What are the main challenges in treating patients with MRI guided Focused Ultrasound ?

Tom Gilbertson

Senior Clinical Lecturer & Honorary Consultant Neurologist

Ninewells Hospital & Medical School

University of Dundee

tgilbertson@dundee.ac.uk

Disclosures

Research Funding from Insightec

What are the main challenges in treating patients with MRI guided Focused Ultrasound ?

- Patient selection
- Achieving a clinically effective thalamotomy
- Managing patients post treatment expectations

Challenges with Patient Selection

- Tremor phenomenology
- Pre-morbid postural instability
- Severity and functional disability

Challenges with Patient Selection

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- **Level I:** Meta-analysis or systematic review
- **Level II:** Single well-conducted RCT.
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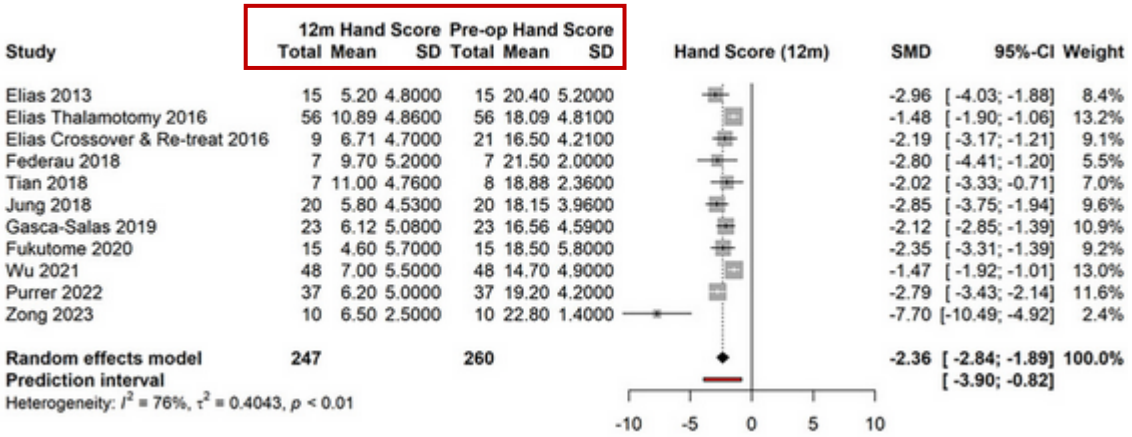
Evidence base for Unilateral MRgFUS in ET

REVIEW

Efficacy and Safety of Magnetic Resonance-Guided Focused Ultrasound Thalamotomy in Essential Tremor: A Systematic Review and Metanalysis

Alyssa Shiramba, MRes,[1,2] Steven Lane, PhD,[3] Nicola Ray, PhD,[4] Tom Gilbertson, MD, MRCP, PhD,[5,6] Rajesha Srinivasaiah, MD, MRCP,[2] Jay Panicker, MD, MRCP,[2] Mark Radon, MD, MRCP,[2] Jibril Osman-Farah, MD, FRCS,[2] and Antonella Macerollo, MD, FRCP, PhD[2,4,7*]



Level I: Meta-analysis or systematic review

University of Dundee

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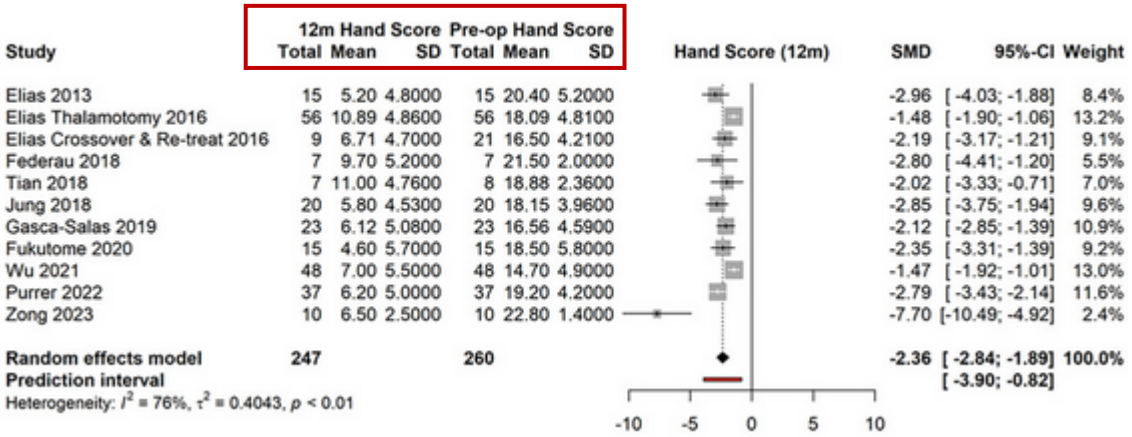

Level I: Meta-analysis or systematic review

RESEARCH ARTICLE

Magnetic Resonance-Guided Focused Ultrasound (MRgFUS)-Thalamotomy for Essential Tremor: Lesion Location and Clinical Outcomes

Alana Arcadi, MD,[1] Iciar Aviles-Olmos, MD, PhD,[2,3] Lain Hermes Gonzalez-Quarante, MD,[1] Arantza Gorospe, MD,[2,3] Adolfo Jiménez-Huete, MD, PhD,[2] Marta Macías de la Corte, MD,[1] Olga Parras, MD,[4] Antonio Martin-Bastida, MD, PhD,[2] Mario Riverol, MD, PhD,[2,3] Rafael Villino, MD,[2,3] Jorge Guridi, MD, PhD,[1] and Maria C. Rodríguez-Oroz, MD, PhD[2,3*]

TABLE 2 *Changes in Clinical Rating Scale for Tremor scores throughout the follow-up period compared with scores at baseline*

	Baseline (n = 127)	1 month (n = 122)			3 months (n = 102)			6 months (n = 78)		
CRST	Mean (SD)	Mean (SD)	*Mean diff. (95% CI)	%	Mean (SD)	*Mean diff. (95% CI)	%	Mean (SD)	*Mean diff. (95% CI)	%
CRST-A+B in treated side	20.3 (6.1)	4.3 (1.7)	15.9 (14.9, 16.9)	82.4	4.5 (4.6)	15.4 (14.2, 16.5)	82.4	5.6 (6.1)	14.4 (13.2, 15.6)	80.5
CRST-A										
Total	13.5 (5.5)	4.5 (3.6)	7.0 (6.3, 7.6)	54.5	6.2 (3.5)	7.0 (6.2, 7.6)	54.5	6.6 (4.0)	6.8 (6.1, 7.6)	55.6
Treated side	11.5 (4.2)	0.8 (1.3)	10.6 (10.1, 11.2)	100	1.2 (1.6)	10.1 (9.5, 10.7)	93.8	1.2 (1.5)	10.2 (9.6, 10.9)	92.3
CRST-B										
Total	25.9 (8.0)	14.7 (6.6)	11.0 (9.8, 12.1)	45.5	14.9 (7.3)	10.1 (8.8, 11.4)	40.4	14.5 (7.9)	11.3 (9.9, 12.6)	41.7
Treated side	14.4 (4.4)	3.9 (3.7)	10.4 (9.6, 11.1)	79.3	4.6 (4.0)	9.4 (8.6, 10.2)	73.3	4.5 (4.1)	9.7 (8.8, 10.5)	75.0
CRST-C	17.7 (6.3)	2.8 (5.2)	14.6 (13.6, 15.7)	100	3.1 (6.0)	14.4 (13.2, 15.5)	100	3.6 (6.0)	13.9 (12.6, 15.1)	94.4
CRST axial (n = 64)	1.0 (1.3)	0.6 (1.0)	0.5 (0.3, 0.6)	87.5	0.2 (0.6)	0.8 (0.6, 1.0)	100	0.2 (0.6)	0.8 (0.6, 1.0)	100

Level IV: Well-designed cohort or case-control studies.

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Evidence base for Bilateral MRgFUS in ET

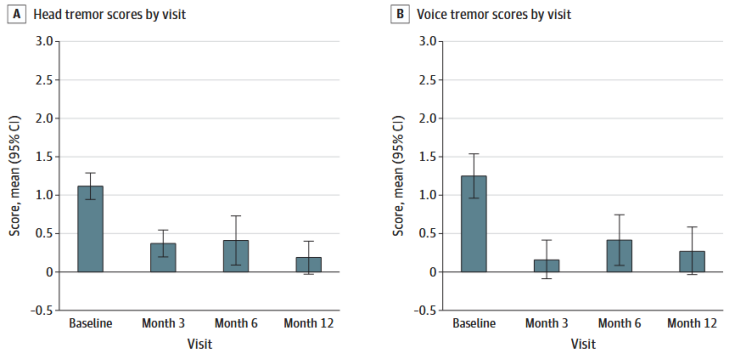
JAMA Neurology | Original Investigation

Safety and Efficacy of Staged, Bilateral Focused Ultrasound Thalamotomy in Essential Tremor

An Open-Label Clinical Trial

Kaplitt et. al., JAMA Neurology 2024

Figure 3. Head and Voice Tremor Scores at Baseline and Follow-Up After Staged Bilateral Focused Ultrasound Ablation



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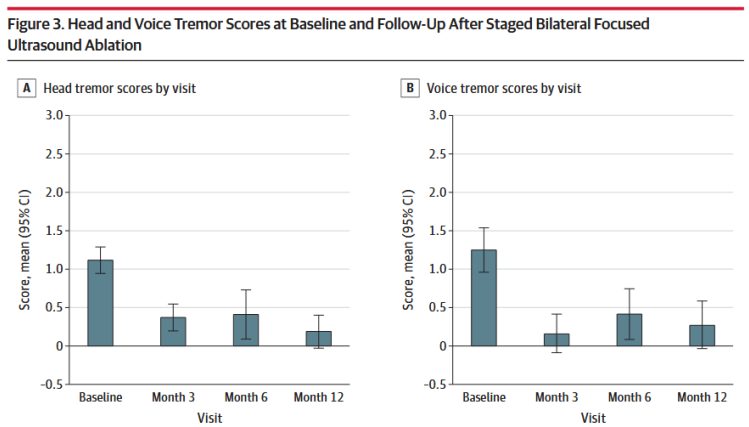
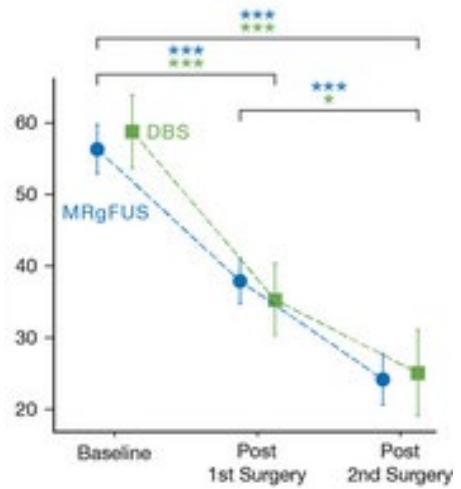


Movement Disorders
Official Journal of the International Parkinson and Movement Disorder Society

RESEARCH ARTICLE | Open Access

Bilateral Focused Ultrasound Thalamotomy for Essential Tremor: Clinical Outcomes Compared to Bilateral Deep Brain Stimulation and Probabilistic Lesion Mapping

Sarica et. al., Mov Dis 2025



Level IV: Well-designed cohort or case-control studies.

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Evidence base for Bilateral MRgFUS in ET

- Following unilateral MRgFUS most patients want the other side treated
- No ***current*** evidence for additional QoL gains from second side treatment
- There is evidence of greater short and long term side-effects
- Cost of the treatment for the non-dominant limb is the same
  - QoL improvement need to justify the cost

Challenges with Patient Selection

- **Tremor phenomenology**
- Pre-morbid postural instability
- Severity and functional disability

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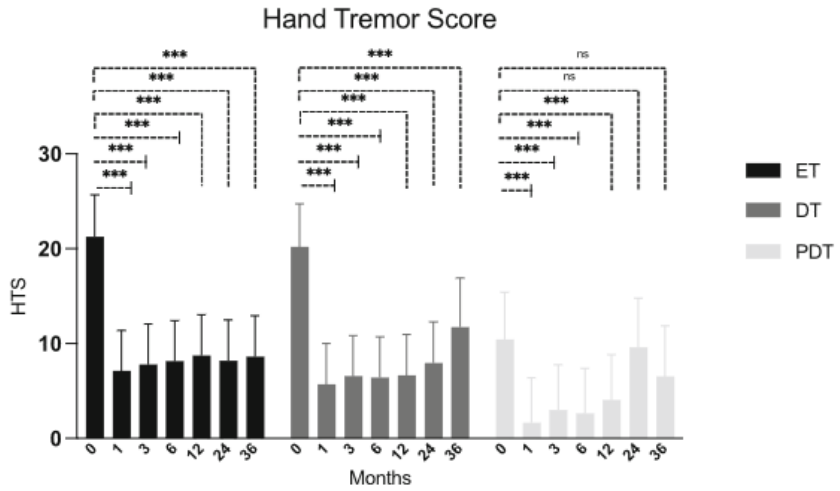
Non-ET Tremor syndromes

RESEARCH ARTICLE

Outcomes of Focused Ultrasound Thalamotomy in Tremor Syndromes

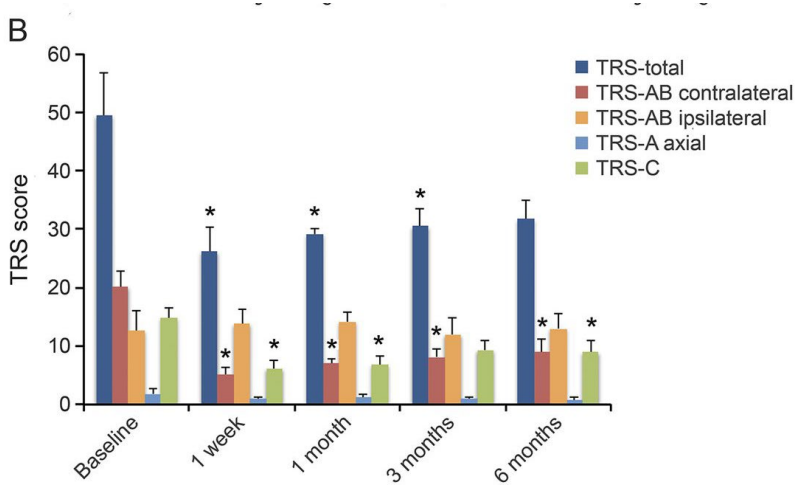
Peters et. al., Mov Dis, 2024



Neurology®

MRI-guided focused ultrasound thalamotomy in non-ET tremor syndromes

Fasano et. al., Neurology, 2017



Level IV: Well-designed cohort or case-control studies.

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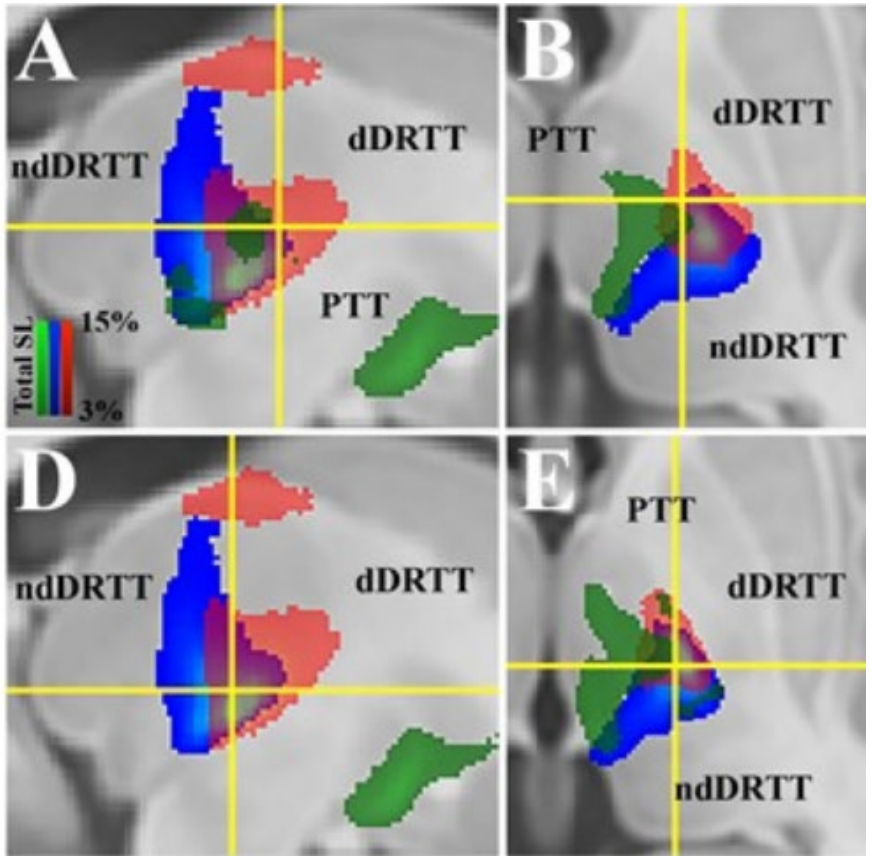
Our experience – Complex tremor is difficult to treat with **Vim** thalamotomy

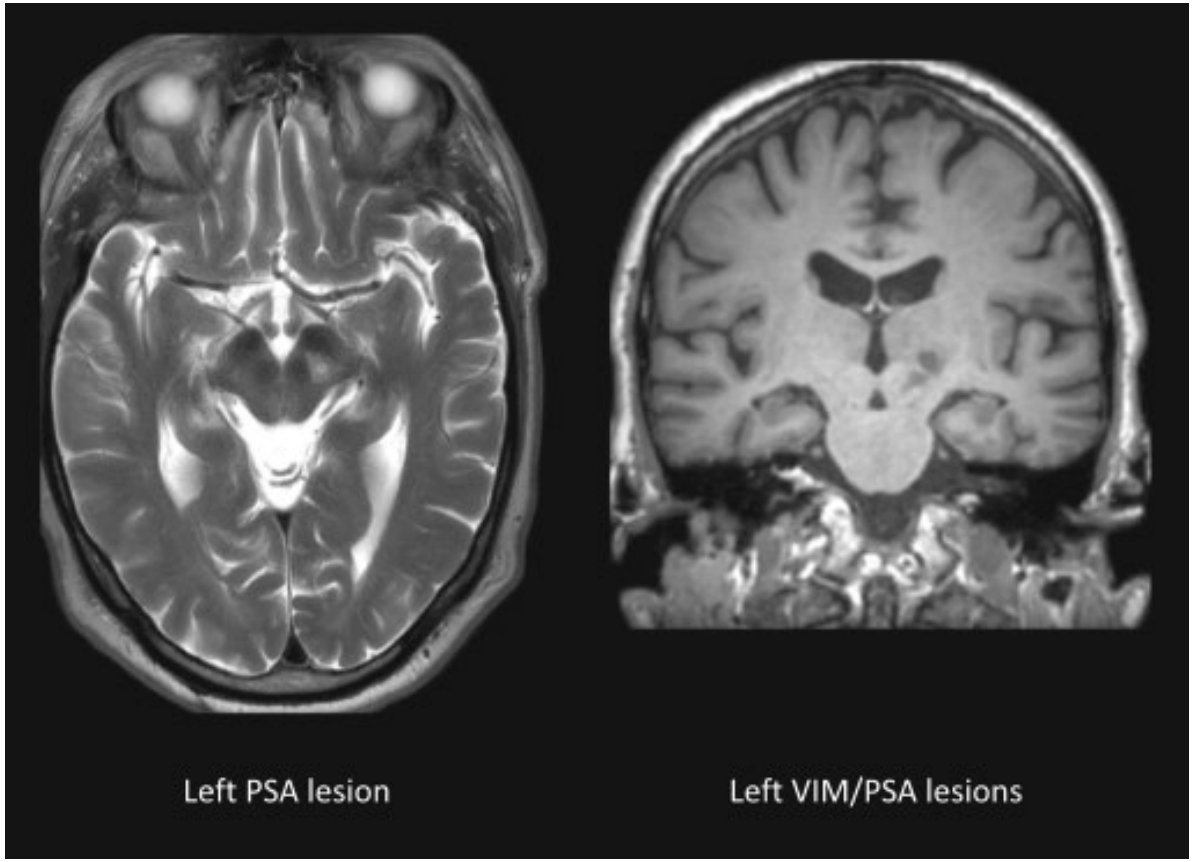
75 RHD 6 months “ classical ET “

65 RHD 6 months Dystonic tremor

Vim is safe but may not be be effective in DT



Tsuboi et. al., Brain (2021)



Jameel et., al, B J Neuro (2022)
Peters et. al., Mov Dis (2024)

Challenges with Patient Selection

- **Tremor phenomenology**
  - **Unilateral thalamotomy for upper limb tremor**
  - **Classical ET phenotype – non ET target remains a research question**
- Pre-morbid postural instability

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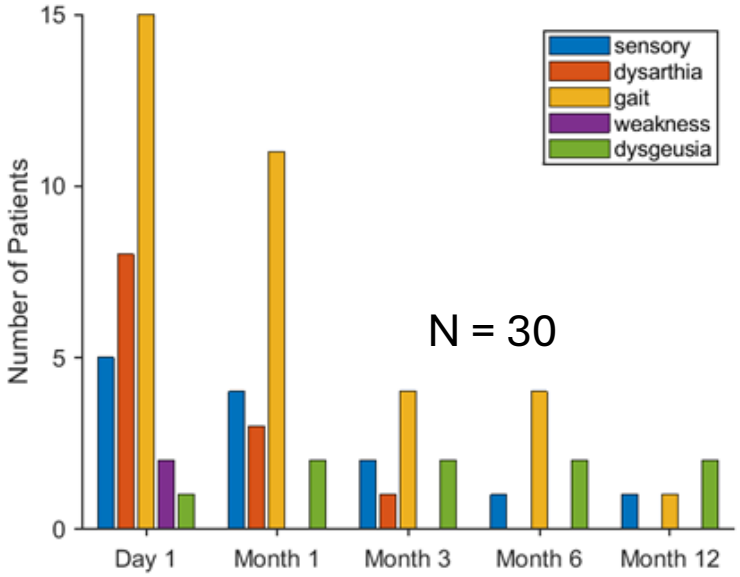
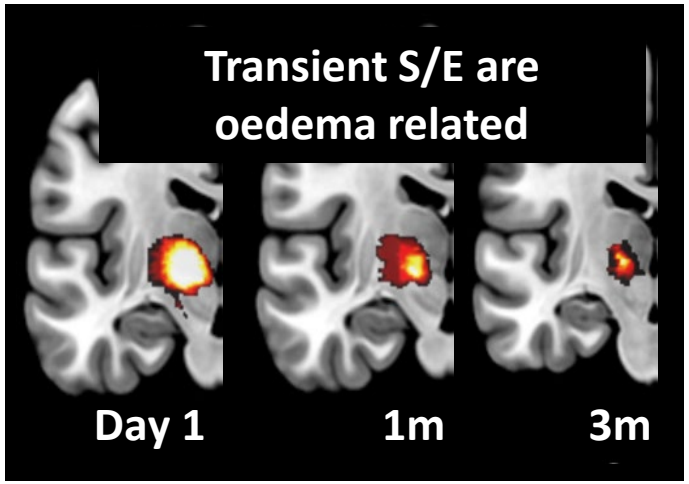
Challenges with Patient Selection

- Tremor phenomenology
  - Unilateral thalamotomy for upper limb tremor
  - Classical ET phenotype
- **Pre-morbid postural instability**

Gait related side effects of MRgFUS





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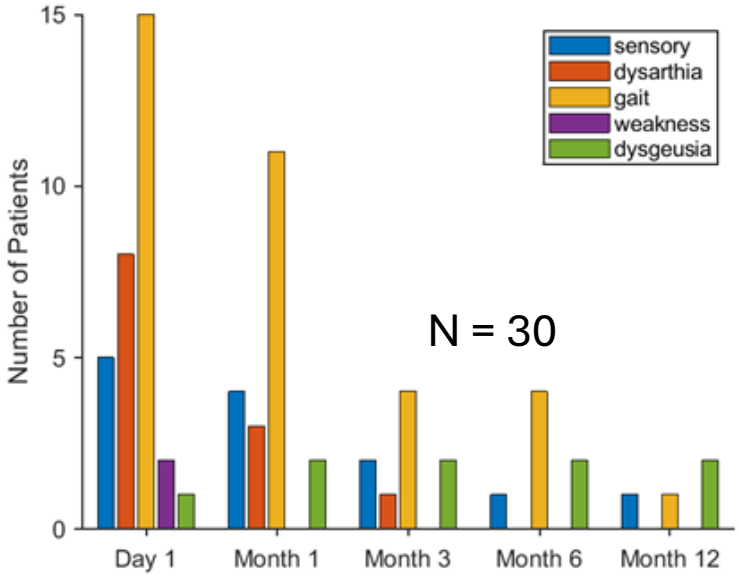
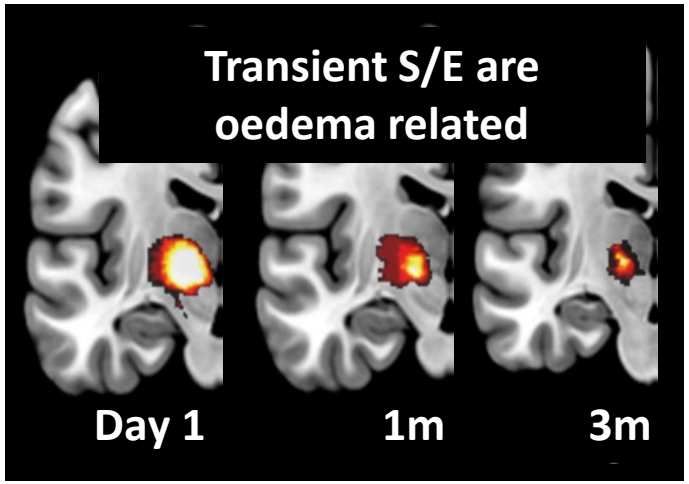
Gait related side effects of MRgFUS

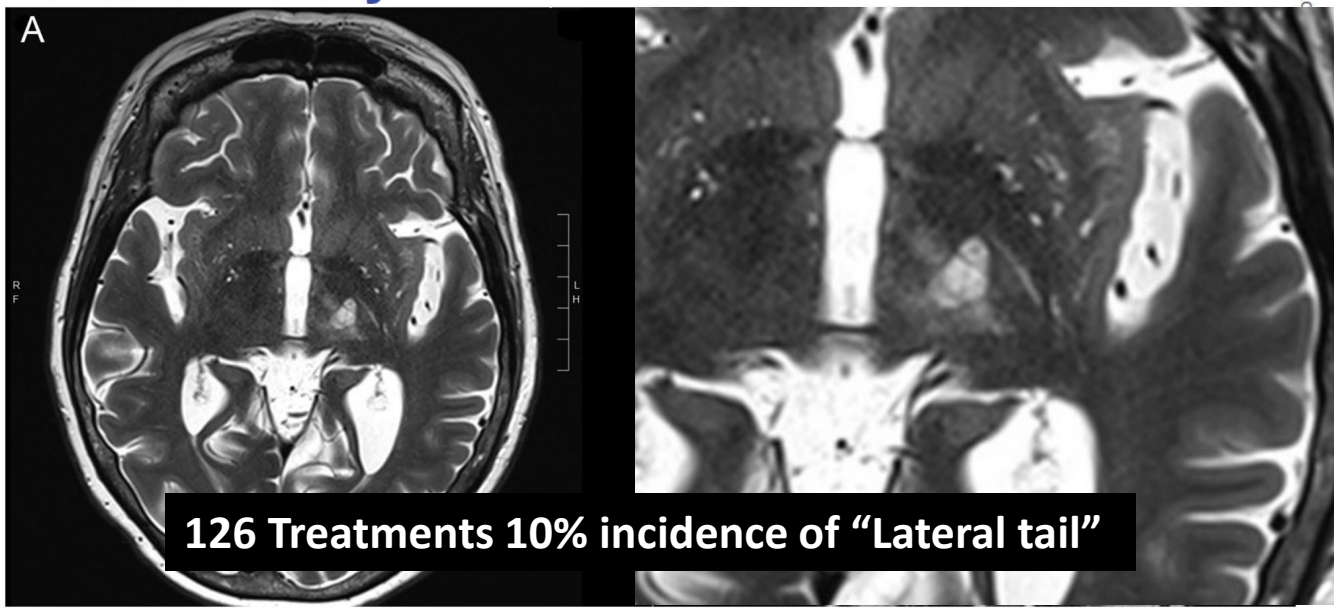




doi:10.1093/brain/awab176 BRAIN 2021: 144; 3089–3100 | 3089

BRAIN
ORIGINAL ARTICLE

Lesion location and lesion creation affect outcomes after focused ultrasound thalamotomy



Segar et. al., Brain 2021

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Natural history of ET is a cerebellar syndrome

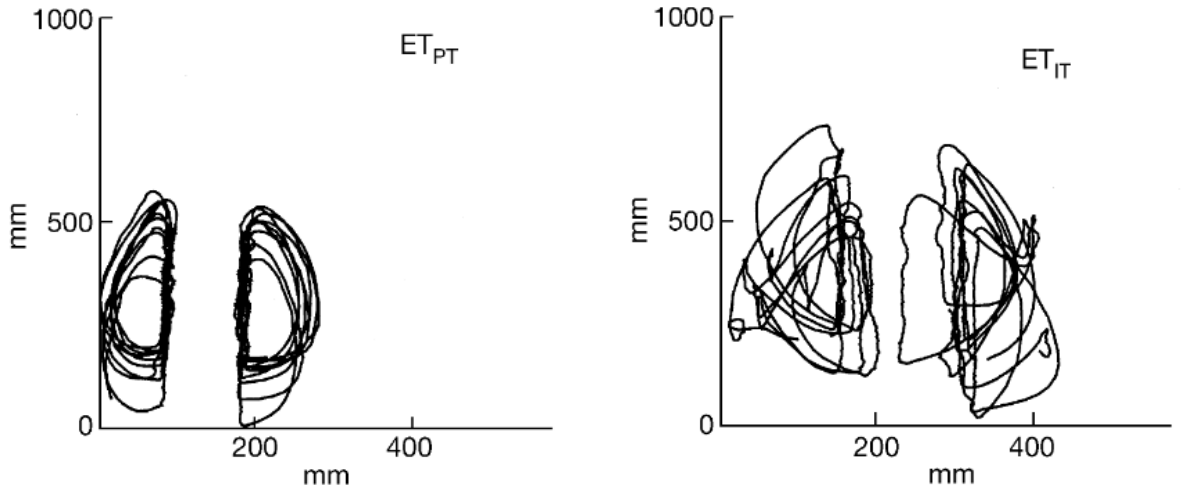
Brain (2001), **124,** 2278–2286

The gait disorder of advanced essential tremor

Henning Stolze, Gesche Petersen, Jan Raethjen, Roland Wenzelburger and Günther Deuschl

Department of Neurology, Christian-Albrechts-Universität Kiel, Germany

Correspondence to: Professor Dr Günther Deuschl, Neurologische Klinik der Christian-Albrechts-Universität zu Kiel, Niemannsweg 147, D-24105 Kiel, Germany
E-mail: g.deuschl@neurologie.uni-kiel.de



Warning: Patients with advanced ET should be treated with extreme caution

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Challenges with Patient Selection

- Tremor phenomenology
  - Unilateral thalamotomy for upper limb tremor
  - Classical ET phenotype
- **Pre-morbid postural instability**

Challenges with Patient Selection

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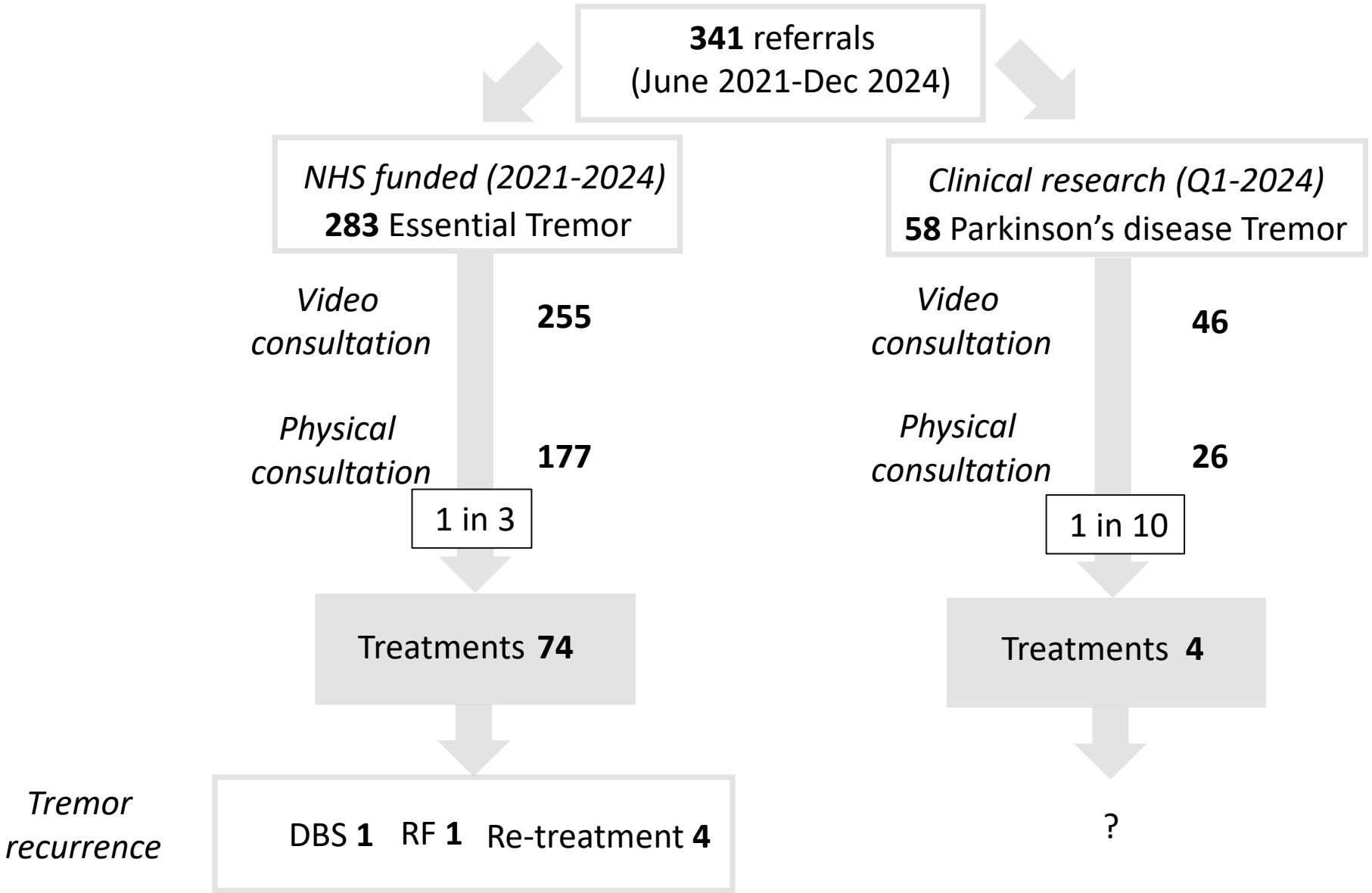
No current studies which delineate the safe threshold postural instability – <u>therefore offer with caution</u>

Early experience of Vim Thalamotomy

Referrals and treatments in Scotland 2021-2024



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Who is the ideal candidate for MRgFUS?

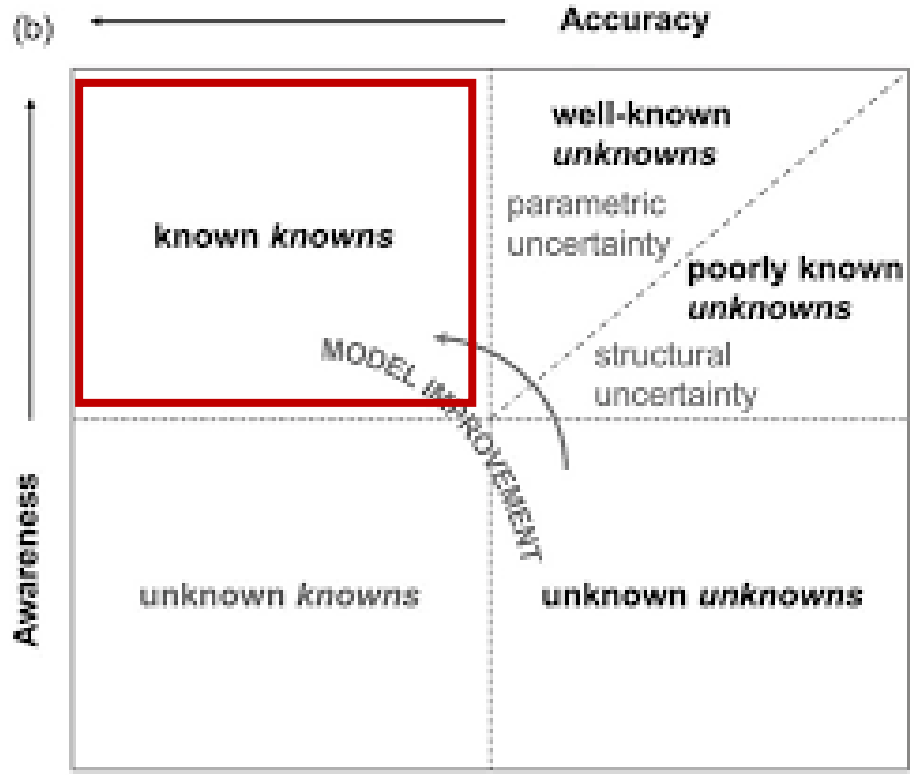
- ✓ Classical ET
- ✓ Minimal axial tremor
- ✓ Moderate functional disability
  Asymmetric dominant limb

What are the main challenges in treating patients with MRI guided Focused Ultrasound ?

- Patient selection
- **Achieving a clinically effective thalamotomy**

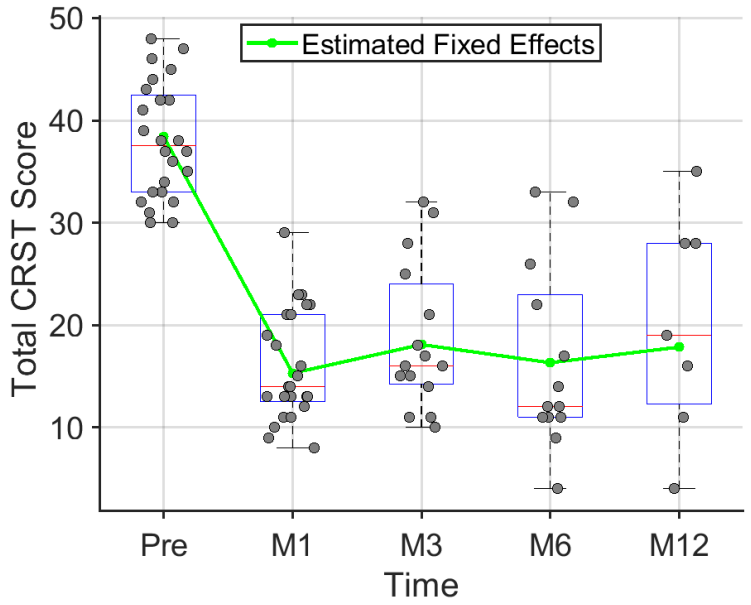
Achieving a clinically effective thalamotomy

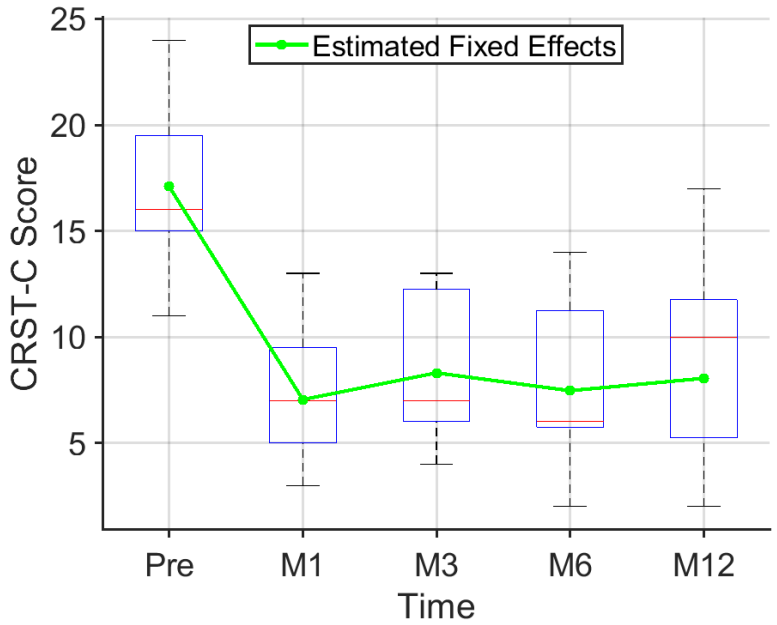
- **Targeting**
- Lesion size / thermal dose
- Clinical phenotype and phenomenology of the tremor (likely feeds into the target)

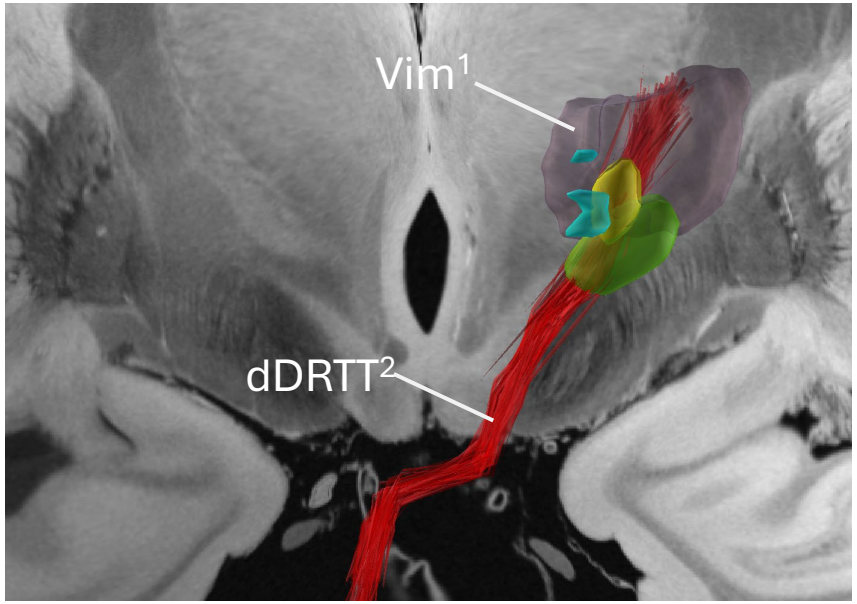


Learning curve from MRgFUS thalamotomy for Essential Tremor

Targeting error predicts long term clinical response







PSA[2] Sweetspot (Z value)*

	Sweetspot MNI coordinate [-12,-17,-2]			
	Day 1	Month 1	Month 3	Month 6
All (multivariate linear model)	R^2 = 0.38 p<0.005	R^2 = 0.45 p<0.005	R^2 = 0.42 p<0.005	R^2 = 0.42 P=0.005
A-P	R^2 = **0.51** **P<0.001**	**R^2 = 0.48** **p<0.001**	**R^2 = 0.41** **p<0.005**	**R^2 = 0.51** **p<0.01**
M-L	R^2 = 0.1 p>0.05	R^2 = 0.08 p>0.05	R^2 = 0.2 p>0.05	R^2 = 0.11 p>0.05
S-I	R^2 = 0.14 p>0.05	R^2 = 0.05 p>0.05	R^2 = 0.11 p>0.05	R^2 = 0.14 P>0.05

**Wilcoxon signed rank test*
p<0.01, q<0.01 FDR corrected

[1]Saranathan et., *Hum Brain Map* (2019)
[2]Neudorfer et al., *Annals of Neurology* (2022)

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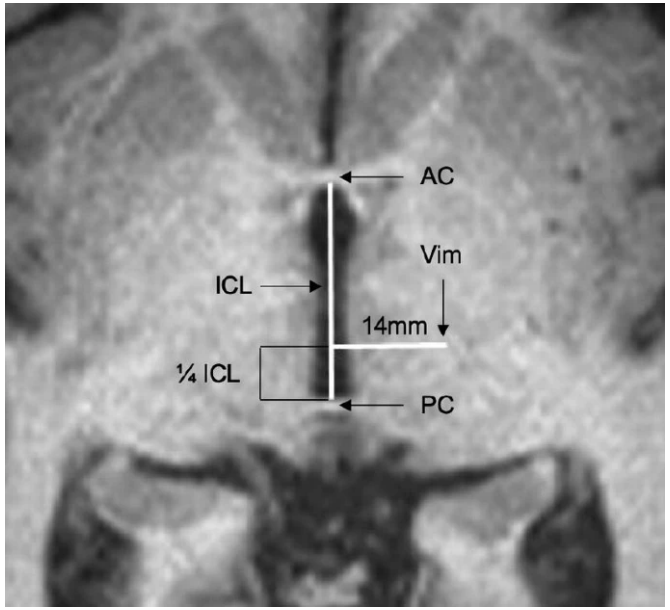
Individualised targeting using DTI and thalamic nucleus segmentation

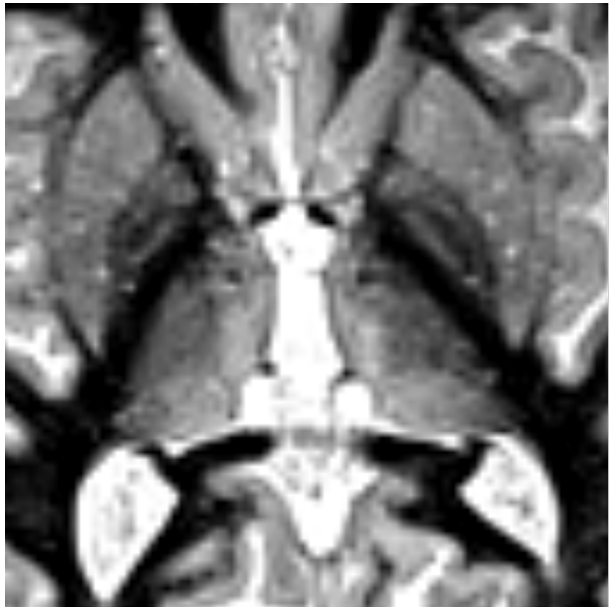
Sequence optimisation for white matter tract and nuclear variation in anatomy

Indirect Targeting



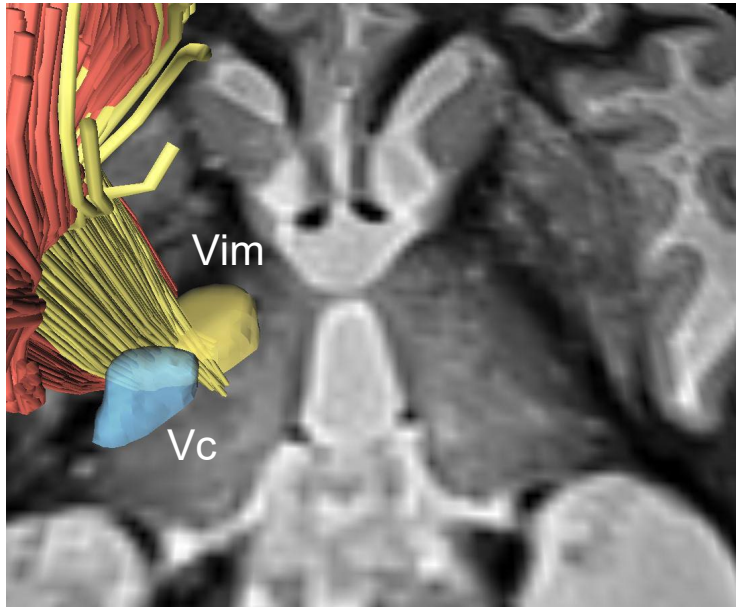
Moosa & Elias Stereotactic & Functional Neurosurgery (2020)

T2WMN



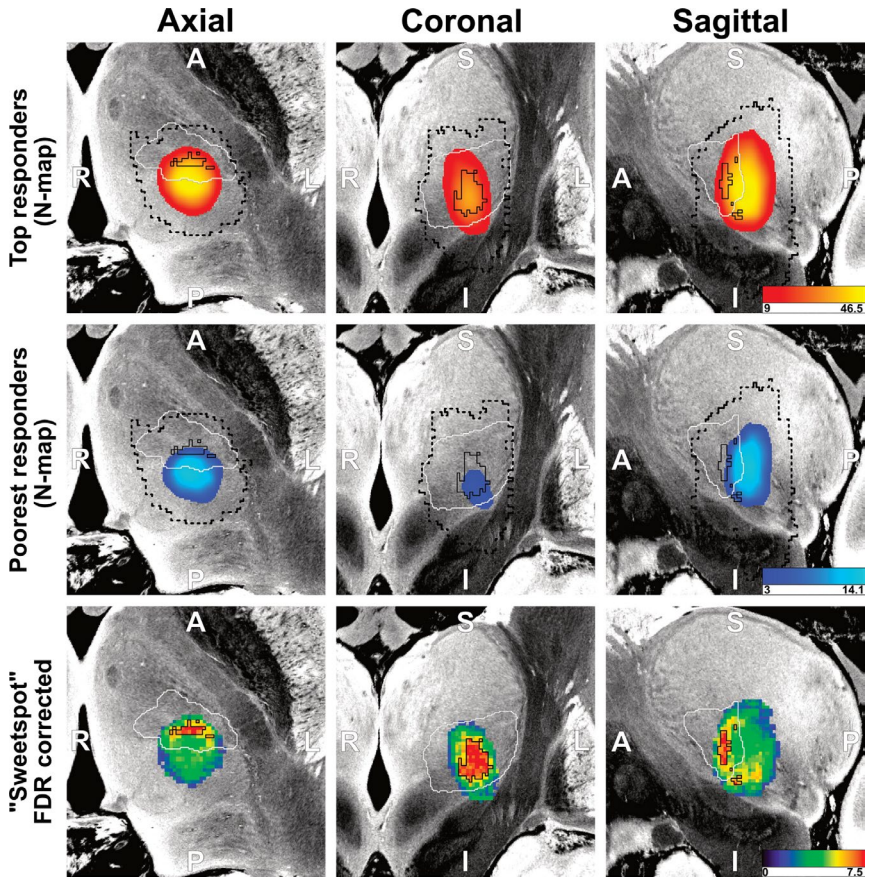
Tourdias et. al., Neuroimage (2014)

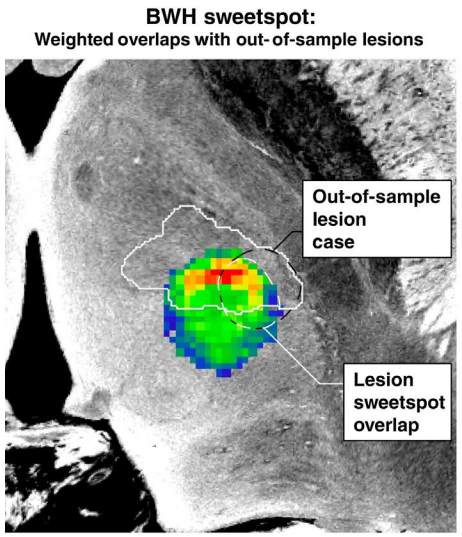
Probabilistic tractography

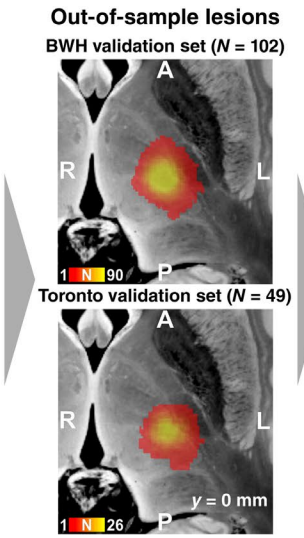


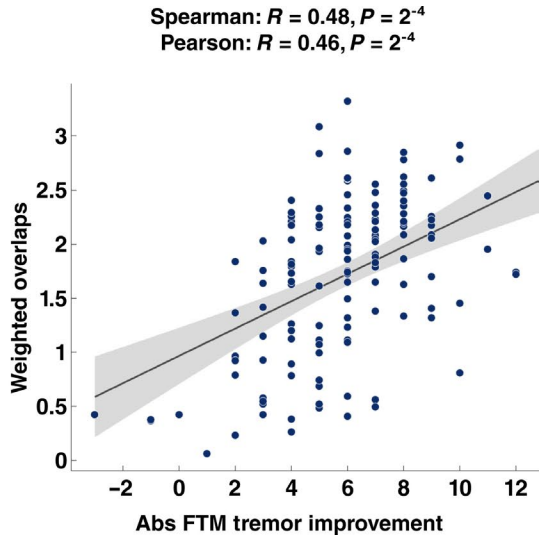
Su et. al., Neuroimage (2019)
Feltrin et. al., Brain Communications (2022)

A sweetspot for MRgFUS thalamotomy in ET









Chua et. al., Science advances (2025)

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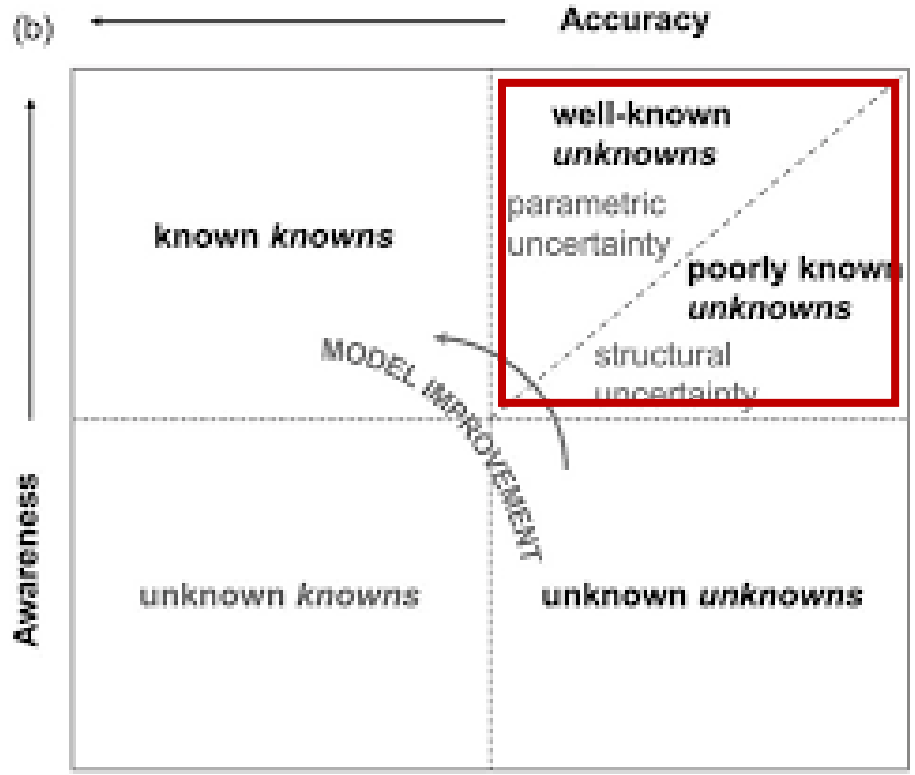
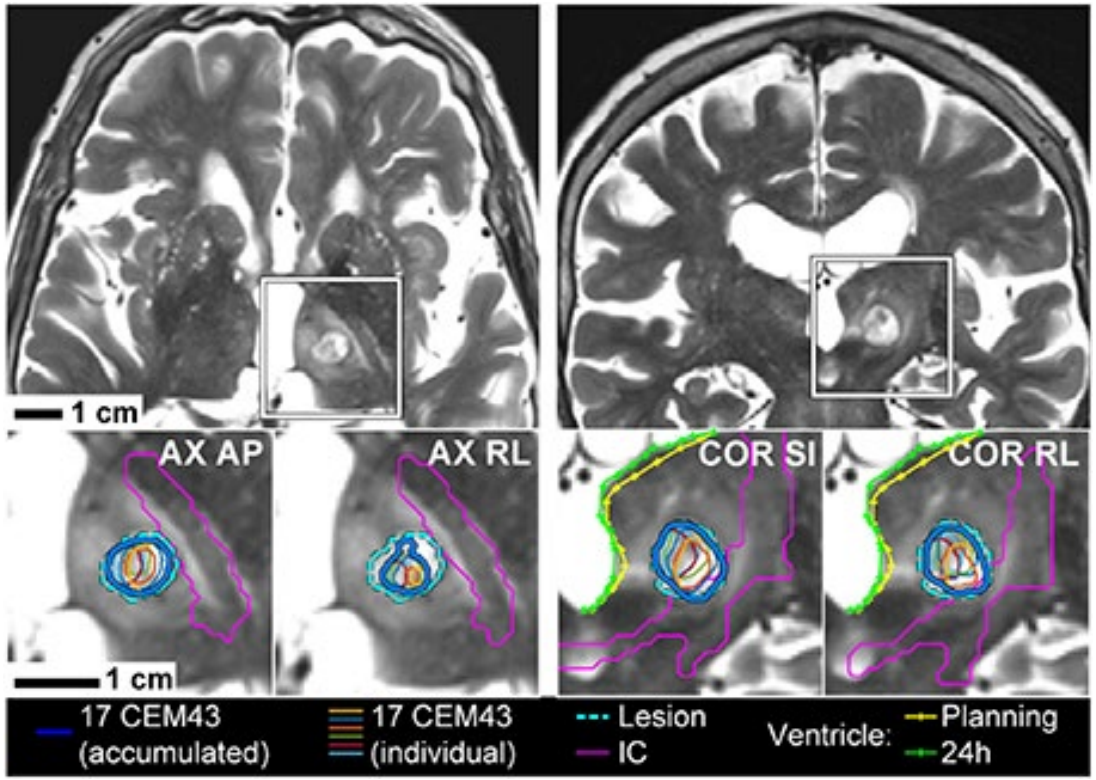
Achieving a clinically effective thalamotomy

- Target
- **Lesion size / thermal dose**
- Clinical phenotype and phenomenology of the tremor (likely feeds into the target)

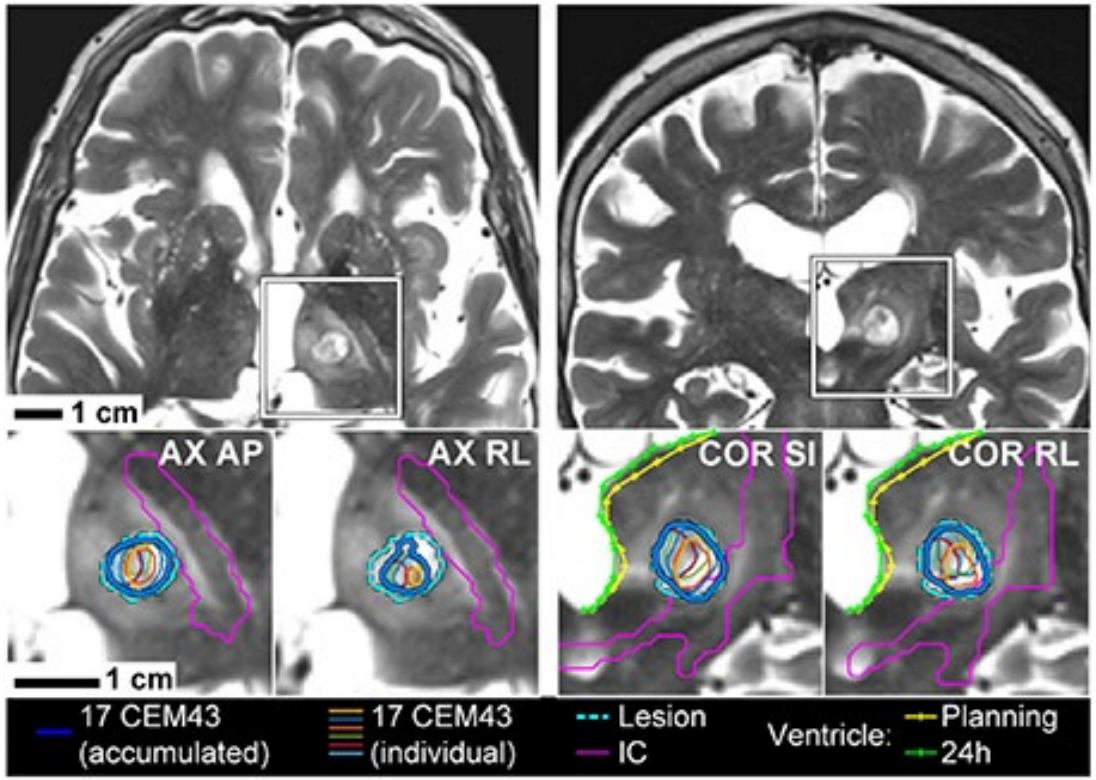


Achieving a clinically effective thalamotomy



McDannold et. al., 2020,
Physics and Medicine in biology

Achieving a clinically effective thalamotomy



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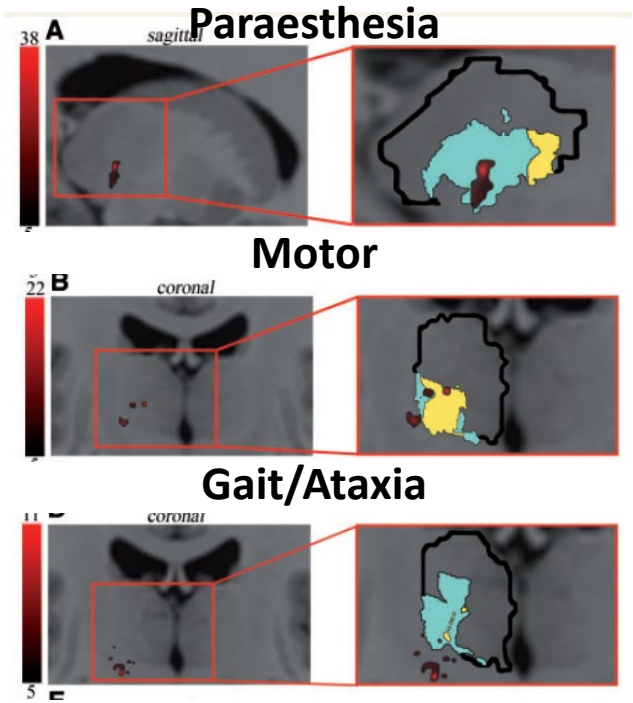
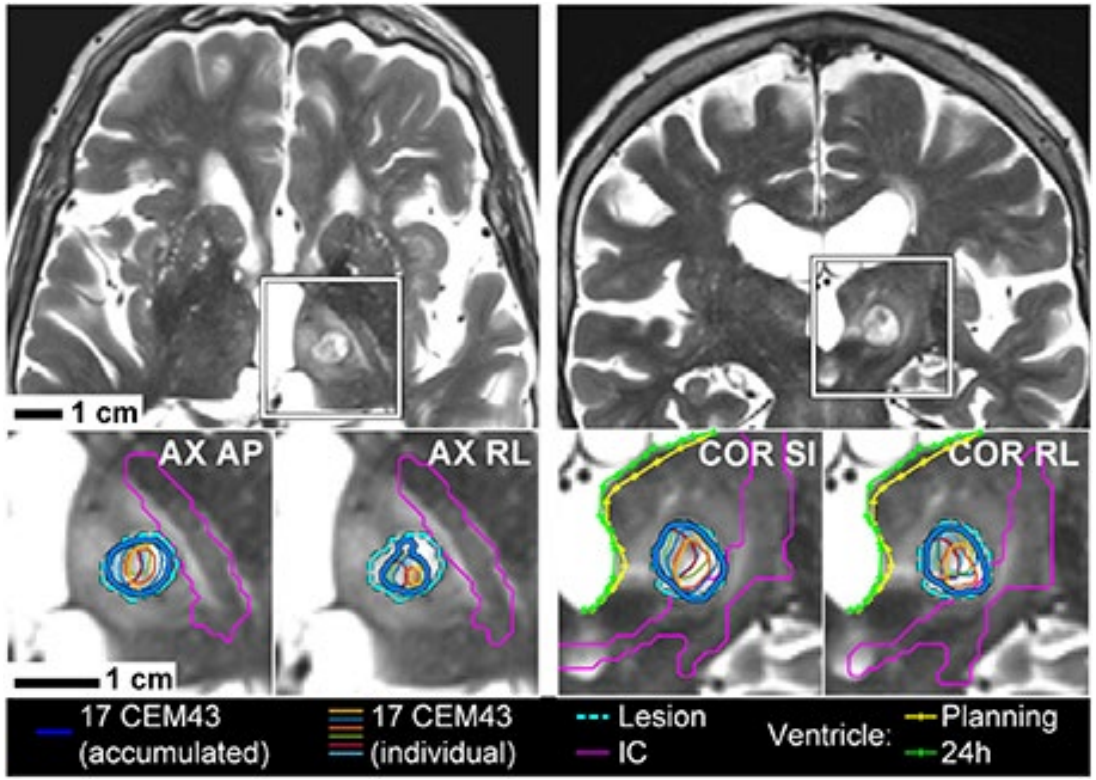
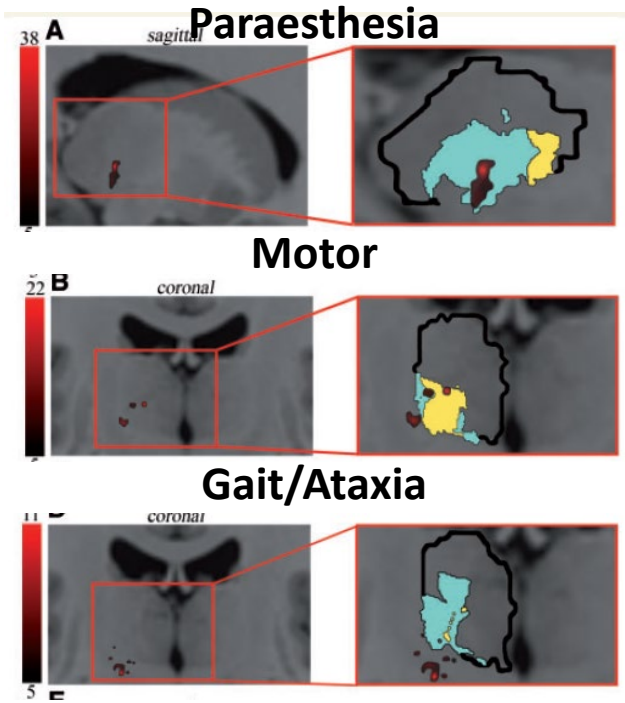


Boutet et. al., *Brain* 2018

Achieving a clinically effective thalamotomy



McDannold et. al., 2020,
Physics and Medicine in biology



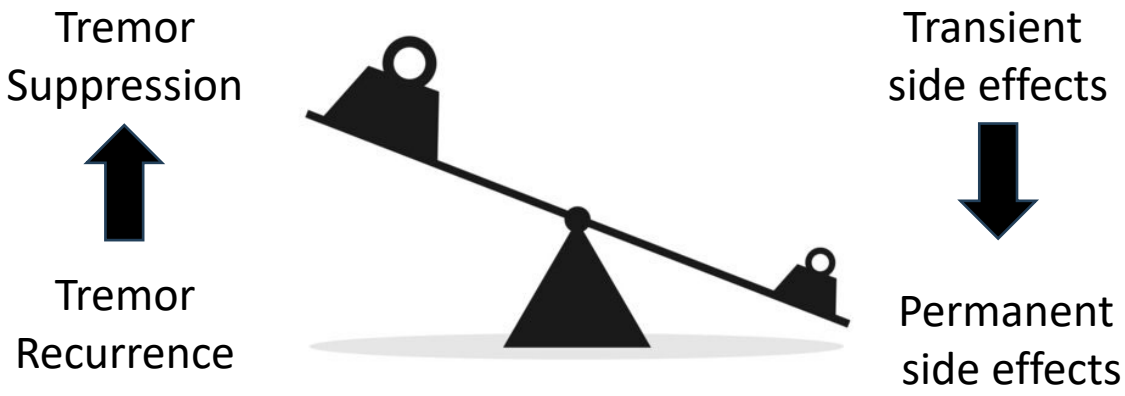
Boutet et. al., *Brain* 2018

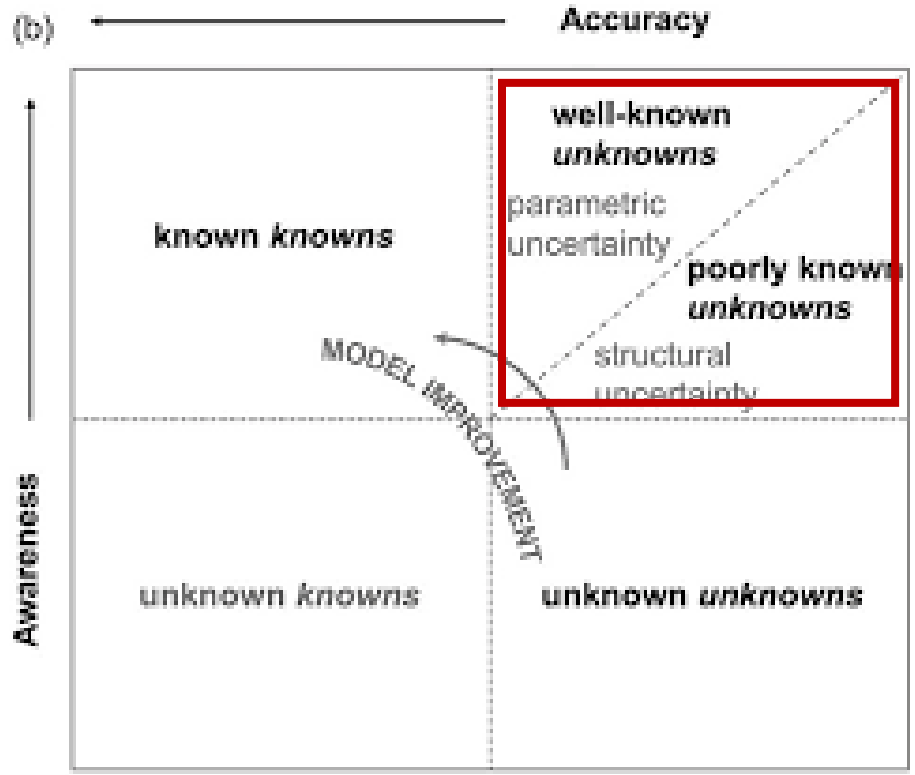
Toronto group Boutet, Brain (2018) 181 ± 86 mm^3 (6 mm^3 to 428 mm^3)
Boston group Segar Brain (2021) 289 mm^3 range (25 mm^3 to 895 mm)

Thousands of MRgFUS thalamotomies performed but still no validated *minimum* thermal dose or lesion volume

Achieving a clinically effective thalamotomy

- Targeting
- **Lesion size / thermal dose**
- Clinical phenotype and phenomenology of the tremor (likely feeds into the target)





University of Dundee

What are the main challenges in treating patients with MRI guided Focused Ultrasound ?

- Patient selection
  - Asymetric, non axial, functionally disabling tremor
  - Good postural stability ? Unclear how good
  - Classical ET phenotype

- Achieving a clinically effective thalamotomy
  - Optimise targeting with pre-operative planning
  - Dose versus side effect compromise unknown
  - Vim thalamotomy for non-ET tremor is a **known unknown**