

## LETTER

## Deep brain stimulation targets in epilepsy: Systematic review and meta-analysis of anterior and centromedian thalamic nuclei and hippocampus

To the Editor,

We read with great interest the systematic review and meta-analysis by Vetkas et al.<sup>1</sup> The authors demonstrated different trends of response with different targets of deep brain stimulation (DBS) among patients with drug-resistant epilepsy (DRE). While this study provides important clinical insights about DBS use, we have identified a few concerning biases in the study.

The meta-analysis included some studies with a low number of patients, as low as three patients. Sterne et al. described the trend of the smaller studies in a meta-analysis to show more positive and favorable treatment effects. Such an effect can also contribute to publication bias in the study.<sup>2</sup> To avoid such a problem, the authors might consider using sensitivity analysis to see the true effect of these small studies.

The authors have used The International Prospective Register of Systematic Reviews (PROSPERO) to publish their protocol (CRD42021268339). They stated that the Cochrane risk of bias tool would be used.<sup>3</sup> However, the authors did not actually use this tool and only used funnel plots tool for evaluation of publication bias. This resulted in less than optimal assessment of risk of bias. In addition, the discrepancy between the published protocol and what was finally reported in the manuscript increases the risk of reporting bias. It's also worth mentioning that even if the authors used Cochrane risk of bias tool, this would have only covered the evaluation of randomized clinical trials; other tools should be used for evaluation of other study designs.<sup>4</sup>

Studies may frequently get reported in more than one publication. However, the unit of interest is the study and not the report.<sup>5</sup> Thus information from multiple reports needs to be collated as including the same study more than once in the meta-analysis can introduce substantial biases.<sup>6</sup> We noticed that the patients from Stimulation of the Anterior Nucleus of the Thalamus for Epilepsy (SANTE) trial<sup>7</sup> were included three times in the meta-analysis from two Salanova et al. follow-up studies.<sup>8,9</sup> The second and third reports include 91% and 90%,

respectively, of the patients in the original report. The weight of the three aforementioned studies in the anterior thalamic nucleus group meta-analysis was 62.6% and 21.7% collectively using the fixed and random-effect models, respectively. A study by Bom and Rachinger showed that the rate of false positives is potentially very large for plausible amounts of sample overlap, which might explain the high seizure-reduction rates among anterior thalamic nucleus patients.<sup>10</sup>

### ACKNOWLEDGMENT

None.

### CONFLICT OF INTEREST

Neither of the authors has any conflict of interest to disclose. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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## LETTER

## Response: Deep brain stimulation targets in epilepsy: Systematic review and meta-analysis of anterior and centromedian thalamic nuclei and hippocampus

To the Editors:

We read the letter by Al-Kraimeen et al.<sup>1</sup> in detail. We agree on the drawbacks imposed by performing a meta-analysis in a heterogenous subset of studies, as was described in our limitations and bias assessment sections in detail. Studies with multiple longitudinal reports did not allow for a reliable identification of unique patients. Additionally, longitudinal studies were included in the analysis to reflect on the possibility of improved seizure response after prolonged deep brain stimulation (DBS) for epilepsy. Performing the meta-analysis of the DBS of the anterior thalamic nucleus after excluding the two follow-up studies by Fisher et al.<sup>2</sup> did not significantly affect the percentage of seizure reduction on a group level (60.8% vs. 59.4%). Thus, we chose to report all included studies. The use of DBS for epilepsy has gained US Food and Drug Administration approval after the study of Fisher et al.<sup>2</sup> and their longitudinal follow-up provides additional evidence in support of the treatment. Further research is required to assess the efficacy of neuromodulation in different types of seizures, and the efficacy of stimulation in less studied targets.

### ACKNOWLEDGMENT

None.

### CONFLICT OF INTEREST

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[Correction added on 20 May 2022., after first online publication: The title has been changed to add: "Response:". ]

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