**Reviewer 1**

Line 223: Change Conan to Conen please. The references in the tables do not correspond with the number in the text or bibliography.

**Response:** The reviewer’s comments are much appreciated. The references in the tables were included in their own bibliography at the end of the tables section. To simplify the references, all citations were merged into one bibliography.

Line: Bibliography of the attached tables and the main bibliography have been merged.

**Reviewer 2**

This is a lengthy introduction to DBS for treatment resistant depression (TRD), but limited to the subgenual cingulate target, which is one of many. The article’s best part is the description of the preclinical/animal work, but there are some issues with the clinical descriptions.

Specifically, they double-count a significant number of patients in their Table 2 which aims to summarize the patient population subjected to this approach. Other specific comments follow:

P.1, Intro: The authors should briefly mention the economic burden of depression and TRD.

**Response:** The reviewer’s comments are much appreciated. The relevant content has been corrected and overlapping information has been removed.

P.1, Intro: The authors are ignoring all the other DBS targets for depression. They should spend some time in the intro acknowledging the other targets and why they are justified in focusing only on the cingulate.

**Response:** The reviewer’s comments are much appreciated. A paragraph has been added to acknowledge past research work on DBS targeting other brain regions for the treatment of depression. It is mentioned that given the rapid development of DBS research on the SCC and vmPFC, the review focuses on the research conducted on these regions.

Lines 63-81.

P.2, Outline: Why only search PubMed? There also needs to be a little more detail. What years were searched? What languages? Were these terms joined with a Boolean OR or AND?

**Response:** The reviewer’s comments are appreciated. The manuscript mentions that English research articles were searched. Boolean functions have been added. The use of searching only PubMed was justified by its extensive index of peer-reviewed journals.

Lines 84-92.

p. 2: The authors mention DBS using HFS (high frequency stimulation). They should parenthetically note here what range of frequencies count as “high frequency” to clarify for readers.

**Response:** The clarification of high frequency is rightly noted. A sentence giving the general range of frequencies has been added on page 6 line 97.

p. 2-3: DBS for OCD is approved by the FDA under a humanitarian device exemption. It does not have a standard FDA approval. This is a very important distinction and should be noted.

**Response:** The reviewer’s clarification on device exemption is appreciated. The specific details of FDA approval have been added.

Lines 101-103.

p. 3: “With the discovery of the limbic system…” The limbic system wasn’t “discovered” but rather defined. Broca refers to it in 1878 in his paper on “le grand lobe limbique”. So the authors are way off on their history here.

**Response:** The reviewer’s correction is well acknowledged. This sentence has been removed to make the article more concise.

p. 3: The authors mention Jose Delgado, but what about Heath and other early pioneers of DBS for mood disorders? One good review was published recently in Lancet: vol 17, iss 9, p748 by Seth Oliveria.

**Response:** The reviewer’s correction is well acknowledged. This sentence has been removed to make the article more concise.

p. 3: The Eitan et al. study discusses two stimulation frequencies. Can the authors explicitly note what frequencies they used?

**Response:** The clarification of the frequency used is acknowledged. In the review, where Eitan is discussed, we mentioned that Eitan did not observe significant mood improvements at both high and low frequency, but that switching from low to high frequency at 6 months improved the response of patients in the low frequency group. The sentence has been further amended for clarity. In line 234-237, we quote the frequency of Eitan’s high frequency stimulation that was effective.

p. 5: “fiber tract activity”. The referenced studies have no way to determine fiber tract activity. Do the authors mean putative fiber tract activation as determined by computational modeling?

**Response:** A more accurate terminology has been adopted.

Line 263-264.

When discussing trials, the authors should discuss the various depression rating scales (Hamilton, BDI, MADRS) and the pros/cons of each one. That will help the reader understand what’s being evaluated here.

**Response:** The author’s suggestion is greatly appreciated. A paragraph has been added to discuss the strengths and weaknesses of the depression rating scales used by researchers or completed by patients.

Table 1: For the Table’s entry under “Holtzheimer et al. 2012”, it was a SHAM controlled trial, not a SHAME controlled

**Response:** The reviewer’s meticulous correction is much appreciated. The typo in Table 1 has been corrected

Table 2: Many of these studies are reporting on the same subjects, yet the authors are double-counting them. Examples is the Smart paper, which reports patients also from the Holtzheimer paper.

**Response:** The reviewer’s comments are much appreciated. To avoid double counting, Table 2 has been amended to reflect the response and remission rates of the studies, which allows for more accurate reporting of the results across the studies.

Line 417, p. 34: “also reported a slight fold increase”. ‘slight fold’ doesn’t mean anything. What was the actual increase?

**Response:** The reviewer’s comments are much appreciated. The relevant details have been amended to show a 1.2-fold increase in BDNF expression level, as mentioned in the article.

Line 456-467.

**Reviewer 3**

The authors have generated a review looking at two aspects of Deep Brain Stimulation (DBS) targeting the “subcallosal cingulate” (SCC) region for the treatment of refractory depression: 1) published clinical series in actual human patients; and 2) pre-clinical studies addressing putative mechanisms of action of DBS in homologues of the SCC in animal models, with heavy emphasis on the ventromedial prefrontal cortex (vmPFC)/infralimbic cortex in rodents.

I acknowledge that the authors have gone through considerable effort in reviewing a substantial—and ever-growing—body of literature related to SCC DBS in depression. The tables summarizing clinical and preclinical studies, in particular, are comprehensive. However, I have several significant concerns with the manuscript as it stands:

My most significant concern relates to the purpose of manuscript. Simply, there is a fairly glaring lack of focus, resulting in a bloated manuscript without clear take-home messages. The lack of focus is immediately apparent with the choice of title. Indeed, “A decade of progress in deep brain stimulation of the subcallosal cingulate for the treatment of depression” would imply a focus on the last decade of progress with SCC DBS, but instead the manuscript covers areas related to the history of psychiatric surgery more generally, and the review of the clinical SCC DBS literature in particular lists several papers published more than 10 years ago.

**Response:** The title has been amended to better reflect the contents of the review.

Similarly, the running title is both overstated and somewhat misleading: there is considerable debate among functional neurosurgeons as to the actual efficacy of SCC DBS, particularly in light of recent RCTs which did not meet pre-defined endpoints for efficacy, and so to state that SCC DBS “ameliorates depression” is inaccurate.

**Response:** The reviewer’s comments are accurate and rightly noted. This sentence has been amended to better reflect the effect of DBS in reducing depressive symptoms, rather than ameliorating them.

Line 3 Running Title Page 2

The entire section on clinical experience with SCC DBS in depression is largely descriptive and provides little insight into the key advances and challenges facing the therapy. The authors primarily provide a narrative review of all case series of SCC DBS without any obvious organizational framework.

**Response:** The reviewer’s comment is much appreciated. The organization has been improved to further reflect the focus of each intended section, with subheadings added for clarity.

No attempt is really made to evaluate the quality of the evidence in support of SCC DBS, which is problematic because—as mentioned above—the double-blind sham-controlled trial by Holtzheimer et al. in 2017 called into the question the efficacy of the therapy, and has had a chilling effect on DBS for depression more generally. The authors spend very little space addressing this road block (a mere 5 lines from 160-165), nor do they cite the several position papers covering DBS for depression which have addressed this issue already (e.g., Bari et al. J Neurol Neurosurg Psychiatry. 2018 Aug;89(8):886-896).

**Response:** The reviewer’s suggested amendments are greatly appreciated, and this oversight has been addressed. The outcome of Holtzheimer’s paper has been further summarized and elaborated upon. Additionally, Bari et al. has been cited to support the counterargument.

Line 196-214.

I question the value of simply listing all published case series of SCC DBS, and then making unsubstantiated claims about its effectiveness (e.g., “evidence-based” on line 108, or “55% response rate” on line 246-246) without using any meta-analytic techniques, or more critical evaluation of the clinical experience to date.

**Response:** The reviewer’s comments are much appreciated. Table 2 has been amended to reflect the response and remission rates of the studies, which allows for more accurate reporting of the results across studies.

In keeping with the theme of a lack of focus, the entire preamble in section 3 on the development of DBS for depression is unnecessary, cursory at best, and filled with errors. As an example, the use of the term “psychosurgery” is generally avoided today because of its relationship to the dark past of frontal lobotomy. As another, the development of SCC DBS per se is largely the result of neuroimaging work in major depressive disorder (MDD) by Mayberg and others, and not directly the result of greater understanding of limbic circuits based on preclinical models.

**Response:** The reviewer’s correction is well acknowledged. This section has been removed to make the article more concise.

A key citation missing is the recent paper by Ramasubbu et al. (Lancet Psychiatry. 2020 Jan;7(1):29-40) which is another RCT for SCC DBS.

**Response:** The reviewer’s suggested paper has been added.

There are terminological inconsistencies throughout. As the authors should know, there is considerable debate as to the exact target of stimulation within the subcallosal region, and so DBS studies have variably referred to the target as the subgenual cingulate, subcallosal cingulate, and area 25, among others.

It is confusing that the authors call the target the “subcallosal cingulate” in the title and running title, but then refer to it as the “subgenual cingulate” throughout the text. This is a missed opportunity to try to clarify for uninformed readers what exactly we believe we are stimulating in this region in patients with depression.

**Response:** The reviewer’s suggested clarification is rightly noted. The terminology of subcallosal cingulate is used 18 times, whereas the term subgenual cingulate was used three times. The use of the term “subgenual cingulate” was kept in one instance, as it repeated the terminology of the source paper (Neimat et al. 2008), but the other two instances of this term have been edited to “subcallosal cingulate”.

Line: Throughout the manuscript.

There are other missing references in the paragraphs aiming to review attempts to improve targeting and patient selection for SCC DBS; as an example, the authors omit Sankar et al. J Psychiatry Neurosci. 2020 Jan 1;45(1):45-54 which looked at neuroanatomical variations in patient response to SCC DBS.

**Response:** The reviewer’s suggested paper has been added into the list of reviewed papers. The contribution is greatly appreciated as it adds critical information on the profiles of patients who respond to DBS, as the available information is scarce.

Tables 1 and 2.

Overall, the section reviewing preclinical studies of DBS targeting the rodent homologues of the SCC region is stronger and more logically coherent than the clinical portion of the manuscript. However, the absence of subtitles in section 4.2 to group together conceptually similar subsections makes it difficult to absorb.

**Response:** The reviewer’s suggested clarification is rightly noted. The use of the term subcallosal cingulate in-text has been edited accordingly. Subtitles have been added throughout the review for clarity and to improve flow. Additionally, clarification of the vmPFC region as a homolog of the BA25 has been added.

Line 310-319.

There are several awkward and imprecise uses of language throughout. As an example, what do the authors mean by “This finding allows for more comfortable regimen in the post-operative care of patients” on line 467?

**Response:** The reviewer’s suggested clarification is rightly noted. The language has been amended throughout.

Broad motherhood statements permeate the text, such as (on line 555) “Generally speaking, care must be taken in the design of experiments and data analysis of preclinical studies to increase their translational value to clinical studies.” These types of statements are imprecise and of little value to readers. As a result of these significant concerns, I cannot recommend publication of the manuscript.

**Response:** We thank the reviewer for the comments. The concerns have been addressed in the revised manuscript.