reductions are permitted, but also clarify for what reasons they can be reduced. In their experience, do EpCS patients require medication reduction after implantation?

Response: Dose reductions were permitted if improvements ere seen and patient was able to maintain clinical benefit or decrease the current or newly expressed side effects without worsening of symptoms. Increases in medication dose were advised against as higher doses of concurrent medications pose unknown combinatory risks. This has been included in the manuscript. We comment on medication reduction in EpCS patients in the Discussion, as including it in the Protocol would not follow JoVE’s guidelines.

Protocol, 1.3. - please explain the rationale behind modifications to VNS use.

Response: We advised that if patients were implanted with a vagus nerve stimulation (VNS) therapy device, they turn the device off for at least 6 months prior to, and 1 year following, their enrollment. The acute use of concurrent implantable neuromodulation techniques has not been explored and therefore we advise to turn off prior implantable devices to avoid unknown synergistic negative effects, including minimizing safety risk to patient. This has been included in the manuscript.

Protocol, 1.3.1 - please explain why ECT/TMS/DBS should not be provided (I assume the authors are thinking about potential safety issues). They do state later that DBS is MRI-safe, so this later statement will need to be reconciled with what is described here.

Response: In the longer 5-year follow-up period, VNS stimulation parameters and medications were allowed to be changed in type or dose however ECT, TMS and DBS were not be provided. This is due to conservatively minimizing risk to the patient. Also, given the placement of the implant, we believed that the electrode could potentially be damaged by external magnetic or electrical stimulation targeting nearby or underlying cortical areas. VNS is excluded from this list as it is implanted outside of the skull and its direct cortical effects are relayed polysynaptically rather than directly as ECT, TMS, and DBS do. This has been included in the manuscript.

Protocol, 2.1. - spell out abbreviations used for the first time.

Response: Abbreviations used for the first time have been spelled out.

Protocol, Phase 2 - please describe impedance and the importance of impedance testing.

Response: The importance of impedance testing has been elaborated in the Modifications and Troubleshooting section, where we outline how excessive impedance accounted for two treatment failures and how to avoid this in future studies.

Protocol, 5.2 - describe how to determine optimal settings.Much more description is needed about the trial and error nature of desirable frequency/pulse width. Please describe how this is done for these patients and provide any thoughts on how best to approach this important issue. This should include keeping a log of parameters tested.

Response: Further detail has been added to sections 5 and 6 detailing the adjustment of the stimulation parameters. Not all parameters need be adjusted, and we realize this was not clear in the initial draft of the manuscript. Recommended frequency and pulse width settings are now stated in these sections, and cite previous 5-year follow-up data in which these settings were refined. The setting that may need adjustment is voltage, and this setting is therefore stated as a possible range (4.5-6.5V). Logging parameters has been included as well.

Protocol 6.3.2 - please remove the phrase "which less like DBS stimulation." Not only is this grammatically incorrect, some DBS centers will turn off the device at night.

Response: This phrase has been removed.

Representative Results/Sample Characteristics - this section should read like a CONSORT diagram, i.e., the section should start by saying 6 patients were enrolled, 1 withdrew prior to implantation.., etc. Also, for this paragraph, sentences should not start with a number.

Response: We have corrected all sentences that begin with a number and have adjusted paragraph flow to better fit the CONSORT diagram format.

Table 3 - CGI differences between Preop and 5 year outcomes are reported to be significantly different (p = .043), yet baseline CGI is 5.6 (1.1) and 5-year outcome is 5.4 (3.3). Please explain/elaborate.

Response: This was an error and has been omitted.

**Reviewer 3:**

In Discussion, 2nd paragraph, "If coupled with a more quantitative approach for capturing affect change such as a quantitative intraoperative facial musculature(60-62) assessment(63) that could be linked to an acute antidepressant assessment(64), this may lead to further optimization of placement and dose". I do not understand to what Refs. 60-62 refer to and why you add another one after "assessment". Further on, "Particularly is TBS is utilized later, the intraoperative motor threshold would be of use in further determination of %MT for chronic stimulation(70)", the first is should presumably be if. You did not abbreviate theta-burst stimulation as TBS on your first occasion and then went on using both terms promiscuously. Please be sure to abbreviate as soon as possible (about page 17) and then to use only TBS.  
Response: These sentences were removed in an effort to trim the Discussion as suggested by the other Reviewers.

You should stress stronger that this technique could be used after noninvasive techniques, like rTMS, dTMS, and tDCS have failed. So, the resistant patients you select for this technique should be more resistant than the ones selected for noninvasive methods.  
Response: We agree. This comment has been added the *Significance with respect to existing methods* subsection of the Discussion

In your methods, it's not clear what were the criteria for TRD. Did you refer to any particular definition? Any reference to provide?

Response: The criteria for TRD have been included in the last sentence of the first paragraph of the Introduction: “Roughly 41% patients fail to respond to two adequate trials of pharmacologic treatment, the definition of treatment resistant depression (TRD).”

Was the participant who withdrew a man or a woman? Please, specify.

Response: Unfortunately we no longer have demographic information on the participant that withdrew from the original study.

In Adverse events, before the Tables, you state "nor did detailed cognitive testing reveal any deficits" and so on. Since you don't name the tests used, you should refer to Table 4 at this point.

Response: Reference to table 4 has been included.

You did not abbreviate theta-burst stimulation as TBS on your first occasion and then went on using both terms promiscuously. Please be sure to abbreviate as soon as possible (about page 17) and then to use only TBS.

Response: Mentions of theta-burst stimulation and TBS have been removed from the manuscript.

We hope that you find our edits satisfactory, and we look forward to hearing from you.

Sincerely,

Nolan Williams, MD *et al.*