

Research Article

Gamma-Knife Thalamotomy for Essential and Parkinsonian Tremor: Predicting Response to Treatment Using Pre-Therapeutic Cerebral FDG-PET

Nathan De Lissnyder^{1,*} , Gil Leurquin-Sterk² , Nicola Trotta² , Philippe David³, Florence Lefranc⁴ 

¹Department of Neurosurgery, Vrije Universiteit Brussel, Brussels, Belgium

²Department of Nuclear Medicine, Hôpitaux Universitaires de Bruxelles – Erasme, Brussels, Belgium

³Department of Neuroradiology, Hôpitaux Universitaires de Bruxelles – Erasme, Brussels, Belgium

⁴Department of Neurosurgery, Hôpitaux Universitaires de Bruxelles – Erasme, Brussels, Belgium

Abstract

Essential tremor and parkinsonian tremor affect approximately 5–7% of individuals over the age of 65. Pharmacological therapies yield sustained clinical improvement in only about 50% of cases. For patients ineligible for deep brain stimulation, Gamma Knife thalamotomy (GKVIM) offers a non-invasive alternative, demonstrating a tremor reduction efficacy of 70–80%, typically with a latency of approximately 4.8 months. This study aimed to identify regional cerebral metabolic patterns predictive of clinical response to GKVIM using [¹⁸F]-FDG positron emission tomography (FDG-PET). Fifteen consecutive patients diagnosed with essential tremor (n=10) or parkinsonian tremor (n=5) underwent preoperative cerebral FDG-PET imaging within 24 hours prior to GKVIM at Erasme University Hospital between January 2020 and January 2023. All patients were clinically followed for a minimum of six months (mean follow-up: 9 ± 3 months) by experienced neurologists or neurosurgeons. Statistical Parametric Mapping (SPM) was used to compare metabolic patterns between treatment responders (n=11; 73%) and non-responders (n=4) to identify potential predictors of therapeutic response. As a secondary objective, metabolic differences between patients with essential tremor and healthy controls (n=54) were analyzed to explore neurobiological correlates of disease pathophysiology. Those analysis revealed that responders exhibited significant hypometabolism in the prefrontal cortex and supramarginal gyrus, alongside cerebellar hypermetabolism. In the secondary analysis, patients with essential tremor demonstrated distinct metabolic alterations, notably involving the inferior olivary nuclei. This study thus identifies specific regional cerebral metabolic patterns associated with favourable clinical response to Gamma Knife thalamotomy, suggesting potential neuroimaging biomarkers for patient selection. Moreover, the observed metabolic changes provide additional insight into the pathophysiological mechanisms underlying essential tremor.

Keywords

Gamma-Knife, Metabolism, Parkinson, Radiosurgery, Thalamotomy, Tremor, FDG-PET

*Corresponding author: nathan.delissnyder@gmail.com (Nathan De Lissnyder)

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1. Introduction

Tremor is defined as an involuntary, rhythmic, oscillatory movement of a body segment [1]. Essential Tremor (ET) and Parkinsonian Tremor (PT) represent the two most common etiologies of tremor globally, with an increasing prevalence in aging populations [2, 3].

1.1. Essential Tremor

ET is the most prevalent cause of tremor, affecting approximately 5% of individuals over the age of 60. It typically presents as a bilateral action or postural tremor of the upper limbs, though it may also involve the head, voice, facial muscles, or axial structures [4, 5].

The pathophysiology of ET remains incompletely understood despite ongoing investigation. Neuroimaging studies have identified a range of structural, functional, and metabolic abnormalities, primarily involving the cerebellum and its connections [5, 6]. Current consensus implicates dysfunction within the cerebello-thalamo-cortical network as a key mechanism, although the contribution of additional cortical and subcortical regions is under debate. This supports the hypothesis that ET encompasses a spectrum of related disorders rather than a single homogeneous entity [7].

First-line pharmacological treatment typically involves propranolol or primidone; however, up to 50% of patients experience insufficient or unsustained benefit [8, 9]. For selected candidates with medically refractory tremor, Deep Brain Stimulation (DBS) targeting the Ventral InterMediate nucleus of the thalamus (VIM) may be considered.

1.2. Tremor Associated with Parkinson's Disease

PT most commonly presents as a resting tremor that begins unilaterally in the upper limbs, later progressing contralaterally and potentially involving the lower limbs, lips, jaw, or tongue [10]. First-line therapy includes levodopa, dopamine agonists, MonoAmine Oxidase Inhibitors (MAOIs), or combinations thereof [11, 12].

In patients who respond to medical therapy but develop treatment-related complications such as dyskinesia, DBS of the subthalamic nucleus may be indicated, enabling simultaneous control of tremor, rigidity, and bradykinesia [13].

1.3. Gamma Knife Thalamotomy

In patients for whom DBS is contraindicated - due to advanced age, comorbidities, anticoagulant use, cognitive impairment, patient refusal, or previous DBS failure - Gamma-Knife thalamotomy targeting the VIM (GKVIM) may be a viable alternative [14]. This non-invasive stereotactic radiosurgical technique has been in development since the 1990s and relies on high-resolution imaging to ensure accurate targeting [15]. GKVIM allows for treatment without crani-

otomy or general anesthesia, significantly reducing the risk of perioperative complications such as hemorrhage or infection, and typically requires hospitalization for less than 24 hours.

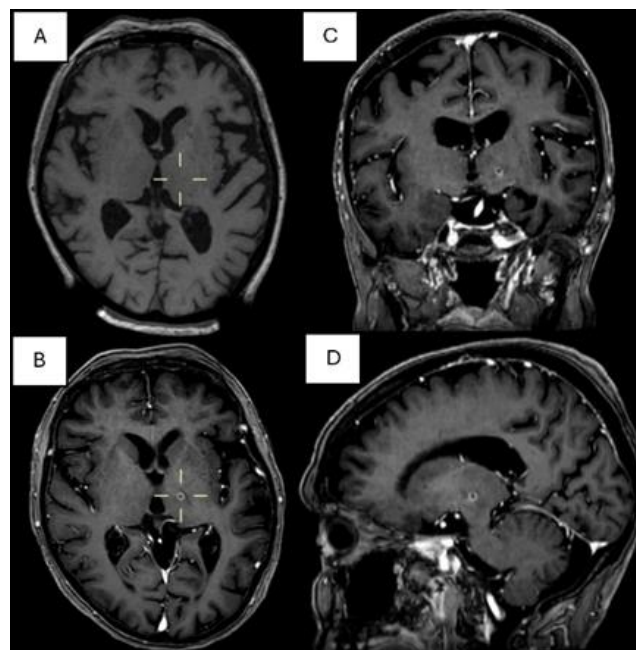


Figure 1. A. Axial section on 3DT1 MRI on the morning of Gamma-Knife treatment; B/C/D. Axial/coronal/sagittal section on 3DT1 MRI with gadolinium at 6 months post-treatment, left thalamic lesion with annular enhancement.

Optimal dosing and targeting remain areas of active research. Current consensus recommends a dose of 130 Gy delivered to the VIM [16]. Clinical studies report a 70–80% efficacy rate in tremor reduction following GKVIM. However, it is noteworthy that some patients report improved quality of life despite persistent tremor, while others do not perceive subjective benefit despite objective improvement [17, 18]. (Figure 1)

As an irreversible lesional procedure, GKVIM differs from the functional nature of DBS. Limitations of GKVIM include delayed therapeutic onset (typically 4.8 months), lack of intraoperative confirmation of target accuracy, and the potential for unpredictable perilesional edema [19]. Although irreversibility is often cited as a drawback, the incidence of permanent complications appears to be lower with GKVIM than with DBS [20].

To date, no prospective randomized controlled trials have directly compared GKVIM and DBS, and therefore no definitive evidence exists to support the superiority of one approach over the other.

Adverse effects following GKVIM occur in 0–8.4% of patients and are generally reversible within several months. The most commonly reported side effects include dysphagia,

hemiparesis, hemisensory deficits, and speech disturbances [19].

Given that 20–30% of patients do not experience meaningful clinical improvement following GKVIM - despite the rare but inherent risks - identifying reliable predictors of response would be of high clinical utility.

Structural imaging parameters (e.g., Fazekas score on MRI), functional imaging (fMRI), and metabolic imaging (FDG-PET) have all shown potential in this context [21–24].

1.4. FDG-PET

[18 F]-Fluorodeoxyglucose positron emission tomography (FDG-PET) enables the assessment of regional brain metabolism by quantifying the spatial distribution of radiolabeled glucose, thereby providing an indirect measure of synaptic activity [23]. In the present study, FDG-PET was used to explore the neurobiological substrates of ET in complement to conventional structural imaging.

1.5. Objectives

The primary objective of this study was to identify regional cerebral metabolic alterations that may predict clinical response to GKVIM in patients with ET or PT. The secondary objective was to investigate disease-specific metabolic patterns in ET patients, with the goal of contributing to a better understanding of its pathophysiology [22, 23].

2. Methods

This study was approved by the Ethical Committee of HUB-Erasme Hospital on April 14, 2023 (project number SRB2023/064; Ethical Committee reference P2023/140).

2.1. Methodology of the Literature Review

A narrative review of the literature was conducted to evaluate the current understanding of clinical response to GKVIM in ET and PT, as well as the pathophysiological mechanisms underlying ET. The search was performed in the PubMed database using combinations of the following keywords: "radiosurgery", "gamma-knife", "PET", "metabolic imaging", "essential tremor", and "Parkinson". Articles published in English and French were considered.

2.2. Study Methodology

2.2.1. Patient Selection

All patients treated with GKVIM for ET or PT at Erasme University Hospital between January 2020 and January 2023 were screened for inclusion. Inclusion criteria were: (1) diagnosis of ET or PT; (2) treatment with GKVIM; (3) availability of a pre-treatment cerebral FDG-PET scan. Patients were excluded if their PET imaging was significantly affected by a prior stroke, if they had undergone bilateral thalamotomy (only the first procedure was considered), or if follow-up data were unavailable. (Table 1)

Table 1. Inclusion and exclusion criteria for patient selection.

Inclusion criteria	Exclusion criteria
Patients who underwent Gamma Knife thalamotomy between January 2020 and January 2023 at HUB-Erasme Hospital.	Presence of a tremor type other than essential or parkinsonian tremor.
Diagnosis of essential tremor or parkinsonian tremor confirmed by a neurologist.	FDG-PET scan significantly altered due to prior neurological events, as assessed by a nuclear medicine physician.
Availability of a cerebral FDG-PET scan performed within one week prior to treatment.	Absence of follow-up consultation with a neurologist or neurosurgeon at least 6 months after treatment, including both clinical and MRI data.

2.2.2. Treatment Protocol

All procedures were performed by the same neurosurgeon using a standardized treatment protocol. Each patient underwent preoperative neuroimaging including 3T brain MRI (T1-weighted, T2-weighted, and DTI sequences) and FDG-PET the day prior to treatment, without application of the Leksell frame.

On the day of treatment, following frame fixation, a 1.5T MRI (T1- and T2-weighted thin-section sequences) and a CT

scan were acquired. These images were co-registered to optimize anatomical localization of the target.

Targeting of the VIM was performed using standard stereotactic coordinates: 25% of the AC-PC distance anterior to the PC along the AC-PC line, 2.5 mm superior in the sagittal plane, and 11 mm lateral to the lateral border of the third ventricle. For additional safety, an anterior offset of 1 mm was applied in the axial plane.

Lesioning was performed using two 4-mm collimator shots at a dose of 65 Gy each (50% isodose), with beam sectors

directed away from the internal capsule. (Figure 2)

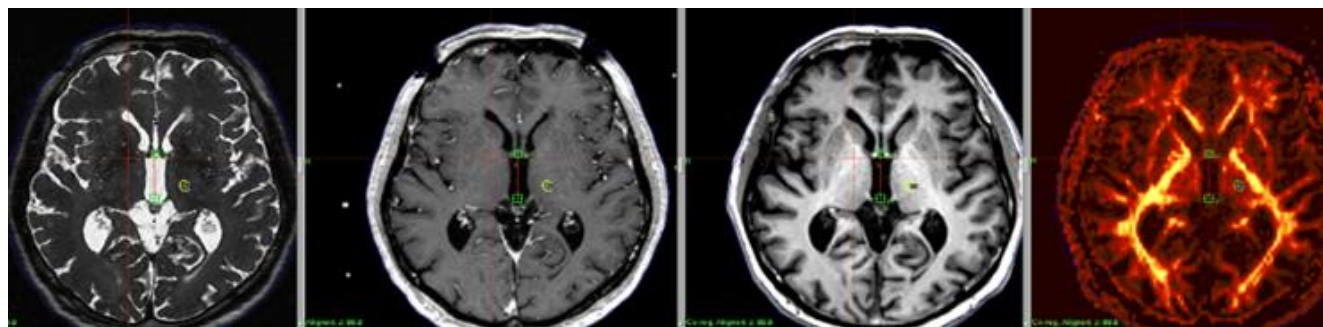


Figure 2. Localization of the target (VIM) and areas at risk (internal capsule) using several MRI modalities. Respectively from left to right, 1.5T T2 thin slice MRI, 1.5T T1 MRI, 3T T1 MRI, 3T DTI MRI.

2.2.3. FDG-PET Acquisition and Processing

FDG-PET imaging was performed according to a standard protocol 40 minutes after intravenous injection of 120 MBq of ^{18}F -FDG. A 7-minute static acquisition was conducted using a Vereos digital PET-CT scanner (Philips Medical Systems, Cleveland, OH, USA), as previously described by Zhang et al. (2018).

Images were reconstructed using the TOF-OSEM algorithm (3 iterations, 15 subsets) with CT-based attenuation correction. Voxel size was $2 \times 2 \times 2$ mm. No post-reconstruction smoothing filter was applied.

2.2.4. Data Collection

Demographic and clinical data were extracted from the Belgian national health network and included age, sex, tremor type (ET or PT), handedness, medical and surgical history, medications, and adverse events. Imaging data (pre- and post-treatment MRI, FDG-PET) were retrieved from the institutional PACS system. Control FDG-PET data from 54 healthy individuals were obtained from a local normative database used in clinical practice.

Clinical outcome was assessed at a minimum of 6 months post-treatment (mean follow-up: 9 ± 3 months), based on patient-reported satisfaction (yes/no) during consultation with a neurologist or neurosurgeon. Patients were thus classified into responder and non-responder groups.

2.2.5. Data Analysis

PET data were analyzed using voxel-wise Statistical Parametric Mapping (SPM8; Wellcome Department of Imaging Neuroscience, London, UK; <http://www.fil.ion.ucl.ac.uk/spm/>). Images were spatially normalized to the Montreal Neurological Institute (MNI) template and smoothed with a 12-mm full-width at half-maximum isotropic Gaussian kernel. Global signal normalization was performed by proportional scaling, as described by Van Bogaert et al. (2000).

Subtractive analyses were conducted to compare:

- 1) Responders versus non-responders (primary objective).
- 2) ET patients versus healthy controls (secondary objective).

To account for lateralization, all PET images were standardized to a left-thalamotomy configuration by applying horizontal flipping when necessary (1 patient). Separate t-contrast analyses were used to identify regions of significant hyper- or hypometabolism. Age was included as a covariate of no interest in the general linear model to limit the effect of cortical atrophy on results.

Associations between clinical response and imaging (Fazekas scores on pre-treatment MRI), demographic, and clinical variables were assessed using binomial logistic regression. Statistical analysis was performed using Jamovi version 2.3.28.

3. Results

3.1. Sampling of Patients

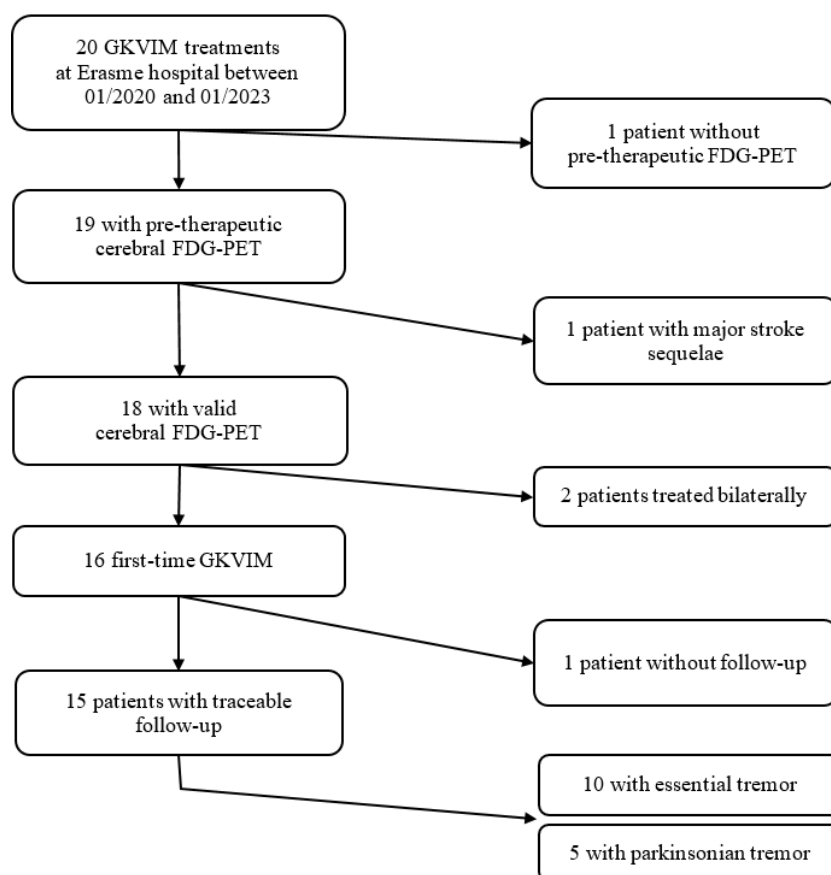


Figure 3. Sampling of patients.

3.2. Characteristics of the Sample

Of the 15 patients included in the study, 11 were classified

as responders and 4 as non-responders, resulting in a response rate of 73%. (*Table 2*) Three patients (20%) experienced reversible post-treatment complications that were potentially attributable to the intervention. (*Table 3*)

Table 2. Clinical and demographic characteristics of patients treated by Gamma-Knife thalamotomy for essential or parkinsonian tremor by treatment response.

	Responders (n=11)	Non-reponders (n=4)	p-value
Age at treatment (years)	75,1+/-9,2	76+/-9,54	0,544
Female sex, n (%)	6 (54,5%)	2 (50%)	0,876
Essential tremor, n (%)	8 (72,7%)	2 (50%)	0,417
On anticoagulants, n (%)	8 (72,7%)	3 (75%)	0,93
Complications, n (%)	2 (18,2%)	2 (50%)	0,236
Fazekas score (n = patients)			0,905
0	3	1	

	Responders (n=11)	Non-responders (n=4)	p-value
1	4	2	
2	3	0	
3	1	1	

Table 3. Types of complications observed following Gamma-Knife thalamotomy.

Complications
Patient 1: Hypoesthesia of the tongue and right thumb with moderate dysarthria
Patient 2: Dyskinesia of the right arm
Patient 3: Right hemiataxia, apathy

3.3. Metabolic Differences

3.3.1. Responders Versus Non-Responders

Statistical Parametric Mapping (SPM) analysis revealed significant metabolic differences in large clusters between responders and non-responders on pre-treatment FDG-PET.

Responders demonstrated: bilateral prefrontal cortex hypometabolism, right supramarginal gyrus hypometabolism, cerebellar hypermetabolism. (*Table 4, Figure 4*)

No statistically significant associations were found between response and demographic (age, sex), clinical (tremor type, anticoagulant use), or radiological (Fazekas score) variables (all $p > 0.05$, *Table 2*).

Table 4. Brain regions with significant metabolic differences between responders and non-responders.

	Cluster size (k_E)	Peak MNI coordinates	Peak z-score	p-value
Hypometabolism in responders				
Bilateral prefrontal cortex	13524	-34; 44; 6	5,04	$p_{FWE-corr} < 0,001$
Right supramarginal gyrus	307	50; -32; 32	4,11	$p_{uncorr} = 0,02$
Hypermetabolism in responders				
Cerebellum	2610	10;-66;-46	4,29	$p_{FWE-corr} < 0,001$

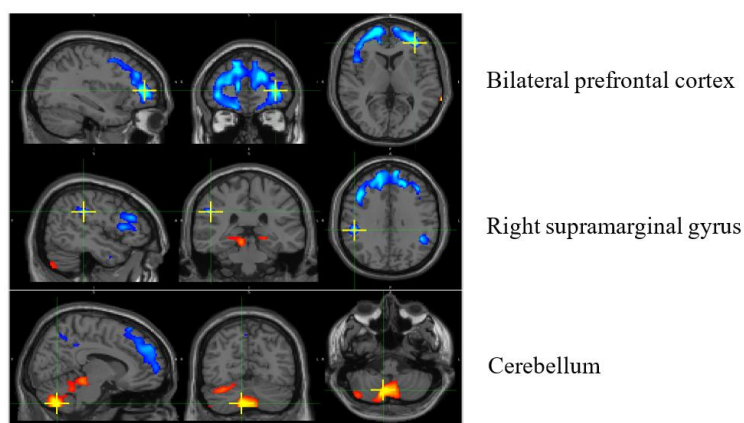


Figure 4. Representation of brain areas showing significant differences in metabolism between responders and non-responders to radiosurgical thalamotomy for tremor.

3.3.2. Essential Tremor Versus Healthy Controls

SPM analysis comparing pre-treatment FDG-PET in ET patients (n=10) versus healthy controls (n=54) revealed multiple cortical and subcortical areas of altered metabolism. (Table 5, Figure 5)

Table 5. Brain regions with significant metabolic differences in ET patients versus healthy controls.

	Cluster size (k_E)	Peak MNI coordinates	Peak z-score	p-value
Hypometabolism in ET patients				
Bilateral medial frontal cortex	1290	2; 36; 30	4,27	$p_{\text{FWE-corr}} = 0,001$
Left superior temporal gyrus	571	-46; -2; -2	3,86	$p_{\text{FWE-corr}} = 0,036$
Hypermeterabolism in ET patients				
Brainstem (inferior olivary nuclei)	4620	-10; -28; -42	5,19	$p_{\text{FWE-corr}} < 0,001$
Left basal ganglia	516	-28; -16; -4	4,1	$p_{\text{FWE-corr}} = 0,049$
Temporal poles	410	-34; 0; -48	4,75	$p_{\text{uncorr}} = 0,024$
Right basal ganglia	318	32; -10; -8	4,13	$p_{\text{uncorr}} = 0,043$
Cerebellum	440	52; -68; -40	4,29	$p_{\text{uncorr}} = 0,02$

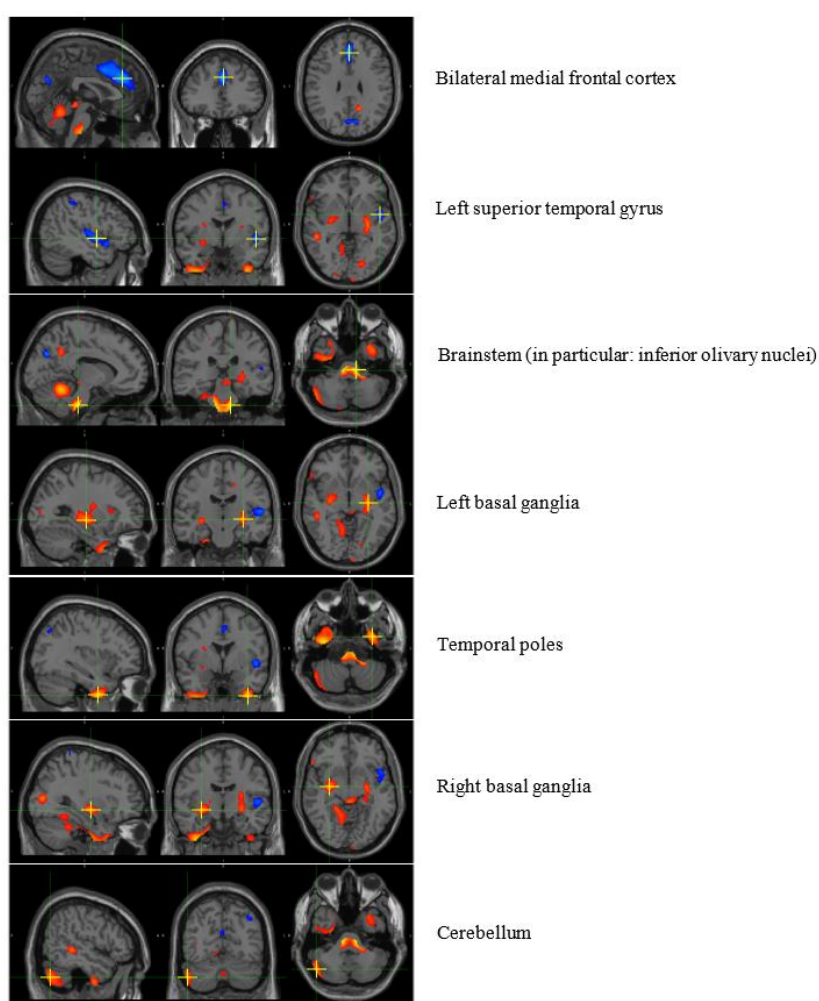


Figure 5. Representation of brain areas showing significant differences in metabolism between patients with essential tremor and healthy controls.

To further refine the interpretation, we classified these metabolic foci by anatomical location using the MNI brain atlas. (Table 6)

Table 6. Classification of altered metabolic peaks in ET patients by anatomical location.

Extra-parenchymal peak (sulcus, subarachnoid space)	Intra-parenchymal peak
Bilateral medial frontal cortex	Inferior olivary nuclei
Left superior temporal gyrus	Basal ganglia
Temporal poles	Cerebellum

4. Discussion

4.1. Comparison Between Responders and Non-Responders

In this study, we report a clinical response rate of 73% following GKVIM, in line with previously published findings on treatment efficacy in tremor [16-18]. Voxel-wise analysis of pre-therapeutic FDG-PET data revealed significant meta-

bolic differences between responders and non-responders, specifically involving the prefrontal cortex, right supra-marginal gyrus, and cerebellum.

Our results partially contrast with those of Verger et al. [23], who reported hypometabolism in the temporo-occipital cortex among non-responders, a finding not replicated in our cohort. While this discrepancy could be attributed to the small sample sizes or differences in acquisition methods it could also reinforce the hypothesis that essential tremor may comprise a spectrum of pathophysiological entities rather than a single homogeneous disorder.

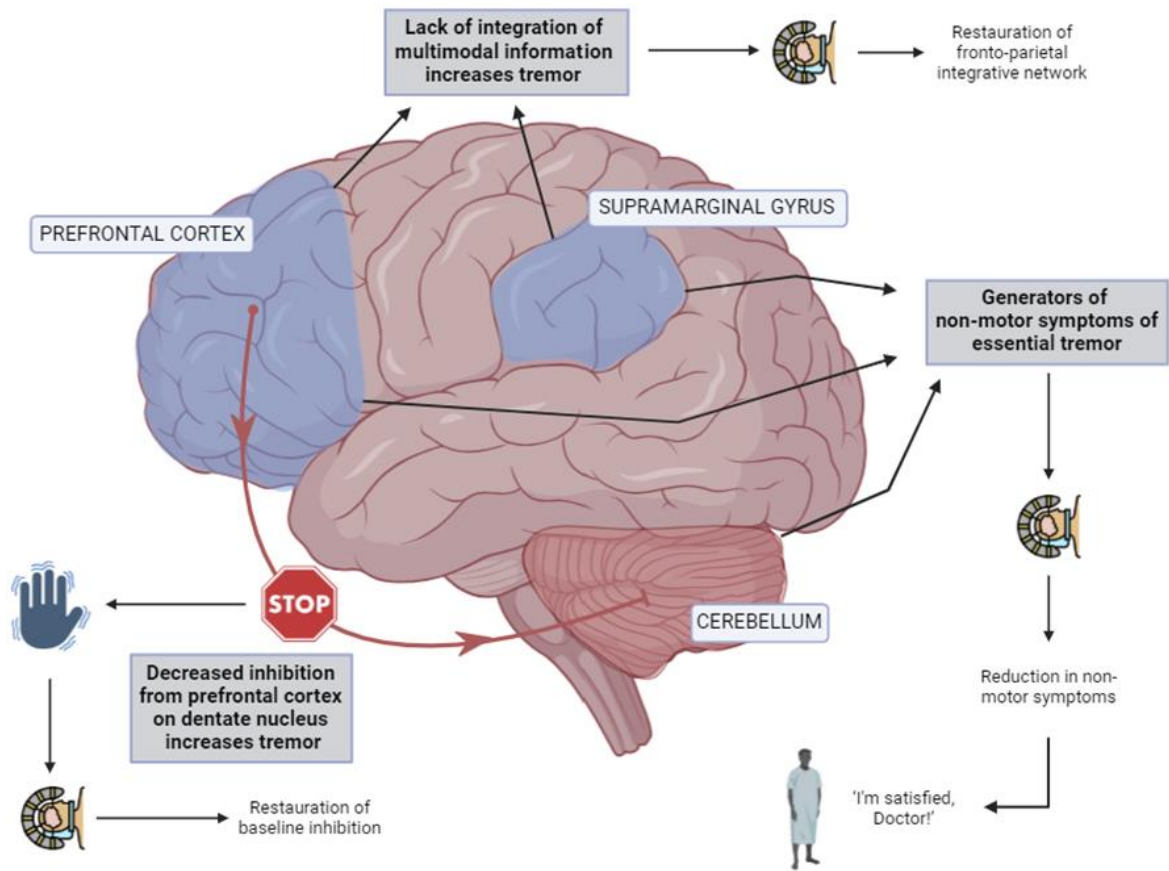


Figure 6. Hypothesis explaining the prefrontal and supramarginal gyrus hypometabolism (blue) as well as cerebellar hypermetabolism (red) found in responders to Gamma-Knife thalamotomy for essential and parkinsonian tremor before treatment.

Zhong et al. [25] have described a reduction in functional connectivity between the prefrontal cortex and the cerebellar dentate nucleus in patients with tremor-dominant Parkinson's disease, positing that prefrontal cortical activity modulates dentate output. Loss of this regulatory interaction may promote tremor. In this context, our findings of prefrontal hypometabolism and concurrent cerebellar hypermetabolism in responders could indicate that clinical improvement is mediated by restoration of functional inhibition of the cerebellum by the prefrontal cortex.

Passamonti et al. [26] suggest that disruption of cerebello-prefrontal connectivity may underlie non-motor symptoms in ET, including cognitive dysfunction, anxiety, and sleep disturbances. Given that our outcome measure was based on subjective patient satisfaction, it is plausible that improvement in these non-motor domains may have contributed to the perceived treatment success. The observed hypometabolism of the right supramarginal gyrus in responders further supports this interpretation. This region has been implicated in cognitive dysfunction in Parkinson's disease, as shown by Li et al. [27]. This highlights the need of systematic cognitive evaluation of ET and PT patients through validated and reproducible tests (Mini-Mental State Examination, Montreal Cognitive Assessment, Frontal Assessment Battery, Token Test) as a way to predict response to treatment and to better classify those patients in pathological subgroups.

An alternative hypothesis, proposed by Nicoletti et al. [28], suggests that impaired integration of multimodal sensory information in the fronto-parietal network contributes to tremor generation. The observed hypometabolism in both prefrontal and supramarginal regions may thus reflect disrupted network integration, with GKVIM potentially exerting its therapeutic effect by restoring fronto-parietal coherence. (Figure 6)

4.2. Comparison Between ET Patients and Healthy Controls

SPM analysis comparing ET patients with healthy controls revealed hypometabolism in the medial frontal cortex and superior temporal gyrus. These findings likely reflect underlying regional atrophy, as supported by previous structural and metabolic imaging studies [29-31]. Such cortical hypometabolism has been associated with cognitive impairment in ET and again highlights the need for systematic cognitive assessment in these patients.

The observed hypermetabolism in the temporal poles is likely artefactual, potentially resulting from spatial normalization and in PET processing.

Of particular interest is the significant hypermetabolism observed in the inferior olivary nuclei (ION), a structure historically implicated in tremor pathophysiology via its role in the Guillain-Mollaret triangle. Although more recent literature tends to favor a distributed network model of ET, our

finding provides the first in vivo evidence of altered ION metabolism in human ET patients. This supports the view that the ION, while not solely responsible, may still play a contributory role in tremor generation [9, 32].

Finally, hypermetabolism in the cerebellum and basal ganglia, structures with a well-established role in ET, corroborates prior findings and reinforces their central position in current pathophysiological models [9, 33].

4.3. Perspectives

This retrospective study provides novel insights into the metabolic predictors of response to GKVIM and the underlying neurobiology of ET. The identification of distinct metabolic patterns in responders versus non-responders supports the feasibility of FDG-PET as a tool for pre-treatment patient selection. Furthermore, our secondary findings regarding ET pathophysiology may inform future efforts to redefine ET as a spectrum of distinct neurobiological entities.

Larger prospective and collaborative studies, incorporating objective clinical scales and multimodal imaging, are needed to validate these preliminary findings. A systematic review of metabolic and functional imaging in ET would also contribute to a more refined understanding of its heterogeneity.

4.4. Limitations

This study is subject to several limitations. Most notably, treatment response was assessed through subjective patient-reported satisfaction rather than objective clinical rating scales such as the Fahn-Tolosa-Marin scale, QUEST, UPDRS, or PDQ-39. Consequently, the influence of non-motor symptoms or placebo effects cannot be excluded. Nevertheless, we advocate that patient-reported satisfaction remains a critical endpoint - particularly in a complex disorder where motor and cognitive symptoms coexist and may variably impact quality of life. In our view, patient-perceived benefit remains a valuable dimension of treatment efficacy, complementary to objective measures.

Moreover, the small sample size limits statistical power, and findings should be interpreted with caution pending external validation. Despite the small cohort, the statistical analysis yielded significant findings, with large cluster sizes aligning with existing literature and family-wise error corrected p-values below 0.001.

5. Conclusion

This study identified specific regional metabolic patterns on pre-treatment FDG-PET that are associated with clinical response to GKVIM in patients with ET and PT. Notably, responders exhibited prefrontal and supramarginal gyrus hypometabolism along with cerebellar hypermetabolism.

In addition, we report for the first time a metabolic altera-

tion of the inferior olivary nuclei in ET patients, providing in vivo support for its debated role in tremor pathogenesis. These findings contribute to the growing body of evidence suggesting that ET comprises multiple pathophysiological subtypes.

The fact that these findings mostly align with existing literature further reinforces the validity and potential of FDG-PET as a valuable approach for understanding both treatment effects and the underlying pathophysiology of essential tremor.

Abbreviations

ET	Essential Tremor
PT	Parkinsonian Tremor
DBS	Deep Brain Stimulation
VIM	Ventral InterMediate Nucleus of the Thalamus
MAOI	MonoAmine Oxidase Inhibitor
MRI	Magnetic Resonance Imaging
fMRI	functional Magnetic Resonance Imaging
GKVIM	Gamma-Knife thalamotomy of the Ventral InterMediate Nucleus
GK	Gamma-Knife
Gy	Gray (Unit)
FDG-PET	[¹⁸ F]-FluoroDeoxyGlucose Positron Emission Tomography
AC-PC	Anterior Commissure – Posterior Commissure Line
SPM	Statistical Parametric Mapping
ION	Inferior Olivary Nuclei
QUEST	Quality of Life in Essential Tremor Questionnaire
UPDRS	Unified Parkinson's Disease Rating Scale
PDQ-39	Parkinson's Disease Questionnaire – 39

Conflicts of Interest

The authors declare no conflicts of interest.

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