INVITED EDITORIAL

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Thalamotomy for tremor: is it worth it?

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Over the past eight decades, the use of lesioning therapies to treat neurological conditions has fluctuated substantially. By 1965, an estimated 25,000 stereoencephalotomies had been performed with various lesioning techniques (e.g. radiofrequency, RF), and the ventral intermediate nucleus of the thalamus (VIM) was well-established as the most effective target to treat medically refractory tremor [1]. In the 1990s, a form of stereotactic radiotherapy called gamma knife thalamotomy (GKT) emerged as another lesioning technique [2], but was soon overshadowed by deep brain stimulation (DBS), which was approved to treat essential tremor (ET) and tremor associated with Parkinson's Disease (TAPD). The 2016 approval of magnetic resonance-guided focused ultrasound (FUS) to treat ET reinvigorated interest in thalamotomies. Elsewhere in this issue of NiNP, Figura et al. report 2-year safety and efficacy data for GKT to treat a small cohort of patients with ET or TAPD [3]. Their study was prompted by the recent European Academy of Neurology/Movement Disorders Society guidelines, which do not recommend GKT as a therapy for PD due to a lack of evidence for efficacy [4]. Prior to this, the MDS review of ET treatments also noted insufficient evidence to conclude efficacy of GKT [5]. While the surgical options of treating ET and TAPD have largely stabilised, questions remain regarding the proper role for thalamotomies in treating patients with ET and TAPD.

This article considers and compares the current surgical options, and should enable practitioners to counsel their patients more transparently.

The VIM is a region of extensive tremor-relevant connectivity particularly related to the dentato-rubro-thalamic and pallidothalamic tracts [6]. The dimensions of this highly interconnected region are 2–4 mm in the anteroposterior dimension, 4–6 mm mediolaterally, and 6–10 mm dorsoventrally [7, 8]. A lesion created by GKT takes months to emerge, but typically consists of a 4–5 mm necrotic core surrounded by a peripheral non-necrotic halo [9]. FUS-generated lesions are usually 6–8 mm in diameter and are visible 24 hours after treatment [10–12]. A recent study of RF thalamotomy in 12 patients reported reliable lesions with an average radius of 3–4 mm [13] (Tab. 1). By comparison, DBS leads are typically 1.3 mm in diameter, although one must take into account the cylinder traversing the VIM and extrathalamic brain regions. The subsequent breadth of coverage within the VIM allows for a volume of tissue activation that can extend for several millimetres from the electrode's surface, yielding non-permanent adjustability. Furthermore, adjusting electrical parameters, e.g. stimulation frequency and pulse width, influences different sizes of neural fibres that can improve clinical responsiveness [14, 15]. One might intuit that this would yield clinical outcomes that were obviously superior compared to thalamotomies, but the verdict has not been so clear-cut.

Among the surgical options to treat ET, only FUS has level I evidence, despite there being little debate that the other options can provide substantial clinical benefit, at least for some time [5]. A review of 151 ET patients across eight studies found tremor control in 35–75% of patients 12 months after unilateral FUS [16]. The quality of that improvement ranged from 37% to 73%, which is within the range reported for unilateral DBS (57.9–82%) and GKT (65%), but is perhaps better than RF (47%) [16]. In a recent study, 96% of patients with TAPD reported immediate tremor improvement following FUS; however, only 63% had sustained improvement, and after 16 months 17% reported complete tremor recurrence [17]. Multiple studies have observed a waning benefit of DBS for tremor, but have generally cited a much more protracted course [18, 19]. In 2006, a prospective study of patients with ET or TAPD observed persistent tremor reduction after unilateral DBS throughout the five-year study period [18].

It is reasonable to assume even better treatment durability today, given the advances in DBS technology, such as electrodes with segmented contacts, electrodes capable of sensing local field potentials, and modelling software that visualises

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Table 1. Comparison of FDA-approved surgical therapies for tremor

	Gamma knife	Radiofrequency	Focused ultrasound	Deep brain stimulation
Headframe	Yes	Yes	Yes	Most cases
Burr hole	No	Yes	No	Yes
Hair removal	No	Partial	Yes	Partial
Test lesion	No	Yes	Yes	N/A
Lesion size (diameter)	4–5 mm necrotic core with non-necrotic halo	6–8 mm	6–8 mm	Microlesion (1.3 mm)
Time to lesion	Weeks to months	Hours to days	Within 24 hours	N/A
Time to clinical benefit	Delayed	Immediate	Immediate	Immediate

a patient's electrode(s) within their own anatomy to enhance programming. Figura et al.'s study of GKT in this issue has failed to identify a significant improvement on relevant clinical rating scales after two years [3]. Pair-wise comparison of tremorometry showed significant differences in several metrics not including peak-to-peak amplitude, which is likely to be the most clinically relevant variable in action tremors.

While generally considered to be safe, there may be differences in the side effect profiles of surgical treatments for tremor. Recent guidelines for invasive therapies to treat PD do not recommend unilateral RF thalamotomy due to a higher number of adverse events compared to DBS [4]. An MDS evidence-based review of ET treatments designated unilateral RF thalamotomy as "likely efficacious" and "possibly useful" in clinical practice after citing two studies of RF thalamotomy including a level I study showing more frequent adverse events compared to VIM-DBS [5, 20]. The aforementioned PD guidelines also emphasise adverse effects with GKT plus the major disadvantage of having no reversible test to confirm lesion location or size [4].

A case series of FUS to treat TAPD was too small (n = 20) to guide a formal recommendation, but it reported persistent adverse effects, including 20% of patients with orofacial paresthesia, 10% with hemiparesis, and 5% with finger paresthesia, ataxia, dysmetria, and/or speech changes [21].

Figura et al. have assessed the long-term side effects following unilateral GKT, and observed no significant worsening of cognition, speech, or balance [3]. They conclude that this lesioning technique is safe when performed at an experienced centre. FUS is relatively new, but the annual number of thalamotomies for ET by FUS surpassed those using GKT in 2017, and continues to rise at an almost exponential rate [22]. The wholesale adoption of FUS has been attributed to the ability it delivers for intraoperative assessment, the device maker's interest in ET, and key opinion leaders' interest in FUS [22]. With such widespread adoption, one would expect a substantial amount of data on the side effect profile of FUS. In the only double-blind randomised clinical trial of FUS, gait disturbance and sensory abnormalities emerged in 38% and 36% of patients, respectively [23]. In 2019, unilateral FUS thalamotomy was thus designated "likely efficacious" and "possibly useful" in clinical practice [5]. In a more recent study of 45 patients (39 ET, one TAPD, two mixed tremor), 45% experienced gait decline, which was more likely among those with a history of neuropathy or joint replacement [24]. Adverse effects were not associated with lesion placement, although the study reported no cases of inadvertent lesion placement, which can lead to permanent side effects [24].

Treatment of tremor has rapidly progressed to the point where we now have four viable surgical options: GKT, FUS, RF, and DBS. However, these options are not equal in terms of their efficacy or safety profile. Despite numerous attempts, direct comparisons of immediate and long-term effects are limited. While the data appears strongest for FUS and DBS, there remains evidence for the efficacy of stereotactic radiotherapy even beyond GKT. Linear accelerator-based stereotactic radiosurgery is one such example, with early data suggesting efficacy rivalling that of FUS but without the need for a headframe or to shave the patient's head [25].

In short, all four methods are probably reasonable treatment options based on experience, availability, patient preference, and contraindications. Clinicians, especially movement disorders specialists, should be intimately aware of the options and be prepared to counsel patients appropriately. Clinicians should also refer patients to high-volume centres in order to increase the likelihood of a positive outcome.

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