Published in final edited form as:

Ann Neurol. 2017 March ; 81(3): 351–353. doi:10.1002/ana.24892.

What is the Pathway Forward for the Surgical Management of Essential Tremor?

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Keywords

Essential tremor; focused ultrasound thalamotomy; deep brain stimulation surgery; treatment

New technologies often generate debate. Such debate is generally healthy, as it helps us to critically evaluate the technology, including both its risks and benefits, and its place in our world. Elias and co-authors recently reported the results of a double-blinded, randomized, sham-controlled trial of magnetic resonance imaging (MRI)-guided focused ultrasound (FUS) to create a unilateral thalamic ablation for the treatment of essential tremor (ET).¹ The study demonstrated the short-term efficacy of FUS in treating patients with ET.¹ FUS, which is a form of thalamotomy, offers certain attractive qualities compared to deep brain stimulation (DBS) surgery. First and foremost is that it is a relatively non-invasive advanced treatment option in tremor patients for whom the idea of an awake brain surgery is intolerable, or for whom the medical risks of anesthesia/surgery are considerable.

Nevertheless, FUS remains an ablative procedure, with many of the same disadvantages as traditional thalamotomy; namely, its irreversible and unmodifiable nature, and the limitations it presents in terms of target selection and unilateral treatment. For these reasons, DBS surgery is generally preferred over more traditional forms of thalamotomy, precisely because of its reversibility by removal of the electrodes, the lack or low level of residual damage, and its adjustability over time via a programmable stimulator. And yet we must return to the fact that DBS surgery is an elective invasive procedure with concomitant associated risks, including intracranial bleeding, malposition of electrodes, infection of

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Author Contributions

Dr Louis wrote the first draft of the manuscript and Drs. Patel and Gerrard edited subsequent drafts.

Potential Conflicts of Interest

Nothing to report.

hardware, the need for repeated battery replacement surgeries, and hardware issues that include lead breakage or migration. We are left to ask, how can our debate regarding new technology guide patient decision-making, when in some senses we are comparing apples and oranges?

One issue that may inform on this dilemma is that of waning clinical efficacy over time (i.e., tachyphylaxis). This is a particularly important issue for FUS, even more so than for DBS, as at the moment FUS is a onetime procedure for which adjustments are not available. Additionally, if FUS precludes or limits the possibility of future DBS surgery, the problem of tachyphylaxis is further magnified. In the study by Elias and colleagues,¹ the primary outcome measure was upper limb tremor score. In the FUS treated group, that score increased considerably (i.e., by 23.2%) during the 12-month post-operative period. The secondary outcome measures were characterized by similar or even greater increases during the 12-month follow-up interval; for example, the Clinical Rating Scale for Tremor score increased by 38.5%.¹ These are not insignificant amounts. One must ask how this waning of efficacy compares to that seen with DBS surgery.

After DBS surgery, “tolerance” (i.e., tachyphylaxis) occurs to varying degrees, and has been hypothesized to be due to a decreased biological response (i.e., habituation) of the neuronal network.² Alternative explanations for loss of DBS efficacy over time include progression of illness and misdiagnosis. In an early study of DBS surgery, which enrolled 20 patients with ET, the threshold intensity for alleviation of tremor required regular increases, in some patients to a level that could not be exceeded due to the induction of paresthesias.² This was associated with a loss of functional benefit, mainly in patients with severe initial tremor who required high intensity stimulation 24 hours per day.² During the initial postoperative period, scores of 3 (i.e., reappearance of a slight tremor on rare occasions) or 4 (i.e., complete disappearance of tremor in all circumstances) were obtained in the upper limbs in 27 (75.0%) of the 36 operated sides. At the last follow up assessment, which was a minimum of 6 months post-operatively, these scores were obtained in only 61.1% of the operated sides.²

In a study of five ET patients who were followed for a mean of 55.2 months after DBS surgery,³ two (40%) developed tolerance. In these two, progressively higher stimulation amplitudes were required to obtain tremor control, until stimulation could no longer be increased because of limiting adverse effects. At the last follow-up assessment, tremor scores (stimulator ON) were similar to those prior to surgery.³ In yet another study of 12 ET patients who had undergone DBS surgery, average ON tremor scores approximately doubled over a two year follow-up period, and this generally occurred in the setting of an increase in all stimulation parameters (i.e., voltage, frequency, and pulse width).⁴

More recent studies provide a mixed story of significant but waning benefit over time. Favilla et al. studied 28 ET patients who demonstrated maintained benefit from DBS, with preserved ON scores at 12, 24 and 36 months post-surgery.⁵ Studies that investigate the long term (> 5 years) follow up of DBS patients are more limited. While they suggest a waning of tremor control over time, most ET patients continue to observe benefit in their clinical or functional assessments and prefer the stimulation ON setting.⁸ Overall, the data vary considerably and it is quite difficult to compare them meaningfully to the short term results

of the recent FUS study. Hence, we have a gap in knowledge that demands further exploration.

To investigate the utility of FUS is not akin to ignoring the pitfalls of ablative treatments. Patients should be well informed that early studies comparing traditional thalamotomy to DBS surgery indicated a slight advantage of the latter.⁶ However, FUS is a different kind of thalamotomy, and the development of a new technology that offers patients more options is almost always a step in the right direction. As a technique, FUS is in some ways akin to gamma knife radiosurgery, which in experienced centers has a lower reported incidence of permanent adverse neurological effects than that cited with traditional thalamotomy.⁷ This improvement upon traditional thalamotomy is observed in spite of treating a typically older patient population.⁷

Similar issues are at play when comparing DBS and levodopa-carbidopa intestinal gel (LCIG) for the treatment of advanced Parkinson's disease. The development of alternative forms of continuous dopaminergic stimulation provides clinicians and patients with greater flexibility in treating bothersome motor fluctuations. The patient for whom brain surgery is not an option due to cognitive impairment, psychiatric illness, or medical co-morbidity may be a candidate for a relatively straightforward percutaneous intrajejunal tube, with a comparable benefit in medication "on" time and reduction in troublesome dyskinesias.⁹ Yet the side effect profile and practical challenges of LCIG when compared to DBS may not make it a provider's or patient's first choice.¹⁰ Understanding differences in treatment effect, side effect profile, and long-term cost effectiveness is critical in providing patients with the best information upon which to decide on their care options. Attempts to answer those questions in the most scientifically rigorous way possible should be encouraged.¹¹

Given the issues raised above, we owe it to our patients to present them with longer term efficacy data before they undergo FUS. At this point, the precise two procedures in question, FUS and DBS, simply have not been directly compared. A longer term (e.g., 5 year) comparison of the two procedures' benefits (including their waning benefits with time), their cumulative side effect profiles, and their associated cumulative costs would be of considerable value in guiding future clinical decision making. Additional consideration as to the relative up-front and long-term costs of the two procedures should also be considered in future comparisons, as these are likely to differ given the technical differences between the two procedures. We should neither rush to refer our patients for this novel procedure and its short-term clinical gains, nor shy away from obtaining the data necessary to answer the question of its ultimate effectiveness.

Acknowledgments

Dr. Louis has received research support from the National Institutes of Health: NINDS R01 NS042859 (principal investigator), NINDS R01 NS39422 (principal investigator), NINDS R01 NS086736 (principal investigator), NINDS R01 NS073872 (principal investigator), NINDS R01 NS085136 (principal investigator) and NINDS R01 NS088257 (principal investigator).

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