The Brain Connectome after Gamma Knife Radiosurgery of the Ventro-Intermediate Nucleus for Tremor: Marseille-Lausanne Radiobiology Study Protocol

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Abstract
Essential tremor (ET) is the most common movement disorder. Deep brain stimulation is the current gold standard for drug-resistant tremor, followed by radiofrequency lesioning. Stereotactic radiosurgery by Gamma Knife (GK) is considered as a minimally invasive alternative. The majority of procedures aim at the same target, thalamic ventro-intermediate nucleus (Vim). The primary aim is to assess the clinical response in relationship to neuroimaging changes, both at structural and functional level. All GK treatments are uniformly performed in our center using Guiot's targeting and a radiation dose of 130 Gy. MR neuroimaging protocol includes structural imaging (T1-weighted and diffusion-weighted imaging [DWI]), resting-state functional MRI, and ^{18}F-fluorodeoxyglucose-positron emission tomography. Neuroimaging changes are studied both at the level of the cerebello-thalamo-cortical tract (using the prior hypothesis based upon Vim's circuitry: motor cortex, ipsilateral Vim, and contralateral cerebellar dentate nucleus) and also at global brain level (no prior hypothesis). This protocol aims at using modern neuroimaging techniques for studying Vim GK radiobiology for tremor, in relationship to clinical effects, particularly in ET patients. In perspective, using such an approach, patient selection could be based upon a specific brain connectome profile.

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Published by S. Karger AG, Basel

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Introduction

Stereotactic radiosurgery (SRS) was invented by Lars Leksell at the beginning of the 1950s, originally as a primary tool for treating functional disorders [1, 2]. Later on, in 1968, Leksell created the Gamma Knife (GK), an SRS tool using cobalt-67 sources of radiation [2]. Currently, clinical applications of GK include benign and malignant tumors, vascular malformations, and functional disorders (including psychiatric) [3, 4].

Mechanism of action varies according to the treated condition [5, 6]. In the particular case of functional disorders, GK is used either to target a specific anatomical point, such as the ventro-intermediate nucleus (Vim) of the thalamus [7, 8], the anterior limb of the internal capsule [9], or the trigeminal nerve [9–11] with high doses, or for targeting larger zones (e.g., epileptic focus) [12], with much lower dosage. Thus, the mechanisms of action can further differ.

Essential tremor (ET) is the most common movement disorder [13]. There are several pathophysiological theories with regard to ET. The most common one presumes tremor as generated by abnormal oscillations within the cerebello-thalamo-cortical axis, corresponding to the motor cortex, ipsilateral thalamic area (e.g., Vim), and the contralateral cerebellar dentate nucleus [13, 14]. Drug-resistant ET can benefit from standard deep brain stimulation [15] or stereotactic radiofrequency lesioning [16]. As a minimally invasive alternative, SRS has been successfully used during the past decades [17]. More recently, high-intensity focused ultrasound, producing an MR-controlled thermocoagulation, has emerged [18]. The majority of surgical procedures aim at the same target, the Vim. However, some authors have advocated also for the use of the zona incerta, with good clinical results [19].

The main limitation of Vim GK for tremor is the inability to predict the 1-year MR signature. Importantly, there is a lack of understanding of the radiobiological effect, with a progressive clinical improvement, after a median time of 3 months, going up to 1 year [20]. Thus, a better understanding of the radiobiological effect may improve our capacity to generate better clinical result.

Methods

Protocol Title and Formal Approval

The title of the protocol in French is "Evaluation des prédicteurs de la réponse clinique et radiologique à la radiochirurgie Gamma-Knife dans le traitement par thalamotomie du VIM" and in English is "Gamma Knife response predictability (GARP)." The first patient included in this protocol was treated in CHU Timone, Marseille, France, in September 2014. The protocol is ongoing. It had received formal approval from the CHU Timone Ethics Committee ID-RCB: 2017-A01249–44. Formal approval was also obtained from Paris, France: September 12, 2017, following the reference methodology CNIL-MR-03.

Study Goals and Objectives

The primary aim of the present protocol is to assess the clinical response after Vim GK for tremor (in particular for ET), in relationship to neuroimaging changes, both at structural and functional level, but also with the genetic analysis, chronobiological details, concomitant therapies, concomitant morbidities, the brain's state on pretherapeutic MRI, or tremor phenotype. Such an approach allows extracting rich information, with minimal patient's compliance. The secondary endpoint is the influence of the paraclinical aspects (see below) on the radiological reaction in terms of timing and amplitude.

Study Design

Our protocol was conceived as prospective, interventional, single group, and bicentric. All SRS treatments have been performed in Marseille University Hospital (CHU Timone; Professor Régis). Clinical and genetic data were analyzed in Marseille, France. Neuroimaging data were blindly analyzed in Lausanne, Switzerland. Enrollment of >100 cases is expected.

Inclusion criteria (Table 1, upper part): patients with tremor (ET, Parkinsonian origin, mixed, Holmes, polyneuropathy context, and multiple sclerosis patients), able to give written informed consent and attend the follow-up visit, with potential medical comorbidities, advanced age, or refusing Vim deep brain stimulation. Exclusion criteria (Table 1, lower part): contraindication to perform brain MRI (cardiac pacemaker), inability to provide written informed consent, patients refusing to enroll in the trial, and previous contralateral Vim surgery for tremor [21].

Vim GK Targeting

All targeting procedures were performed unilaterally by the last author using stereotactic imaging (MRI and CT) for all cases. The Guiot's diagram (see Fig. 1, left) is placed 2.5 mm above the AC-PC line, 11 mm lateral to the wall of the third ventricle. A unique 4-mm isocenter is used. The dose prescribed is 130 Gy in all cases [22]. Beam channel blocking is used to shape the gradient towards the internal capsule (see Fig. 1, right). The "x" coordinate is fine-tuned accordingly to the exact anatomical location of the internal capsule on the nonstereotactic diffusion tensor imaging, acquired the day before GK.

Standard Clinical Evaluation

Tremor severity is always assessed by the second author, using standard tremor scores: Bain's questionnaire, including items such as the activities of daily living [23], Fahn-Tolosa-Marin tremor rating scale (tremor score of the treated hand) [24], and Tremor Research Group Essential Tremor Rating Assessment (TETRAS, head's tremor). The quality of life questionnaire (QUEST) was fulfilled [25]. The exact timing of tremor improvement is noted. The Mattis dementia score is evaluated [26].
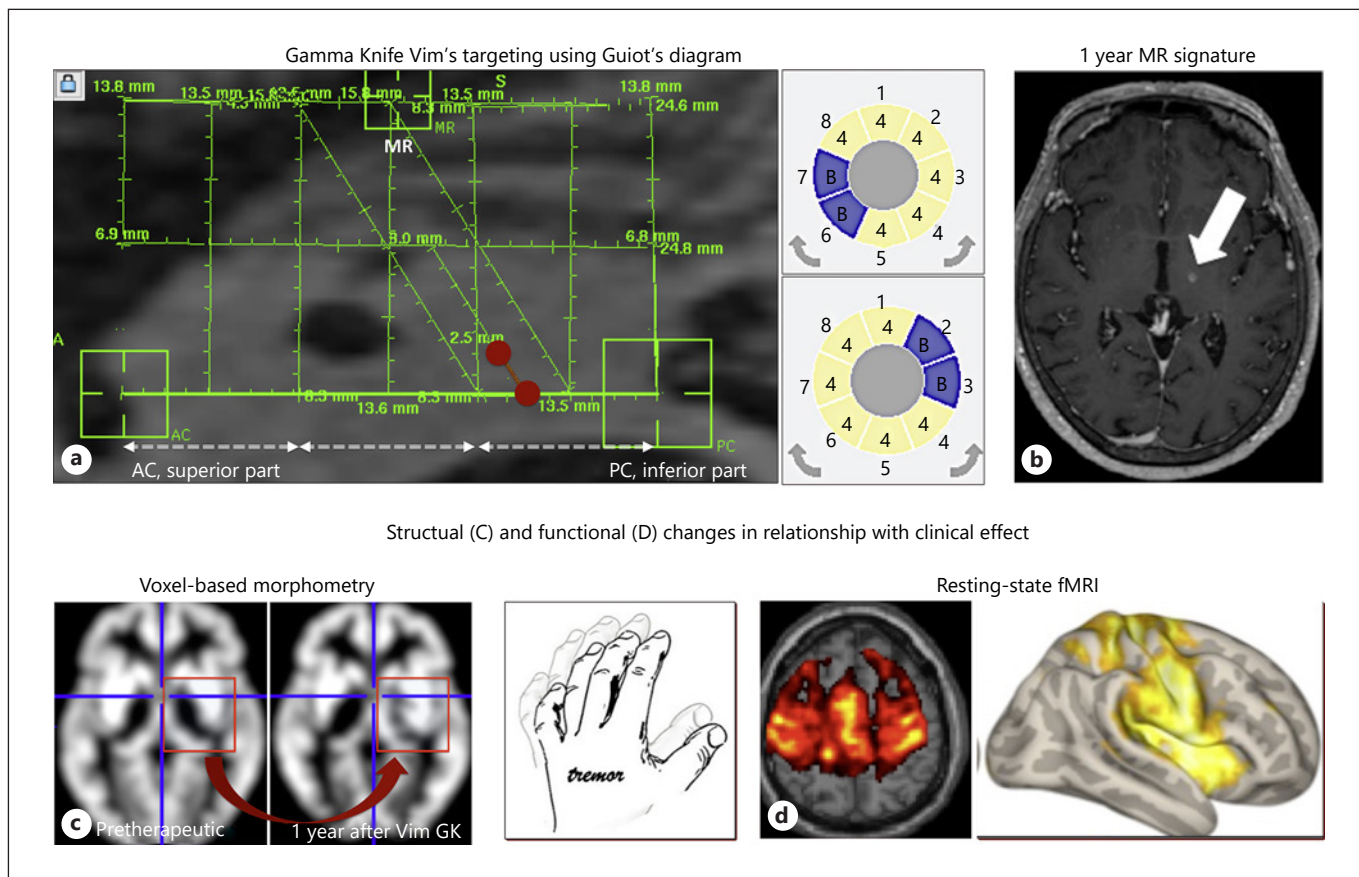
Fig. 1. Vim GK targeting using Guiot's diagram and placement of two isocenters on the same stereotactic coordinates, with different weights and plugging pattern (**a**); 1-year classical MR signature after Vim GK (**b**); voxel-based morphometry illustration as structural data analysis (**c**); and resting-state fMRI as functional data analysis (**d**), and both (**c**, **d**) correlated with clinical effect and tremor score improvement. Vim, ventro-intermediate nucleus; GK, Gamma Knife.

Table 1. Patient inclusion and exclusion criteria

Inclusion criteria
Able to give formal approval and attend all follow-up visits (including intermediate ones at 3, 6, 9, and 12 months minimum)
Essential tremor or other types of tremor diagnosis confirmed by our movement disorders neurologist from clinical history and examination
Drug resistance after adequate trials
Age between 18 and 80
Medical contraindication for DBS or radiofrequency thalamotomy
The Vim thalamic area apparent on MRI
Exclusion criteria
Previous history of stroke or epilepsy, to exclude unrelated networks appearance
Previous contralateral SRT
Standard contraindication for MRI, including non-MRI compatible devices, such as cardiac pacemakers
Pregnancy or lactation
Brain tumors
Significant cognitive impairment, with a score at Mini-Mental State Evaluation ≤24
Unable to provide consent for any reason
Prior stereotactic and/or radiosurgery procedures in the basal ganglia area

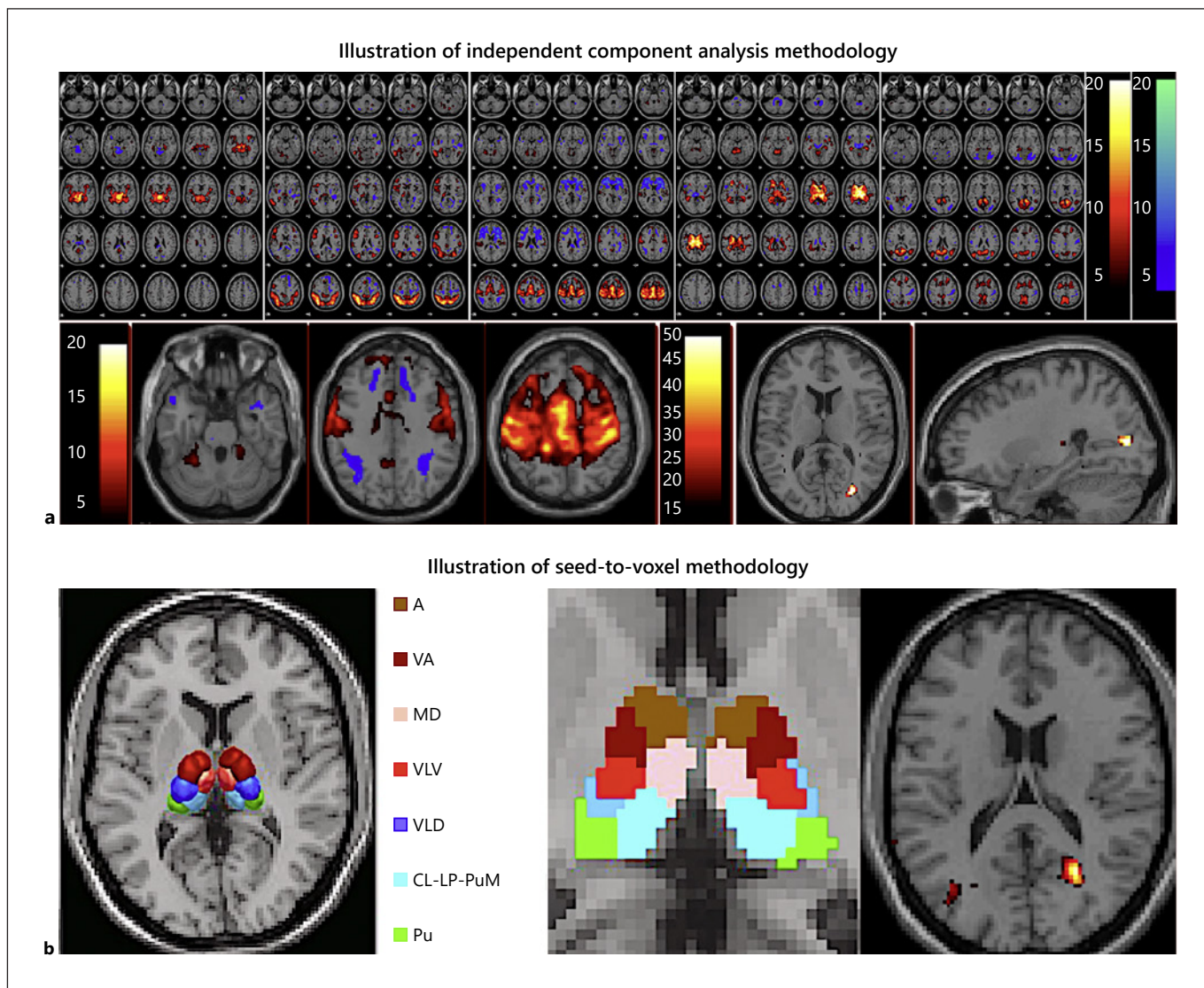DBS, deep brain stimulation; Vim, ventro-intermediate nucleus.

Fig. 2. a Illustration of independent component analysis methodology, with several networks being generated (upper part); moreover, statistically significant networks (motor network, cerebellar lobule 6, illustrated here, lower part, left) are interconnected with visual extrastriate cortex clusters (lower part, right); further statistical analysis is performed using pre- and posttherapeutic tremor scores with values extracted from such relevant clusters. **b** Illustration of seed-to-voxel connectivity: the VLV cluster (Morel nomenclature, left side) is extracted from diffusion tensor imaging data using the specific patient data, for each patient; the VLV connectivity with other voxels of the brain is performed individually, per patient, obtaining a connectivity map (right); further group analysis is performed.

Paraclinical Evaluation

Neuroimaging Evaluation

All neuroimaging is obtained on a 3-T MRI scanner Skyra TrioTrim (Siemens, Munich, Germany). Structural imaging includes the following: T1-weighted imaging (T1, TR/TE = 2,300/2.03, inversion time 900 ms, and isotropic voxel of 1 mm^3 and 192 slices) [27, 28] and diffusion-weighted imaging (DWI, 64 gradient directions and b = 1000 s/mm) [29, 30]. Functional neuroimaging by resting-state functional MRI is further acquired: T2*-weighted fast echo planar imaging (BOLD contrast, before the Gadolinium in-jection, TR/TE = 3.3 s/30 ms/90°, voxel size $4 \times 4 \times 4$ mm^3, and 300 volumes acquired per subject), during 10 min of acquisition, in absence of any explicit task [31, 32]. Several methodologies are being used, including independent component analysis (Fig. 2a) and seed-to-voxel connectivity (Fig. 2b).

^{18}F-FDG PET scans are performed with an integrated PET/CT camera. ^{18}F-FDG is injected intravenously at the activity of 150 MBq, in an awake and resting state with eyes closed in a quiet environment, as previously reported [33]. Image acquisition starts 30 min after injection and ended 15 min thereafter. Images are recon-

structed using the ordered subsets expectation maximization algorithm and corrected for attenuation using a CT transmission scan. In detail, ^{18}F-FDG PET scans were performed before and after GK for each patient, under the same conditions as those for the healthy subjects acquired as the control group. A PET/CT camera (Discovery ST; GE Healthcare, Waukesha, WI, USA) was used with an axial resolution of 6.2 mm, allowing 47 3.27-mm thick contiguous transverse sections of the brain. ^{18}F-FDG (150 MBq) was injected intravenously during both awake and resting states with each patient's eyes closed in a quiet environment. Thirty minutes later, images were acquired over a 15-min period. Reconstruction parameters were 5 iterations and 32 subsets using the ordered subsets expectation maximization algorithm and with a CT transmission scan for attenuation correction. The FDG PET utility is to characterize PET changes in the metabolism of glucose and metabolic connectivity in patients with ET treated by GK through the observational study (comparing the pre- and posttherapeutic state, but also with healthy subjects).

Other Paraclinical Investigations

Besides neuroimaging evaluation, several other investigations are performed. We always acquire blood sampling for genetic analysis, the chronobiological details (the moment of treatment during the day), the concomitant therapies (at the time of SRS and during the following months), concomitant morbidities (diabetes mellitus and vascular problems), and the brain's state on pretherapeutic MRI (lacunar infarcts and brain atrophy).

Follow-Up Periods

Clinical and radiological evaluation was performed at 6 and 12 months and on yearly basis after.

Neuroimaging Correlations

The main neuroimaging analysis includes voxel-based morphometry (for structural imaging) and resting-state fMRI and metabolic PET methodologies, so as to be able to correlate clinical improvement with neuroimaging changes.

Current Status

The trial is currently ongoing. More than 100 cases have been included, up-to-date, of various tremors (ET and Parkinsonian).

The first part focused on ET cases, to have a uniform disease. This part is also, currently, enrolling patients, to upgrade the number of cases.

Discussion

The main challenge is the use of complex computational approaches, so as to be able to extract the relevant structural and functional connectomics, in relationship to clinical effect. Of major importance is the uniform assessment, on the same MRI machine. Other aspect, especially in tremor patients, is to further evaluate motion, as a potential confounding factor. Moreover, establishing neuroimaging metrics to evaluate their correlations with standard tremor scores is of interest.

A major aspect is that the relevant functional data are considered at baseline and 1-year follow-up, to account for the delayed clinical effect. The main expected result is how functional connectomics will change after Vim GK. Moreover, of particular interest is how this relates to clinical effect. The translational impact is of relevance. Such a trial could improve patient selection in the future, based on a specific functional and/or structural connectivity profile.

Statement of Ethics

This study had received formal approval from the CHU Timone Ethics Committee ID-RCB: 2017-A01249-44. Formal approval was also obtained from Paris, France: September 12, 2017, following the reference methodology CNIL-MR-03.

Conflict of Interest Statement

Constantin Tuleasca was a scientific advisor for Elekta Instruments, AB, Sweden, without any relevance, nor funding for the present work; Jean Régis is a consultant and received research grants from Elekta Instruments, AB, Sweden, and from Medtronic.

Author Contributions

Constantin Tuleasca: conception and design, study supervision, and acquisition and interpretation of data; Tatiana Witjas: conception and design, study supervision, and acquisition and interpretation of data; Marc Levivier: conception and design and data acquisition; Nadine Girard: conception and design and data acquisition; Axelle Cretol: data acquisition and keeping the database up-to-date; Nicolas Levy: conception and design and interpretation of data; Jean-Philippe Thiran: interpretation of data; Eric Guedj: conception and design and acquisition and interpretation of data; Dimitri Van De Ville: conception and design, study supervision, and acquisition and interpretation of data; Jean Régis: conception and design, study supervision, and acquisition and interpretation of data.

References

1 Leksell L. Sterotaxic radiosurgery in trigeminal neuralgia. Acta Chir Scand. 1971;137(4):311–4.

2 Steiner L, Forster D, Leksell L, Meyerson BA, Boëthius J. Gammathalamotomy in intractable pain. Acta Neurochir. 1980;52(3–4):173–84.

3 Niranjan A, Madhavan R, Gerszten PC, Lunsford LD. Intracranial radiosurgery: an effective and disruptive innovation in neurosurgery. Stereotact Funct Neurosurg. 2012;90(1):1–7.

4 Regis J, Carron R, Park M. Is radiosurgery a neuromodulation therapy? A 2009 Fabrikant award lecture. J Neurooncol. 2010;98(2):155–62.

5 Szeifert GT, Atteberry DS, Kondziolka D, Levivier M, Lunsford LD. Cerebral metastases pathology after radiosurgery: a multicenter study. Cancer. 2006;106(12):2672–81.

6 Szeifert GT, Salmon I, Lorenzoni J, Massager N, Levivier M. Pathological findings following trigeminal neuralgia radiosurgery. Prog Neurol Surg. 2007;20:244–8.

7 Campbell AM, Glover J, Chiang VL, Gerrard J, Yu JB. Gamma knife stereotactic radiosurgical thalamotomy for intractable tremor: a systematic review of the literature. Radiother Oncol. 2015;114(3):296–301.

8 Witjas T, Carron R, Krack P, Eusebio A, Vaugoyeau M, Hariz M, et al. A prospective single-blind study of Gamma Knife thalamotomy for tremor. Neurology. 2015;85(18):1562–8.

9 Regis J, Tuleasca C, Resseguier N, Carron R, Donnet A, Gaudart J, et al. Long-term safety and efficacy of Gamma Knife surgery in classical trigeminal neuralgia: a 497-patient historical cohort study. J Neurosurg. 2016;124(4):1079–87.

10 Kondziolka D, Zorro O, Lobato-Polo J, Kano H, Flannery TJ, Flickinger JC, et al. Gamma Knife stereotactic radiosurgery for idiopathic trigeminal neuralgia. J Neurosurg. 2010;112(4):758–65.

11 Tuleasca C, Carron R, Resseguier N, Donnet A, Roussel P, Gaudart J, et al. Trigeminal neuralgia related to megadolichobasilar artery compression: a prospective series of twenty-nine patients treated with gamma knife surgery, with more than one year of follow-up. Stereotact Funct Neurosurg. 2014;92(3):170–7.

12 McGonigal A, Sahgal A, De Salles A, Hayashi M, Levivier M, Ma L, et al. Radiosurgery for epilepsy: systematic review and International Stereotactic Radiosurgery Society (ISRS) practice guideline. Epilepsy Res. 2017;137:123–31.

13 Haubenberger D, Hallett M. Essential tremor. N Engl J Med. 2018;379(6):596–7.

14 Al-Fatly B, Ewert S, Kübler D, Kroneberg D, Horn A, Kühn AA. Connectivity profile of thalamic deep brain stimulation to effectively treat essential tremor. Brain. 2019;142(10):3086–98.

15 Benabid AL, Pollak P, Gao D, Hoffmann D, Limousin P, Gay E, et al. Chronic electrical stimulation of the ventralis intermedius nucleus of the thalamus as a treatment of movement disorders. J Neurosurg. 1996;84(2):203–14.

16 Taira T, Horisawa S, Takeda N, Ghate P. Stereotactic radiofrequency lesioning for movement disorders. Prog Neurol Surg. 2018;33:107–19.

17 Martinez-Moreno NE, Sahgal A, De Salles A, Hayashi M, Levivier M, Ma L, et al. Stereotactic radiosurgery for tremor: systematic review. J Neurosurg. 2018:1–12.

18 Elias WJ, Huss D, Voss T, Loomba J, Khaled M, Zadicario E, et al. A pilot study of focused ultrasound thalamotomy for essential tremor. N Engl J Med. 2013;369(7):640–8.

19 Sandvik U, Hariz GM, Blomstedt P. Quality of life following DBS in the caudal zona incerta in patients with essential tremor. Acta Neurochir. 2012;154(3):495–9.

20 Tuleasca C, Régis J, Levivier M. Essential tremor. N Engl J Med. 2018;379(6):595–6.

21 Niranjan A, Raju SS, Monaco EA, Flickinger JC, Lunsford LD. Is staged bilateral thalamic radiosurgery an option for otherwise surgically ineligible patients with medically refractory bilateral tremor? J Neurosurg. 2018;128(2):617–26.

22 Tuleasca C, Pralong E, Najdenovska E, Cuadra MB, Marques JRF, Vingerhoets F, et al. Deep brain stimulation after previous Gamma Knife thalamotomy of the Vim for essential tremor is feasible! Clinical, electrophysiological and radiological findings. Acta Neurochir (Wien). 2017;159(7):1371–3.

23 Bain PG, Findley LJ, Atchison P, Behari M, Vidailhet M, Gresty M, et al. Assessing tremor severity. J Neurol Neurosurg Psychiatry. 1993;56(8):868–73.

24 Elble RJ, Pullman SL, Matsumoto JY, Raethjen J, Deuschl G, Tintner R. Tremor amplitude is logarithmically related to 4- and 5-point tremor rating scales. Brain. 2006;129(Pt 10):2660–6.

25 Troster AI, Pahwa R, Fields JA, Tanner CM, Lyons KE. Quality of life in essential tremor questionnaire (QUEST): development and initial validation. Parkinsonism Relat Disord. 2005;11(6):367–73.

26 Schmidt R, Freidl W, Fazekas F, Reinhart B, Grieshofer P, Koch M, et al. The Mattis dementia rating scale: normative data from 1,001 healthy volunteers. Neurology. 1994;44(5):964–6.

27 Tuleasca C, Witjas T, Najdenovska E, Verger A, Girard N, Champoudry J, et al. Assessing the clinical outcome of Vim radiosurgery with voxel-based morphometry: visual areas are linked with tremor arrest! Acta Neurochir. 2017;159(11):2139–44.

28 Tuleasca C, Witjas T, Van de Ville D, Najdenovska E, Verger A, Girard N, et al. Right Brodmann area 18 predicts tremor arrest after Vim radiosurgery: a voxel-based morphometry study. Acta Neurochir. 2018;160(3):603–9.

29 Tuleasca C, Najdenovska E, Régis J, Witjas T, Girard N, Champoudry J, et al. Ventrolateral motor thalamus abnormal connectivity in essential tremor before and after thalamotomy: a resting-state functional magnetic resonance imaging study. World Neurosurg. 2018;113:e453–64.

30 Tuleasca C, Régis J, Najdenovska E, Witjas T, Girard N, Champoudry J, et al. Pretherapeutic functional imaging allows prediction of head tremor arrest after thalamotomy for essential tremor: the role of altered interconnectivity between thalamolimbic and supplementary motor circuits. World Neurosurg. 2018;112:e479–88.

31 Tuleasca C, Bolton T, Régis J, Najdenovska E, Witjas T, Girard N, et al. Thalamotomy for tremor normalizes aberrant pre-therapeutic visual cortex functional connectivity. Brain. 2019;142(11):e57.

32 Tuleasca C, Najdenovska E, Régis J, Witjas T, Girard N, Champoudry J, et al. Clinical response to Vim's thalamic stereotactic radiosurgery for essential tremor is associated with distinctive functional connectivity patterns. Acta Neurochir. 2018;160(3):611–24.

33 Verger A, Witjas T, Carron R, Eusebio A, Boutin E, Azulay JP, et al. Metabolic positron emission tomography response to Gamma Knife of the ventral intermediate nucleus in essential tremor. Neurosurgery. 2019;84(6):E294–303.