Welcome

The webinar will begin momentarily.

Tractography-based Targeting for Functional Neurosurgery

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Ohio State University

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Tractography-Based Targeting for Functional Neurosurgery

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Assistant Professor,
Center for Neuromodulation,
Department of Neurosurgery and Neuroscience,
The Ohio State University.

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Conflicts of interest

- Medtronic Inc., Minneapolis, MN
  - Research grant

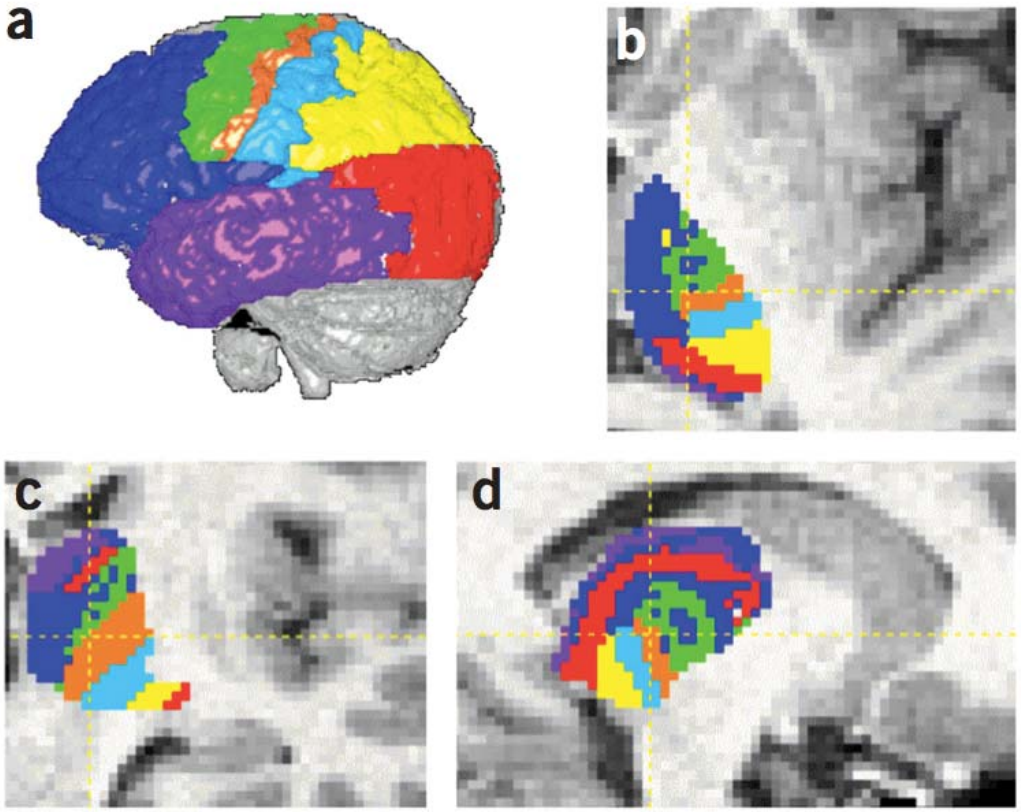
Topics of discussion

- Tractography-based VIM (T-VIM) targeting for tremor surgery
  - Methodology
  - Results from imaging cohort
  - Results from operative cohort
  - Electrophysiology correlates of T-VIM
  - Initial experience with High Intensity Focused Ultrasound thalamotomy
- Tractography-based targeting for other areas
  - Globus pallidus (Gpi)
  - Anterior nucleus (AN)

Current state

- VIM not visible on conventional MRI
- Current methods
  - High field strength MRI (7T, 9T)
  - Special MRI sequences
  - Atlas based segmentation
    - Deformable atlas
  - Atlas based localization (CRAVE)
  - Tractography
    - Probabilistic
    - Deterministic

Tractography based thalamic parcellation

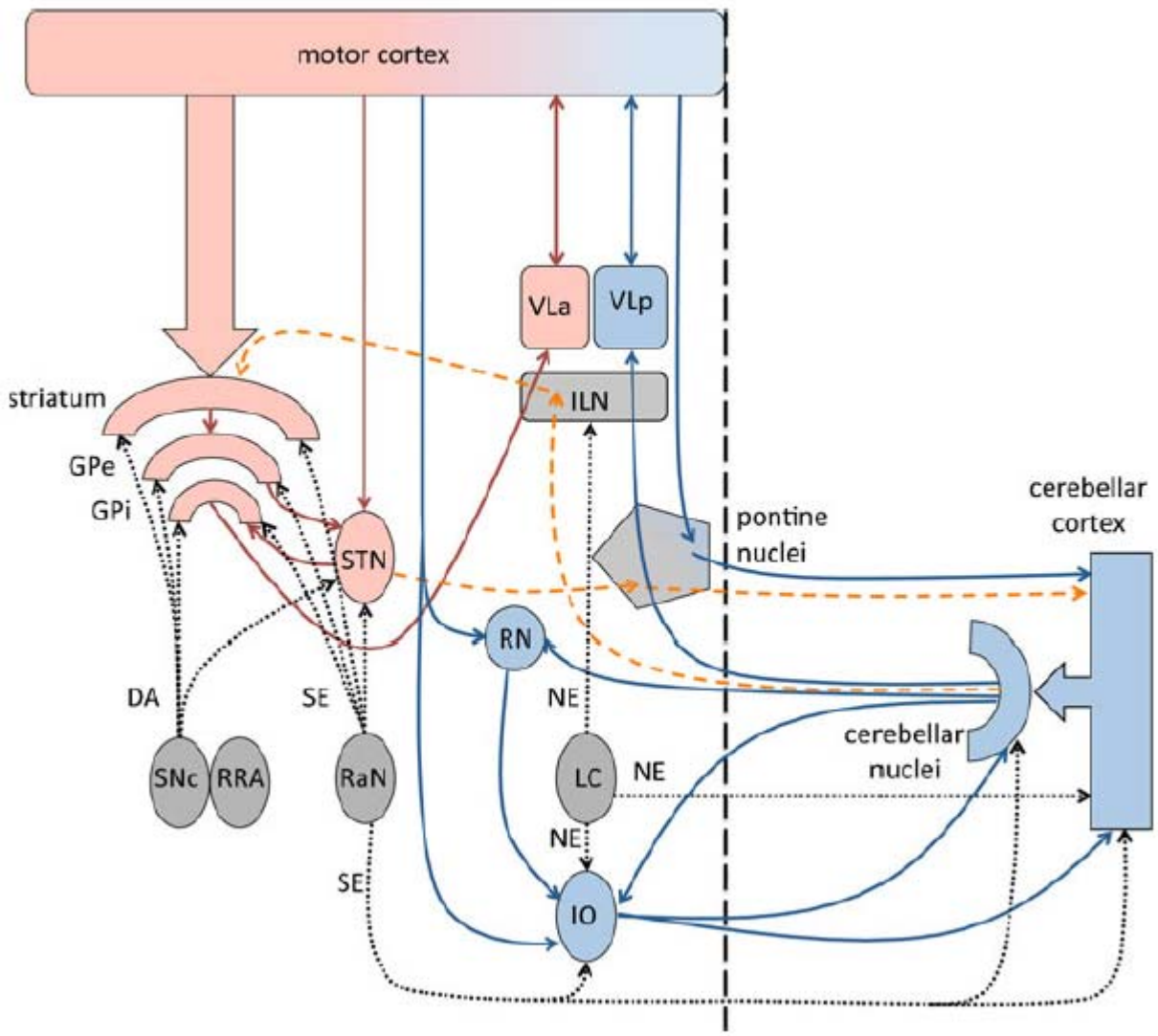


Behrens et al. Nature 2003

Consideration for development of T-VIM targeting method

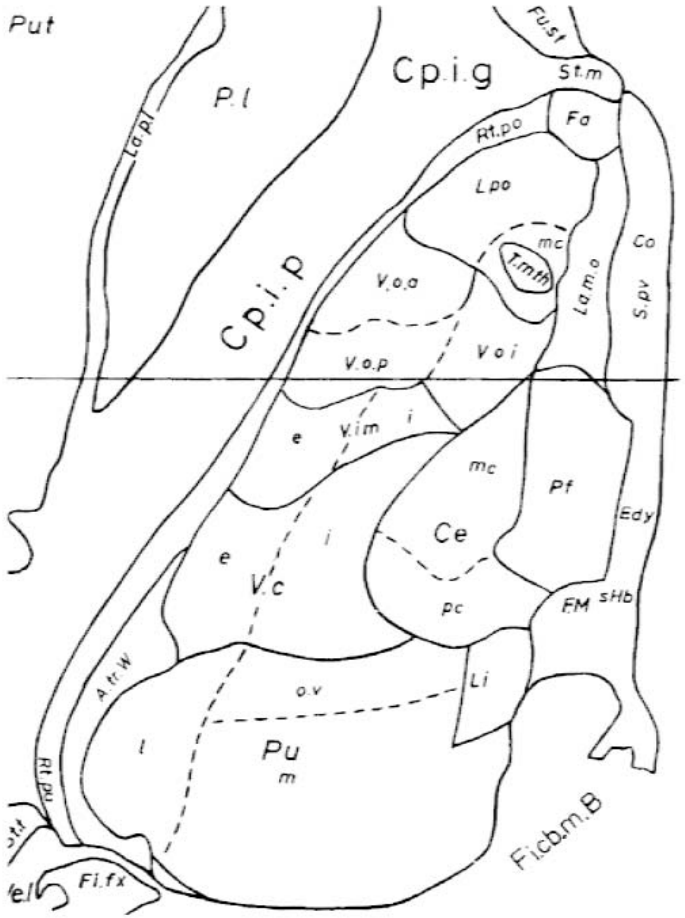
- Should be applicable to individual patient anatomy
  - Anatomy of tremor network
- Should be surgically useful
  - Accurate
  - Improve efficacy
    - Network dysfunction in essential tremor
    - Biomarkers for good clinical outcomes
  - Safety consideration
    - Critical structures surrounding VIM (pyramidal tract and lemniscus)
  - Technical considerations
    - Ease of use

Anatomy of tremor network



Helmich etal. Curr Opi Neurol Neurosci, 2013

ViM is a central node in tremor network



Defined anatomical structure

- 5x5x6 mm
- Vim_i and Vim_e
- Somatotopy

EP identification

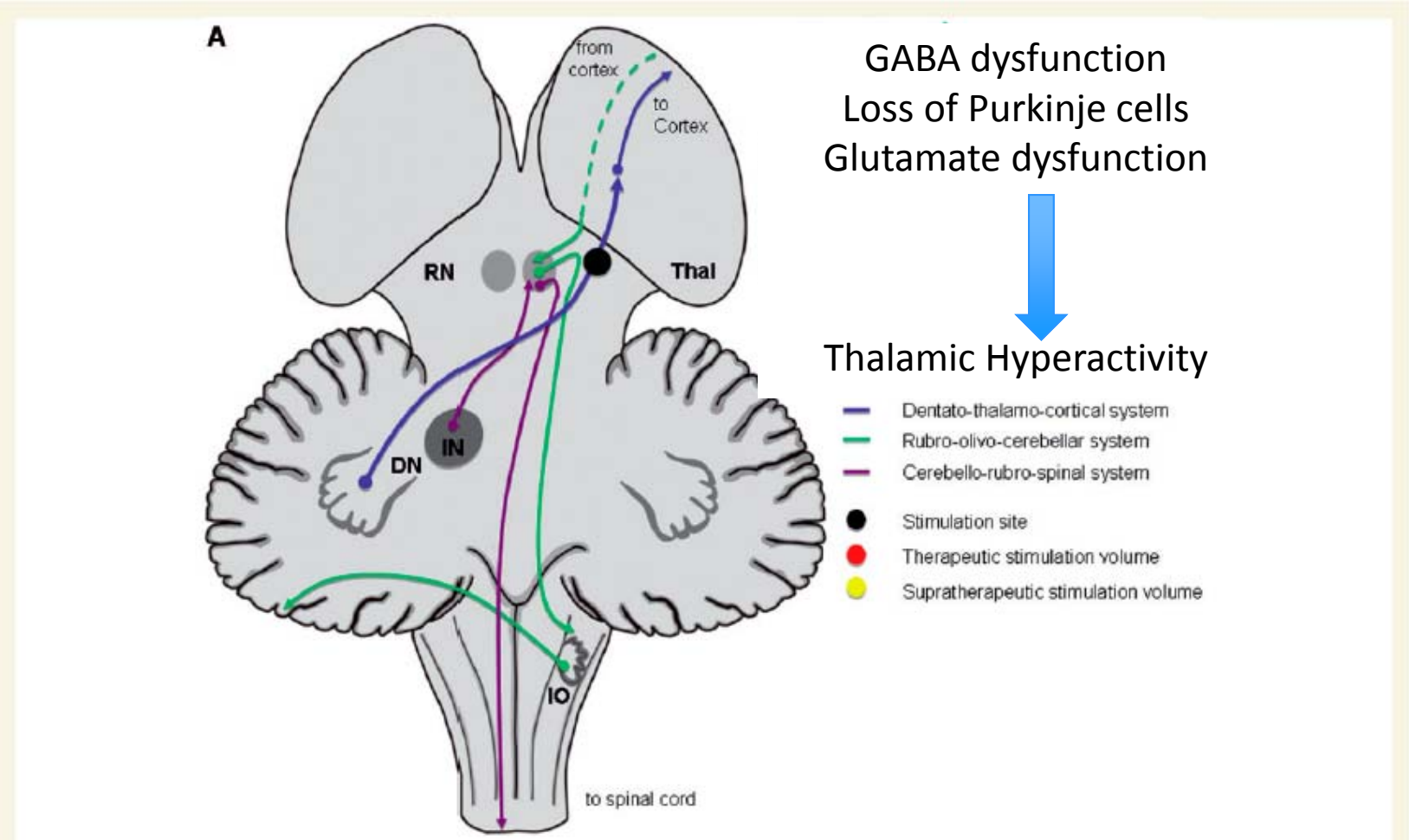
- Kinesthetic cells
- Tremor cells
- Tremor arrest with stim

Cerebellar receiving area

- Dentato-rubro-thalamic tr.

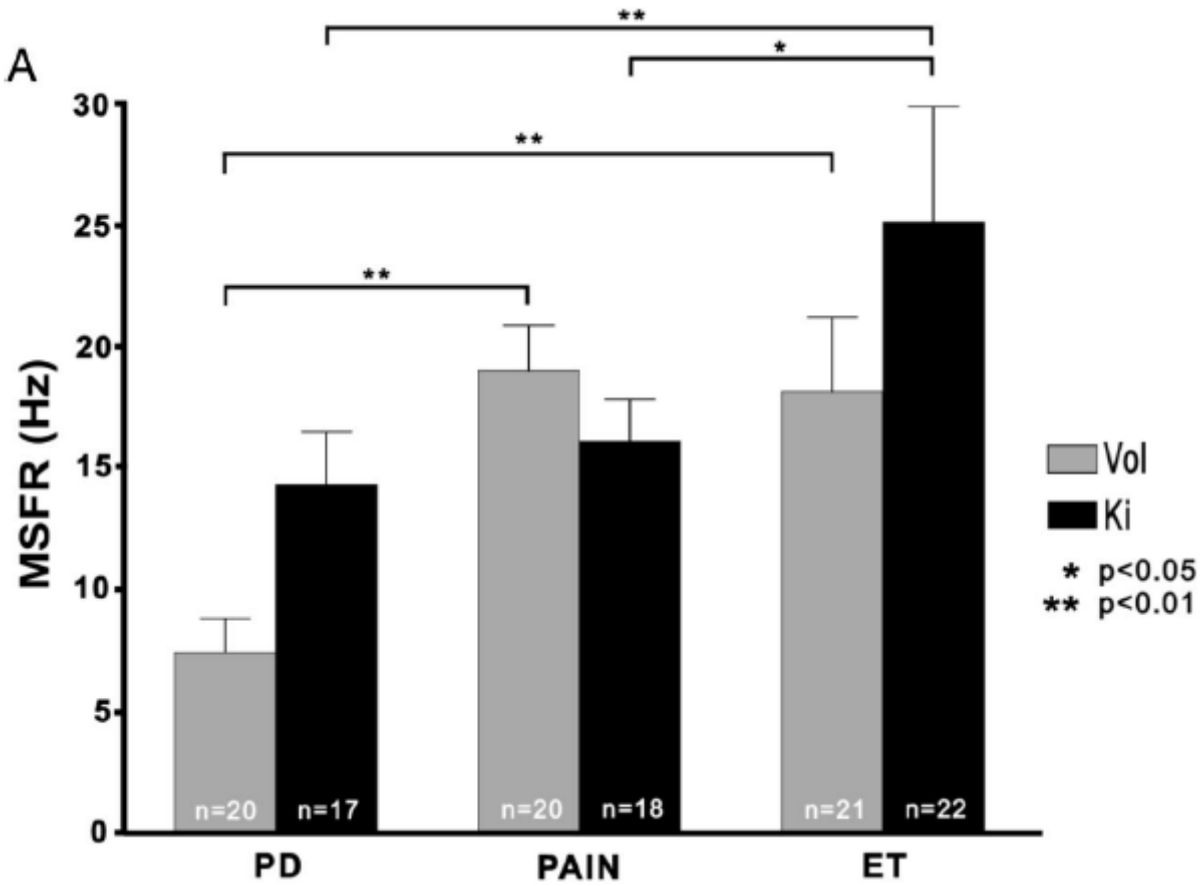
Ilinsky etal. Mov Dis, 2002

Network dysfunction in tremor



Groppa etal. Lancet Neurol, 2014

Thalamic hyperactivity in ET



Molnar etal J Neurophysiology 2005

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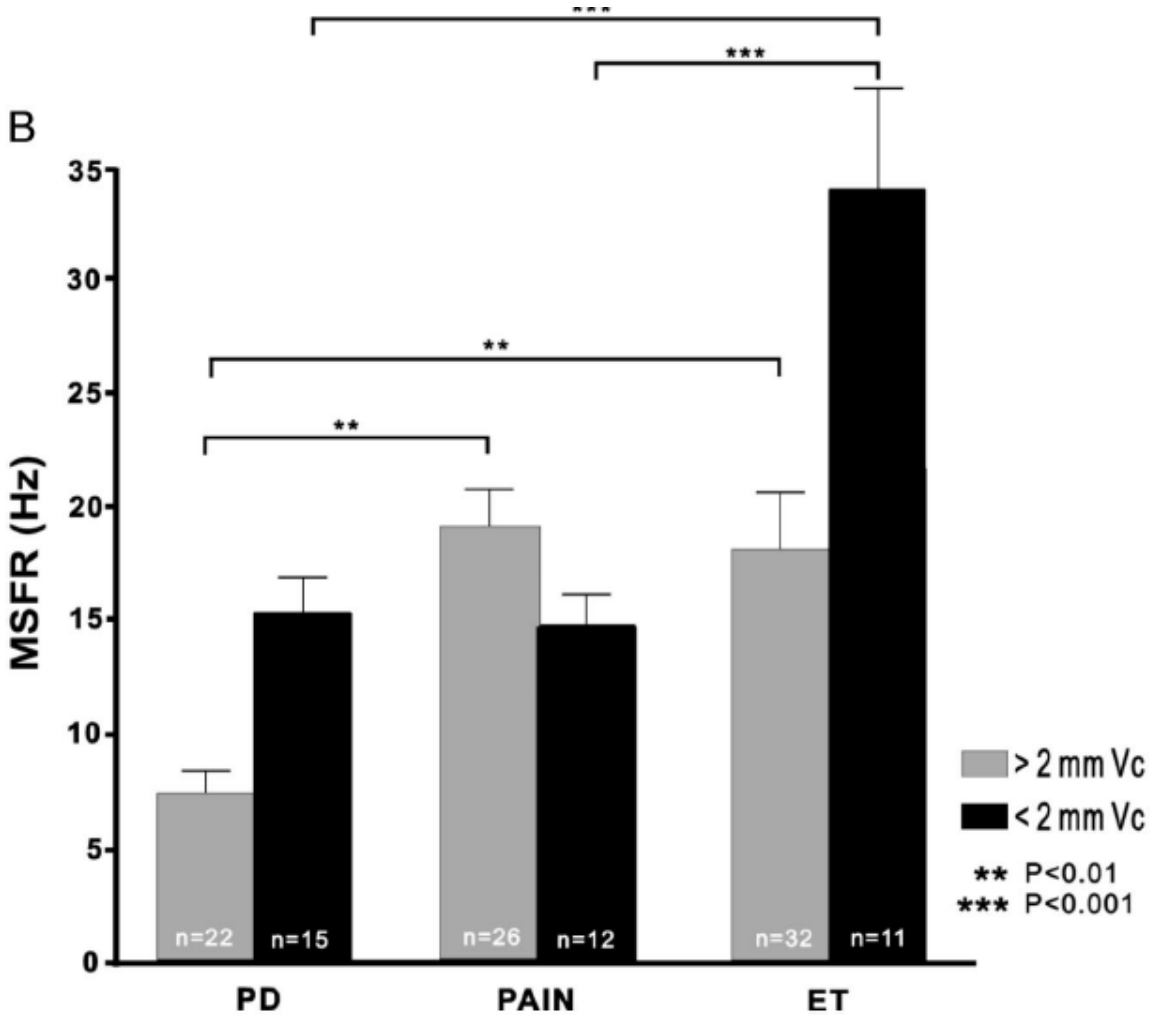
VIM hyperactivity in ET



Molnar etal
J Neurophys 2005

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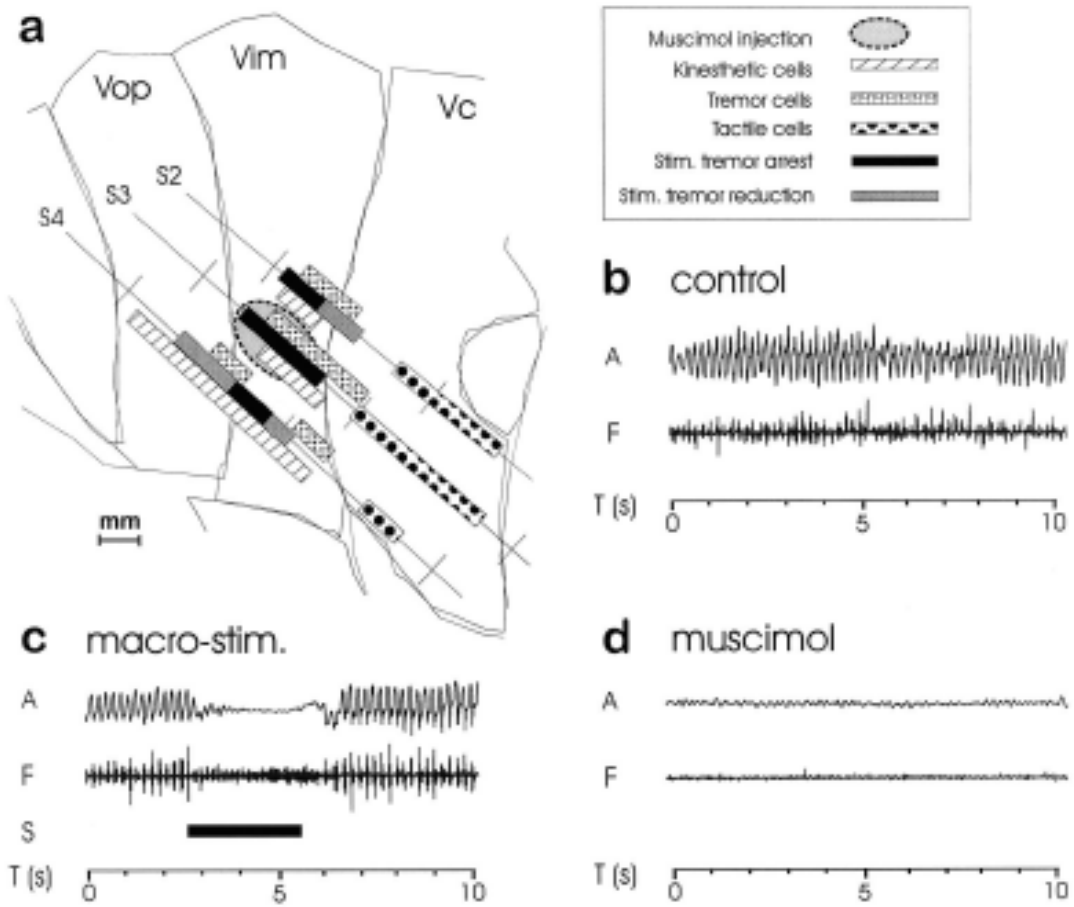
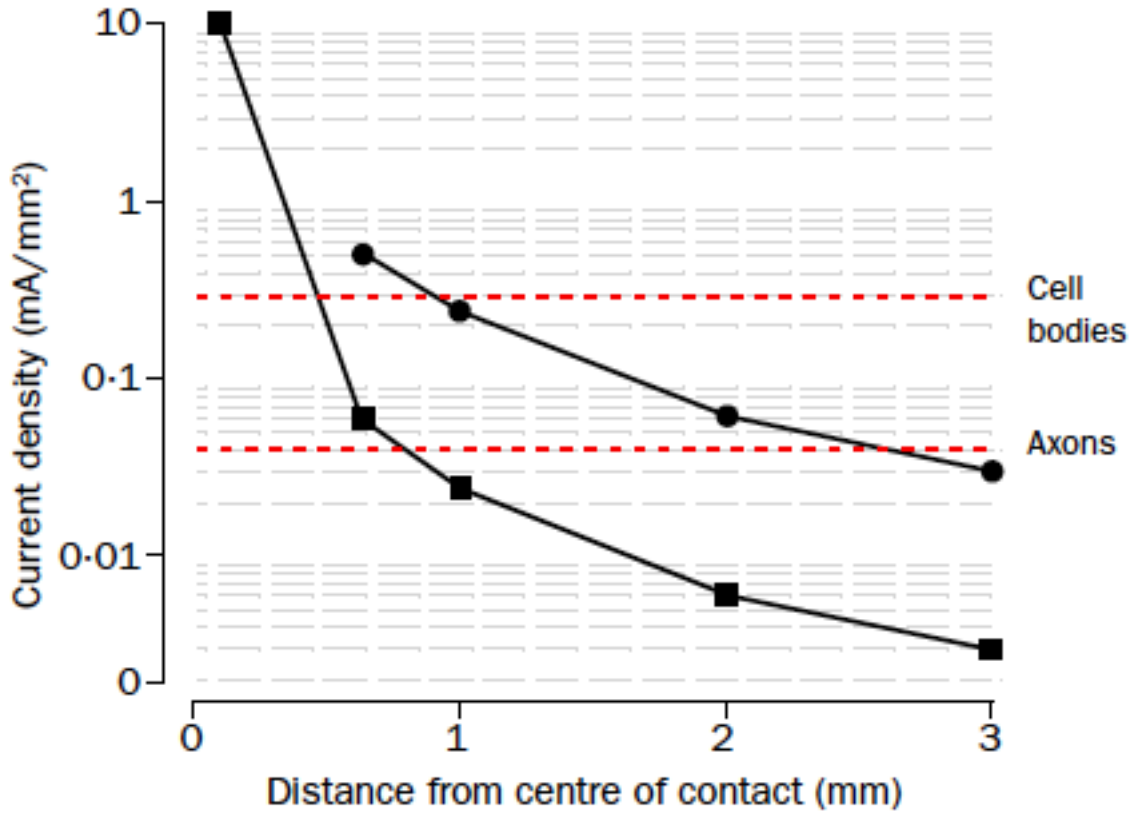
Mechanisms underlying efficacy of tremor surgery

Initial hypothesis for tremor control - VIM inhibition



Pahapill etal. Ann Neurol, 1999

DBS mechanisms of action



Adaptation

Inhibition

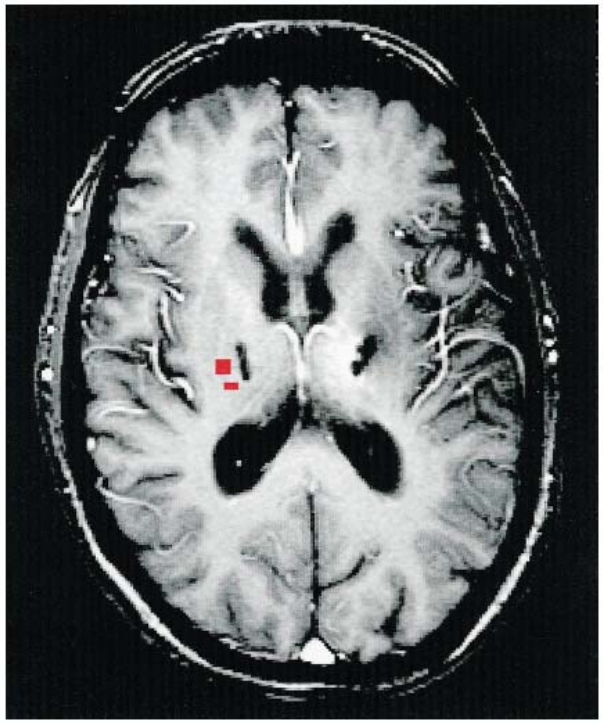
Excitation

Less adaptation

Lozano etal. Lancet Neurology, 2002

- DBS electrode (3 mA, 6 mm²)
- ■ Experimental needle electrode (0.3 mA, 0.03 mm²)

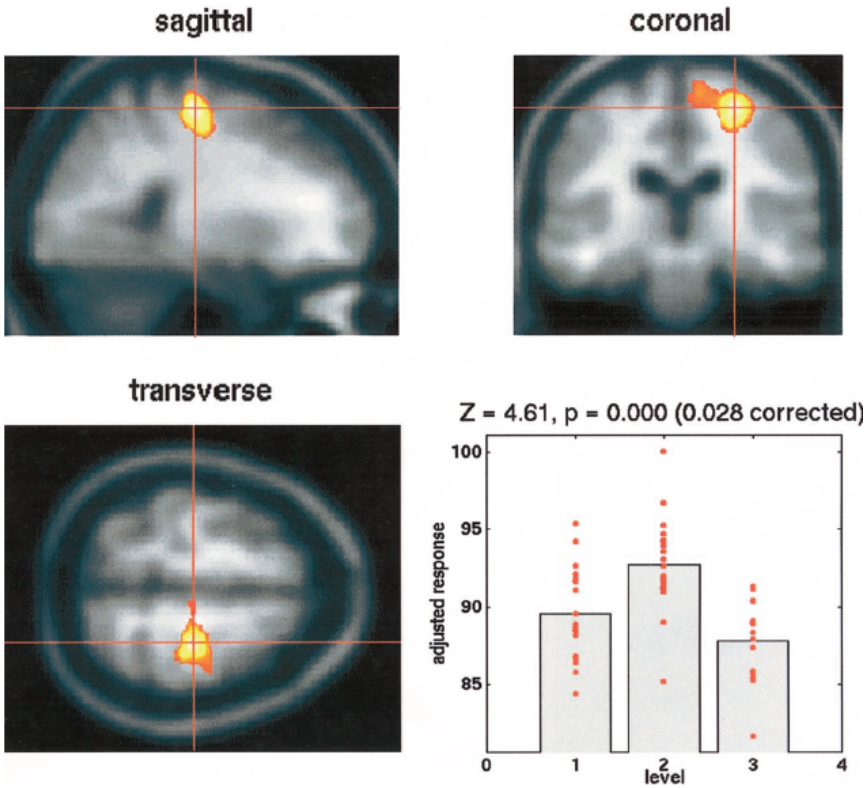
Functional imaging evidence for network modulation



Increased BOLD signal
(ON vs. OFF)

Lateral thalamic wall
Basal ganglia
S-1

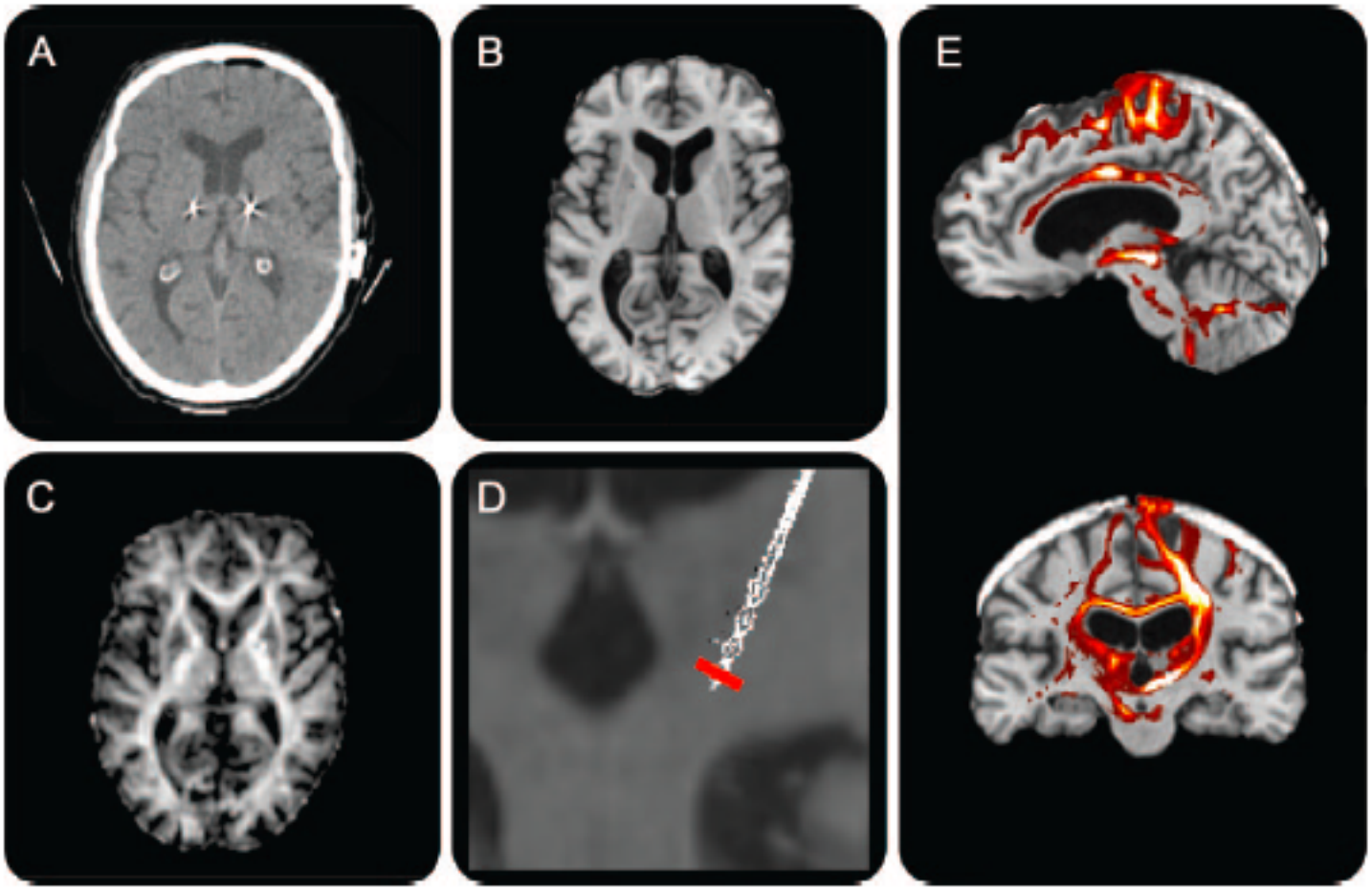
Rezai etal 1999 JNS



Increased PET signal
(Efficacious vs. non-efficacious)
M1 activation

Ceballos–Baumann etal 2001 Neurology

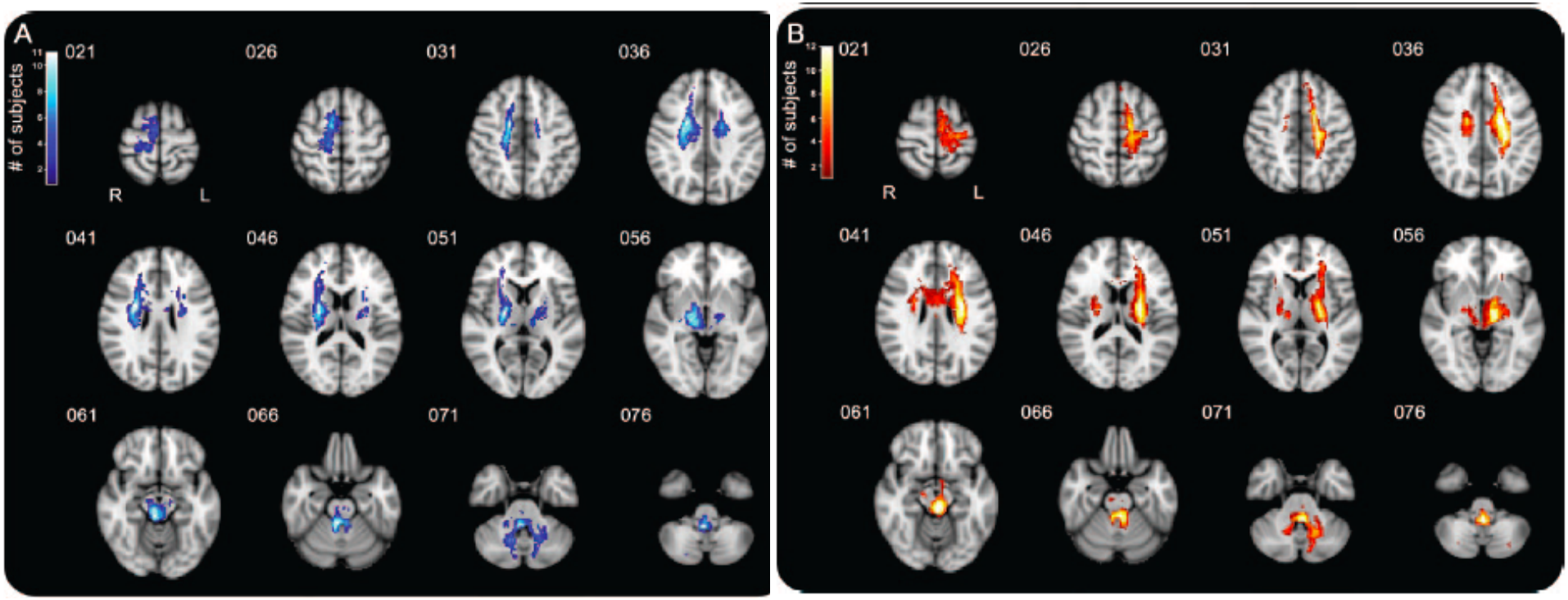
Efficacious VIM DBS modulates tremor network



Klein etal. Neurology, 2012

Biomarker for good clinical outcomes - Modulation of DRT & T-C connectivity

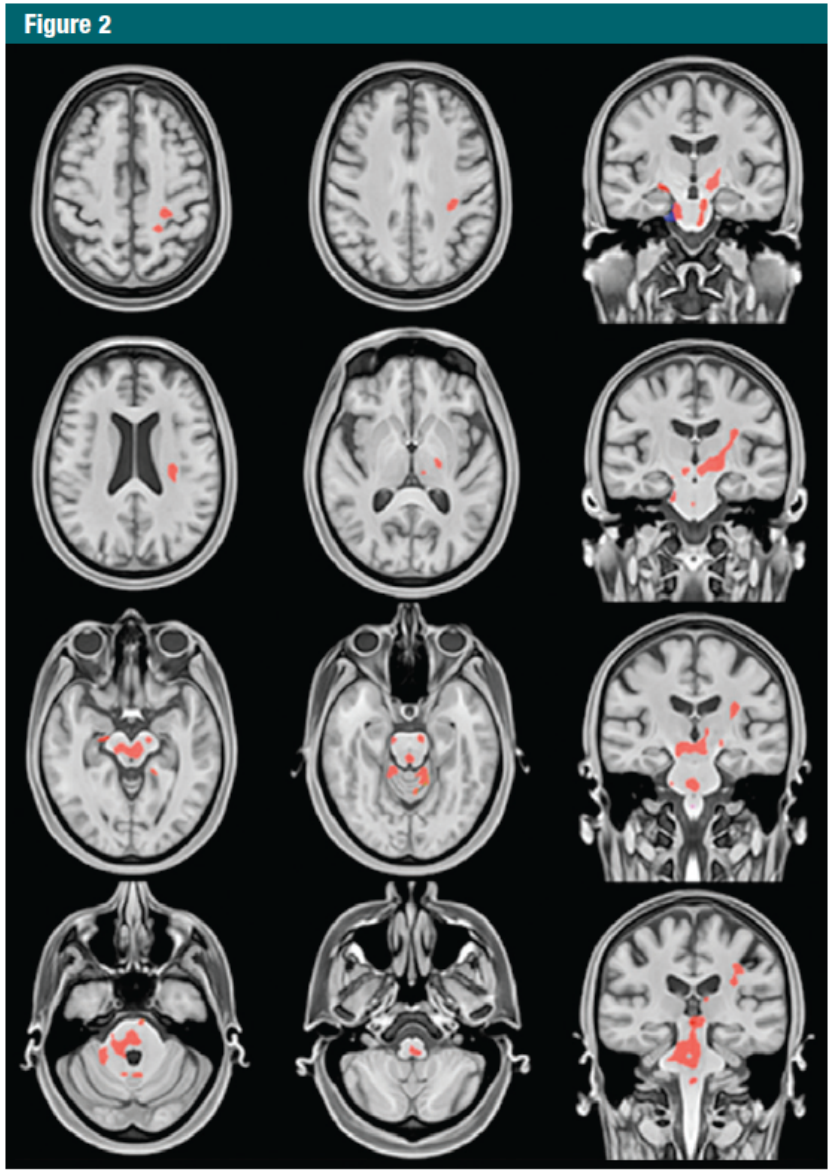
DBS for tremor



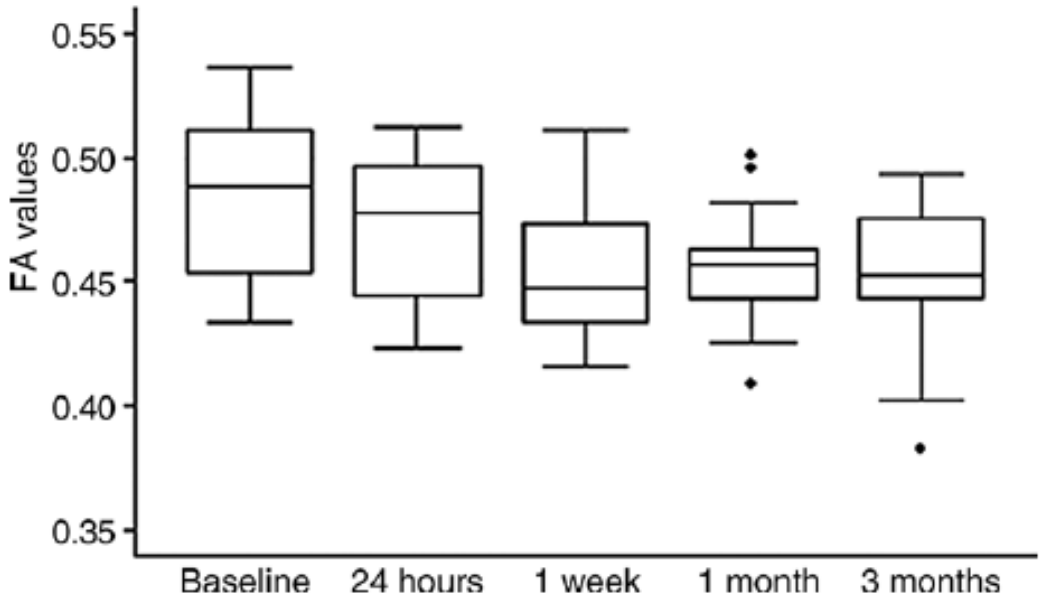
DRT – dentato-rubro-thalamic tract
T-C – thalamo-cortical

Klein etal. Neurology, 2012

Biomarker for good clinical outcomes - microstructural changes in DRT & T-C



HIFU thalamotomy for tremor



DRT – dentato-rubro-thalamic tract
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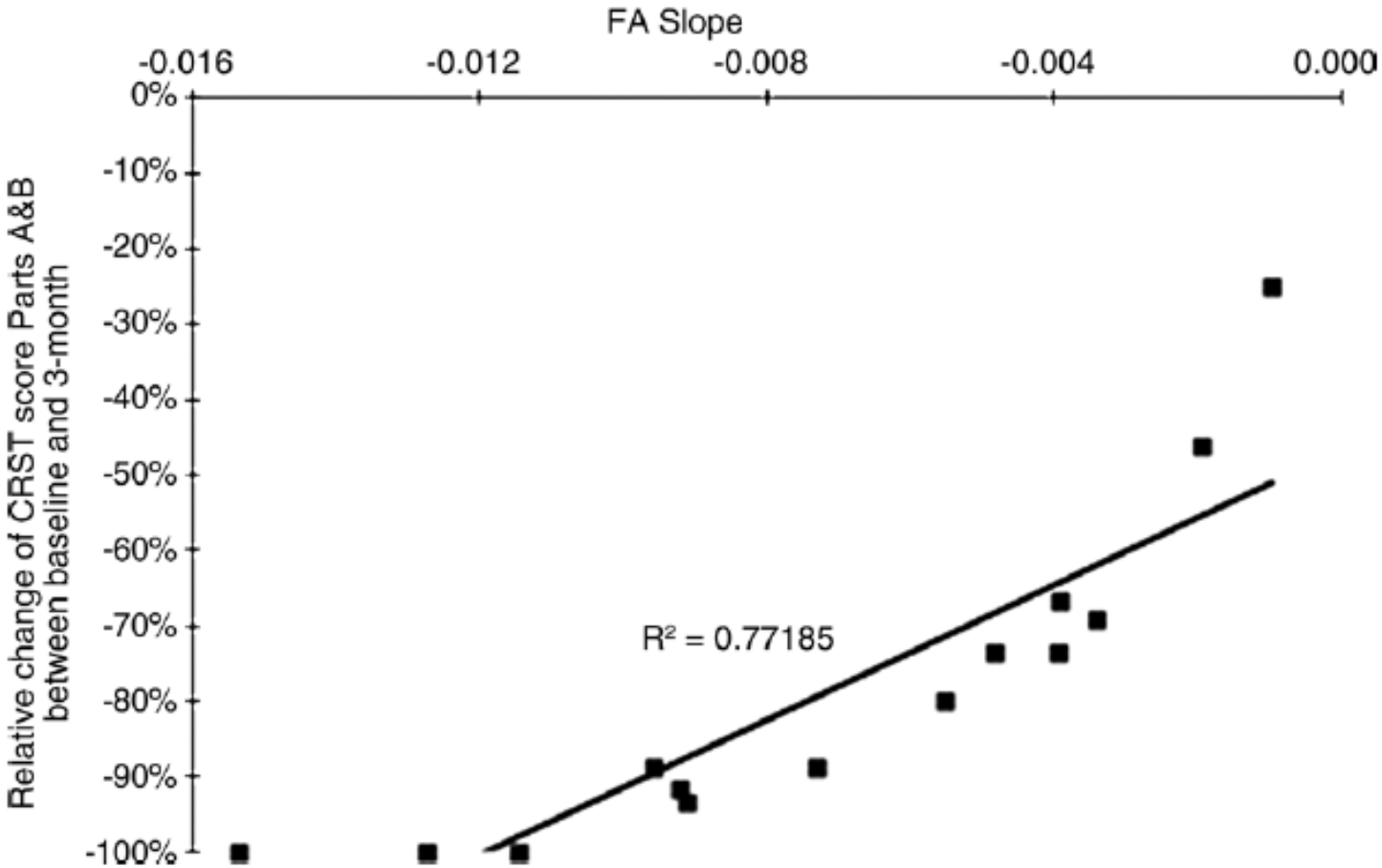
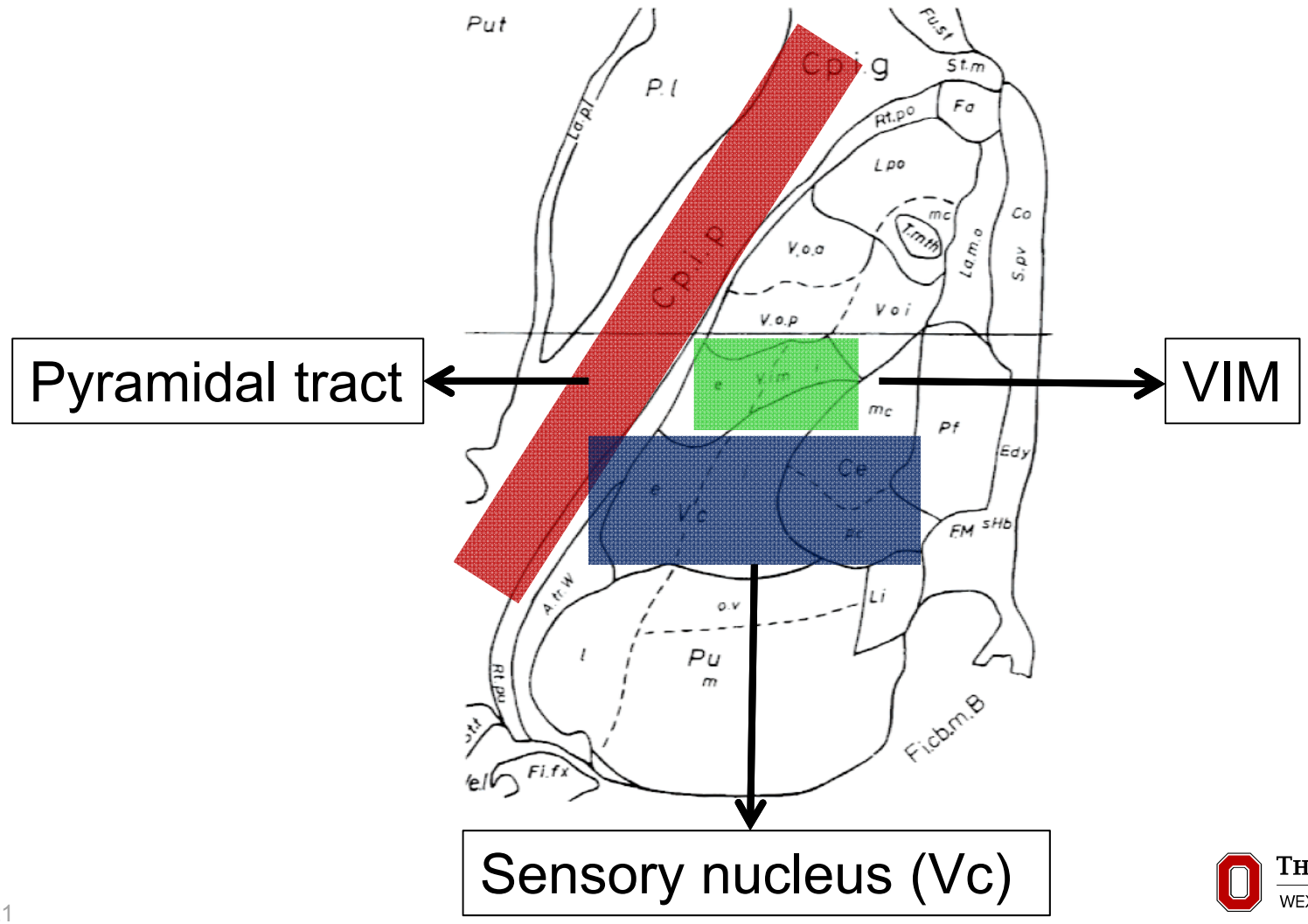
Wintermark etal, 2014 Radiology

Biomarker for good clinical outcomes - microstructural changes in DRT & T-C



Wintermark etal, 2014 Radiology

Critical structures surrounding VIM



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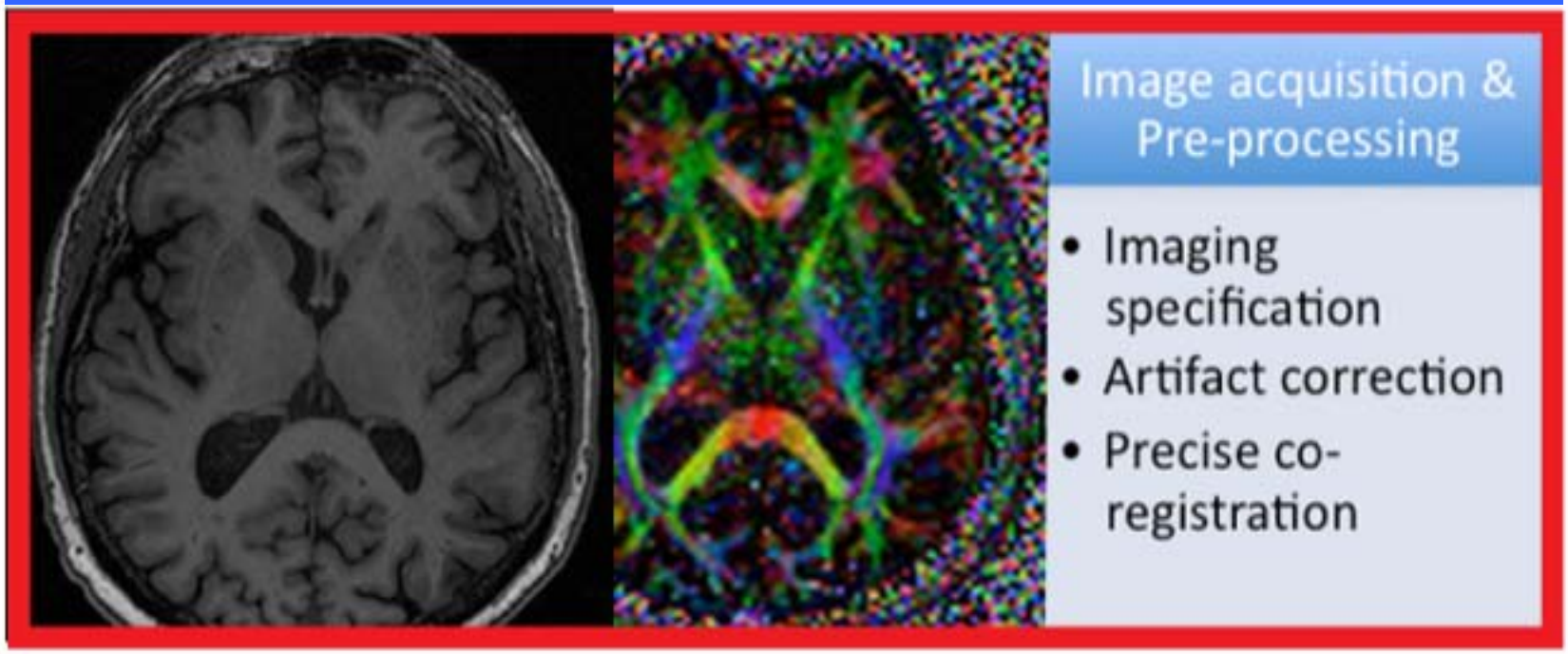
Targeting the tremor network with tractography

Step-1

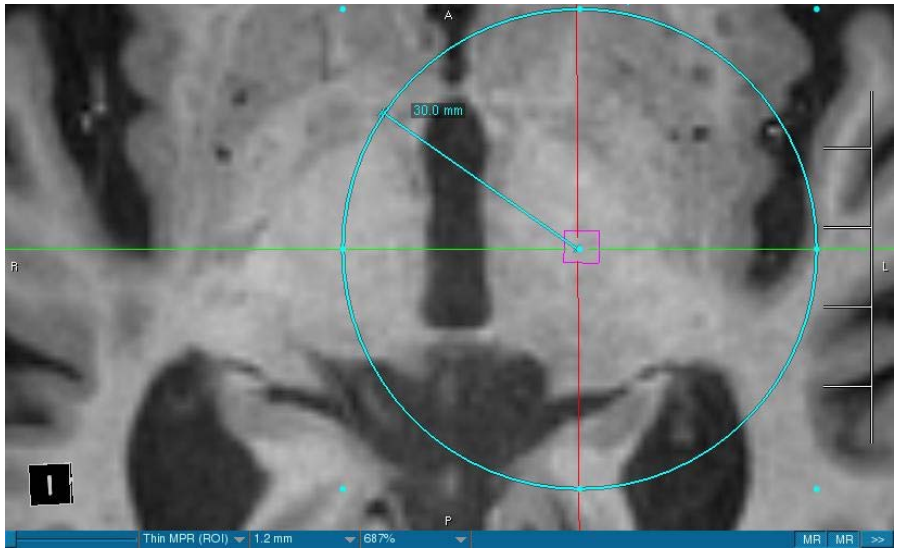


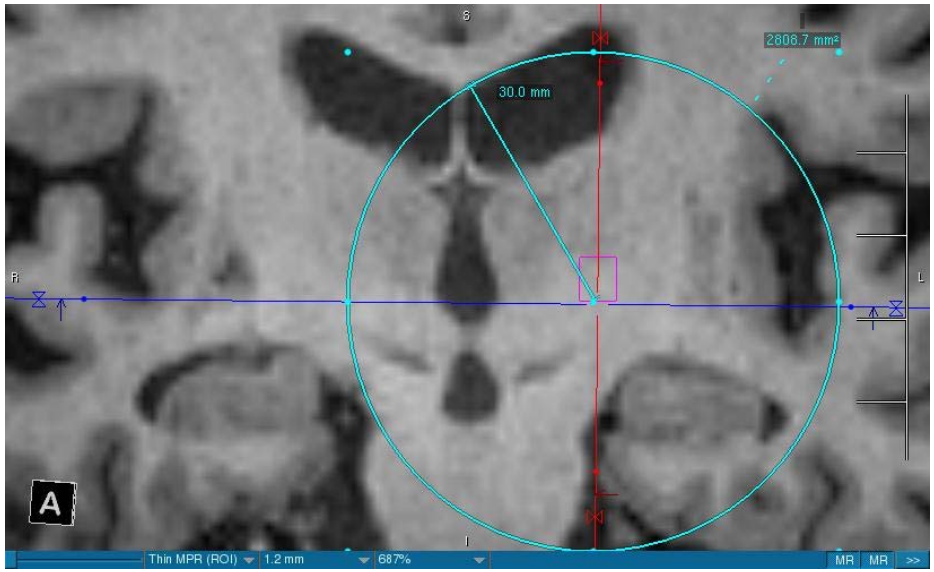
Appropriate DTI sequence

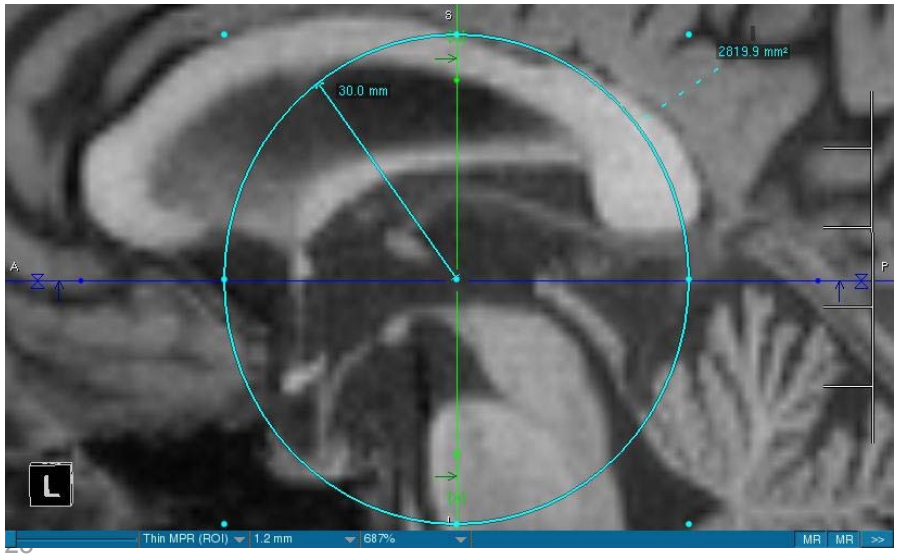
60 directions, slice thickness ≤3 mm (ideally 2 mm isovoxel)

Mov Dis 2016 (in press)

Precise co-registration - 7 out of 10 anatomical landmarks



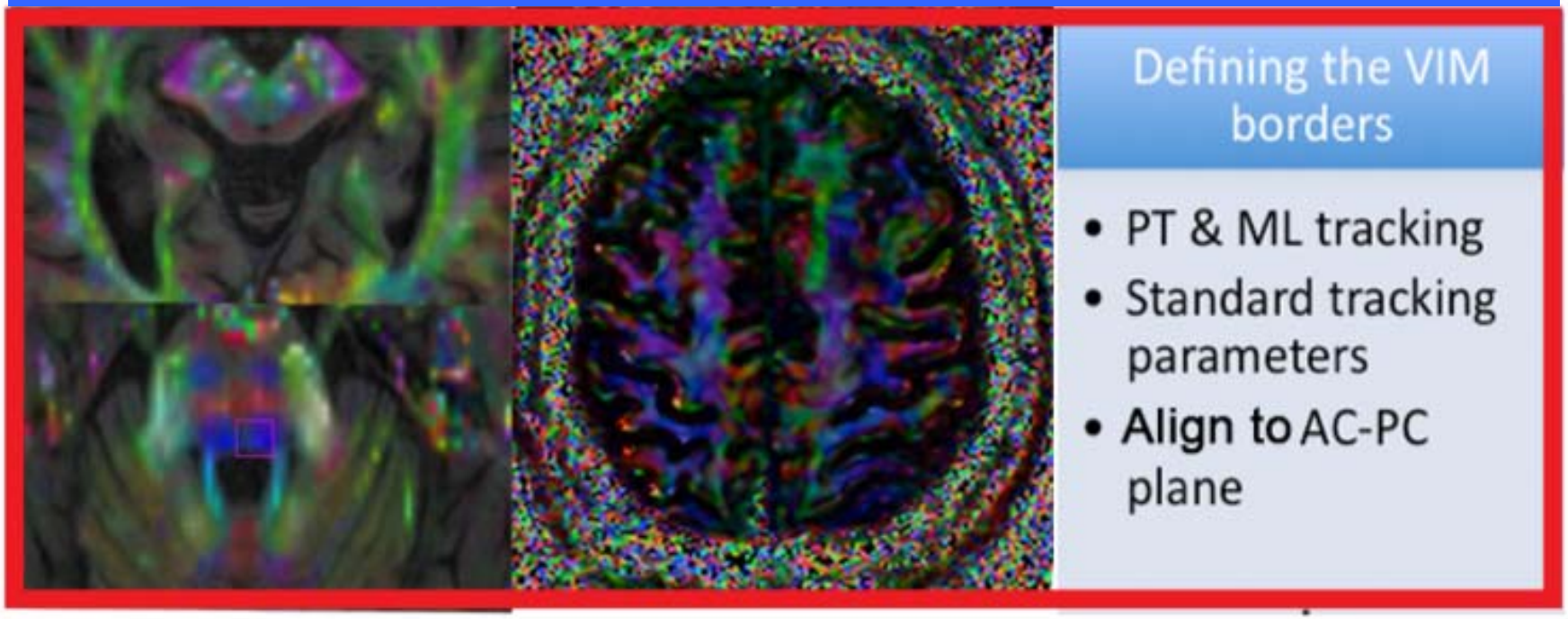




- ✓AC
- ✓PC
- ✓Splenium (Inferior and posterior)
- ✓Colliculi (b/l)
- ✓Superior cerebellar peduncle (b/l)
- ✓Fornix (b/l)

Targeting the tremor network with tractography (T-VIM)

Step-2



FA stop value= 0.2
Seed density =1
Tracking angle = 45^0 & 60^0 for PT & ML

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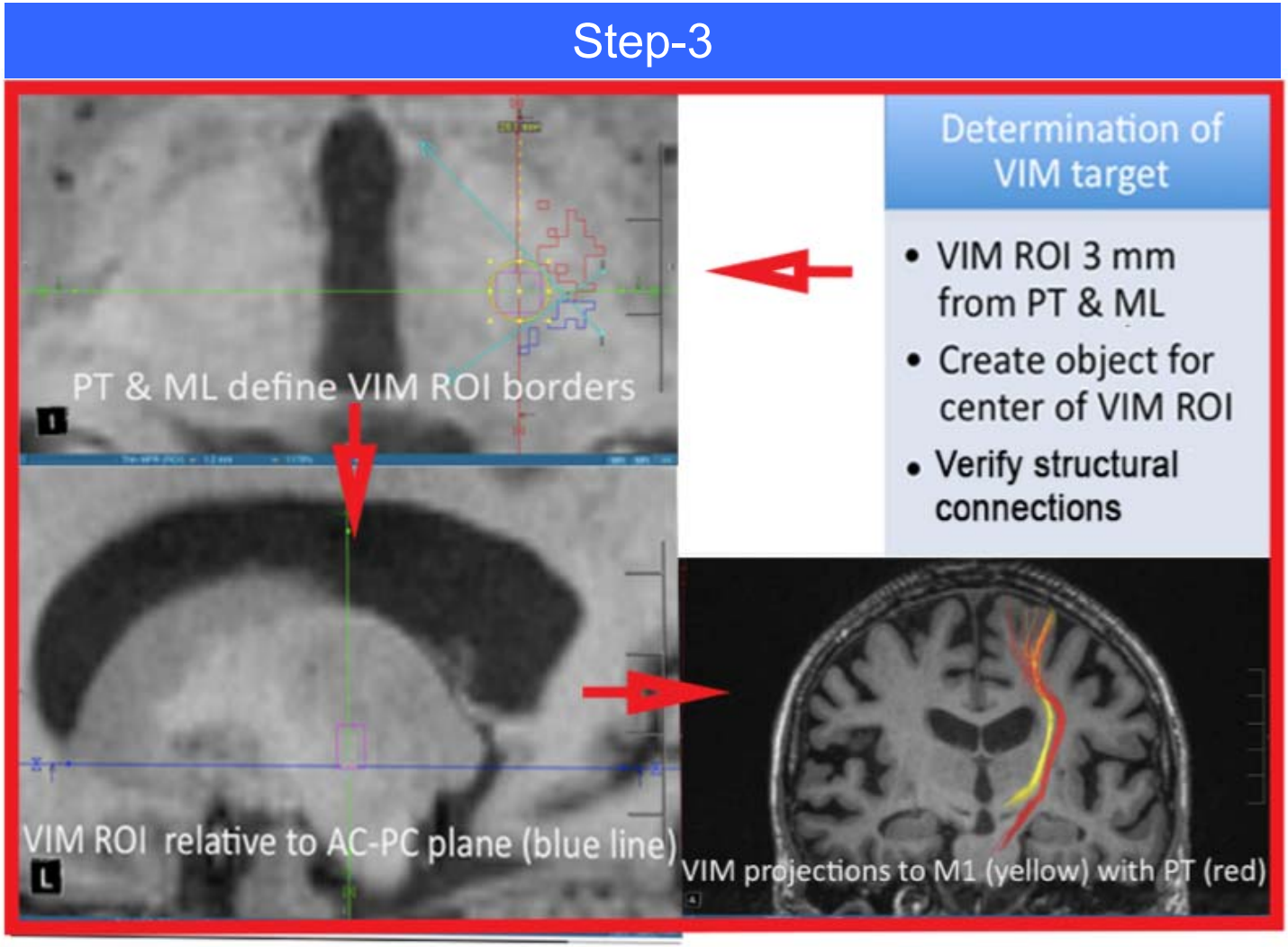
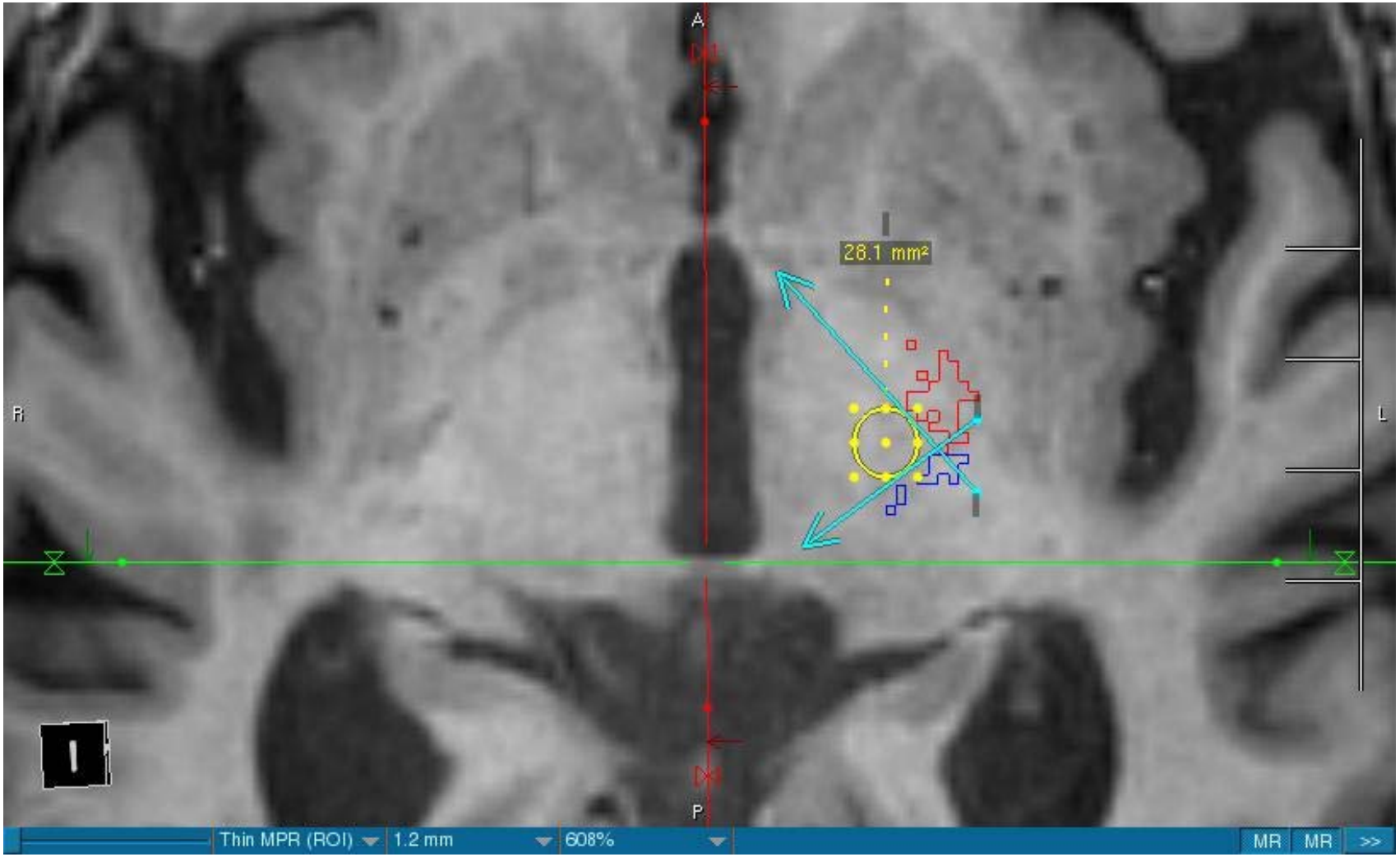
Targeting the tremor network with tractography (T-VIM)



Mov Dis 2016 (in press)

Methodology of selecting T-VIM ROI



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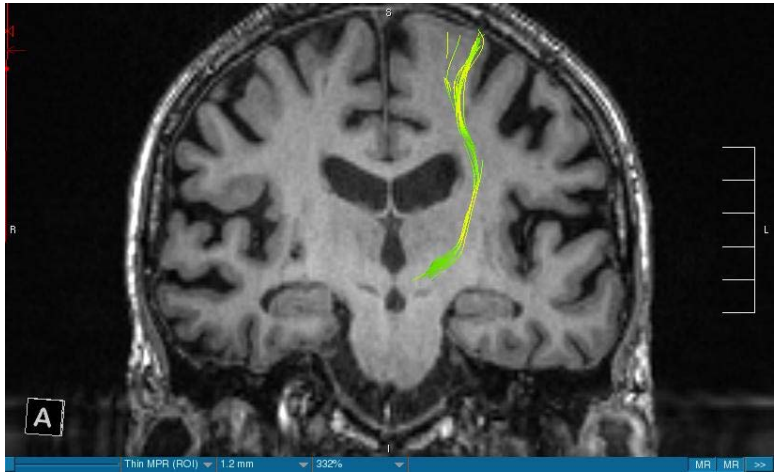
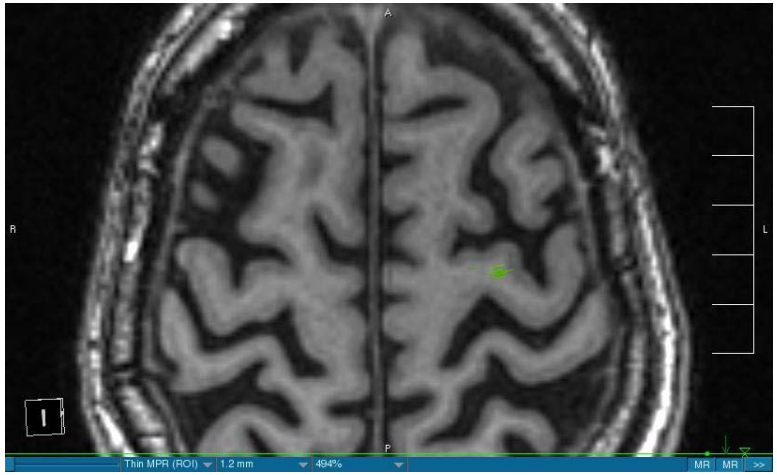
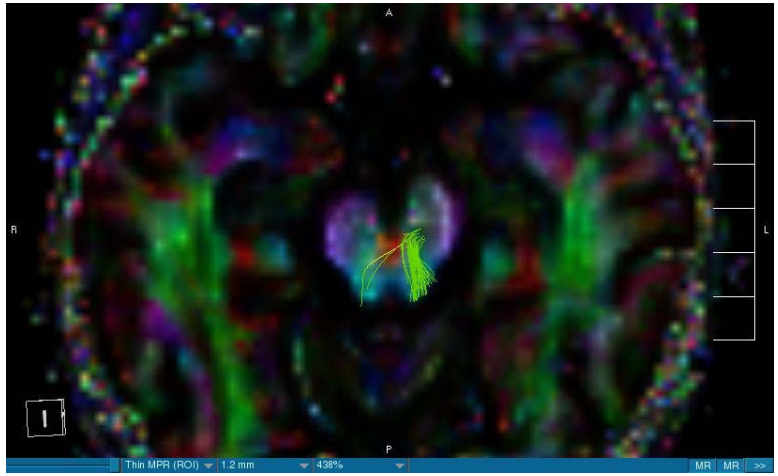
Confirmation of T-VIM connectivity

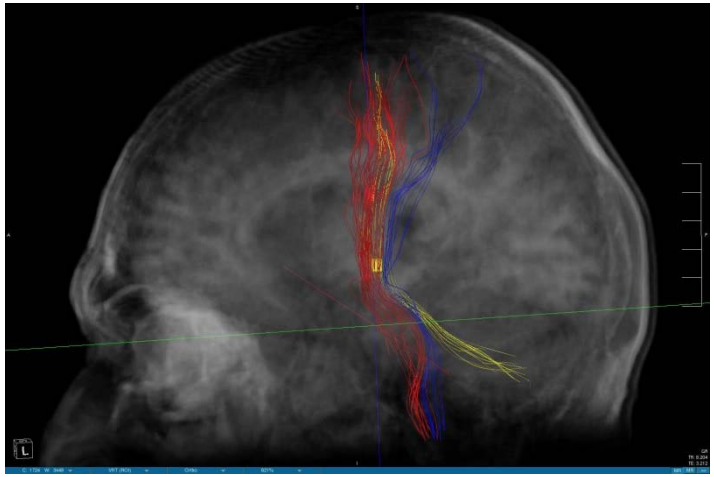
Motor cortex





Dentate Nucleus





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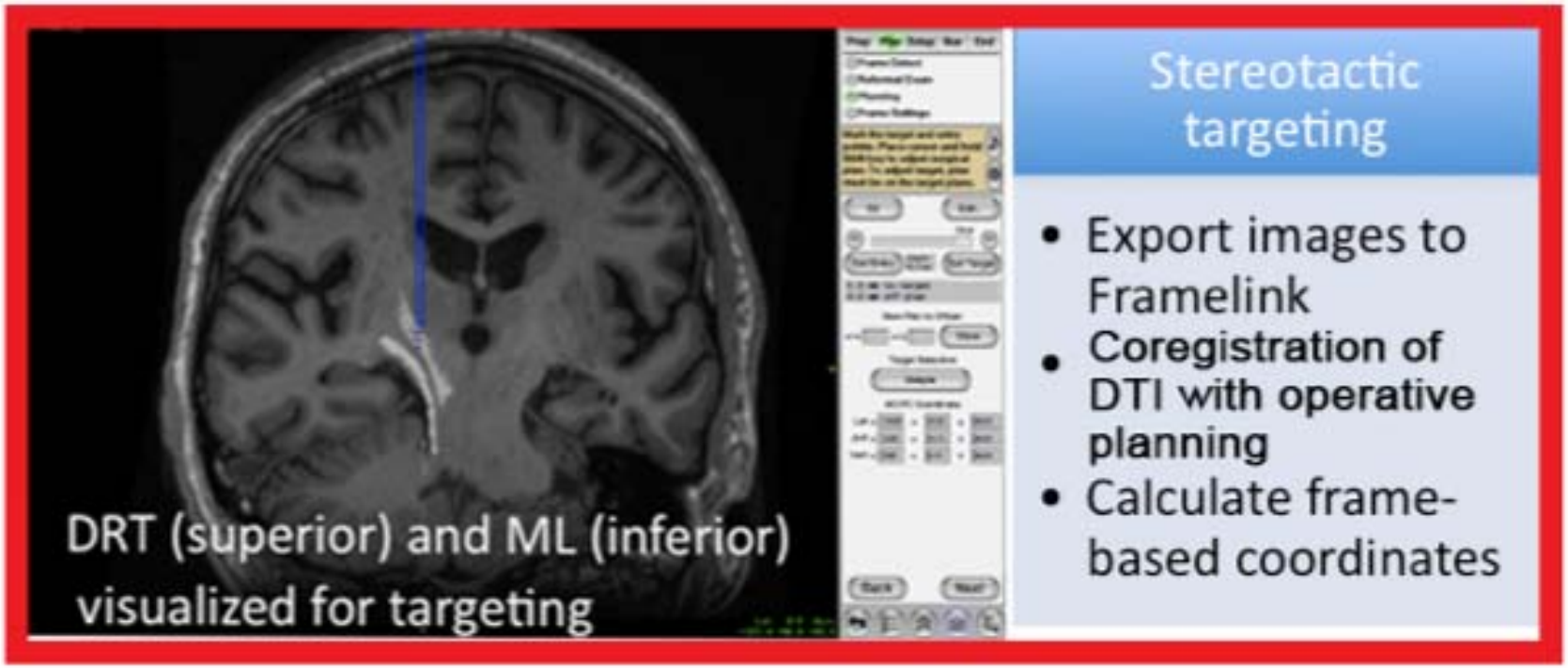
Targeting the tremor network with tractography (T-VIM)

Step-4

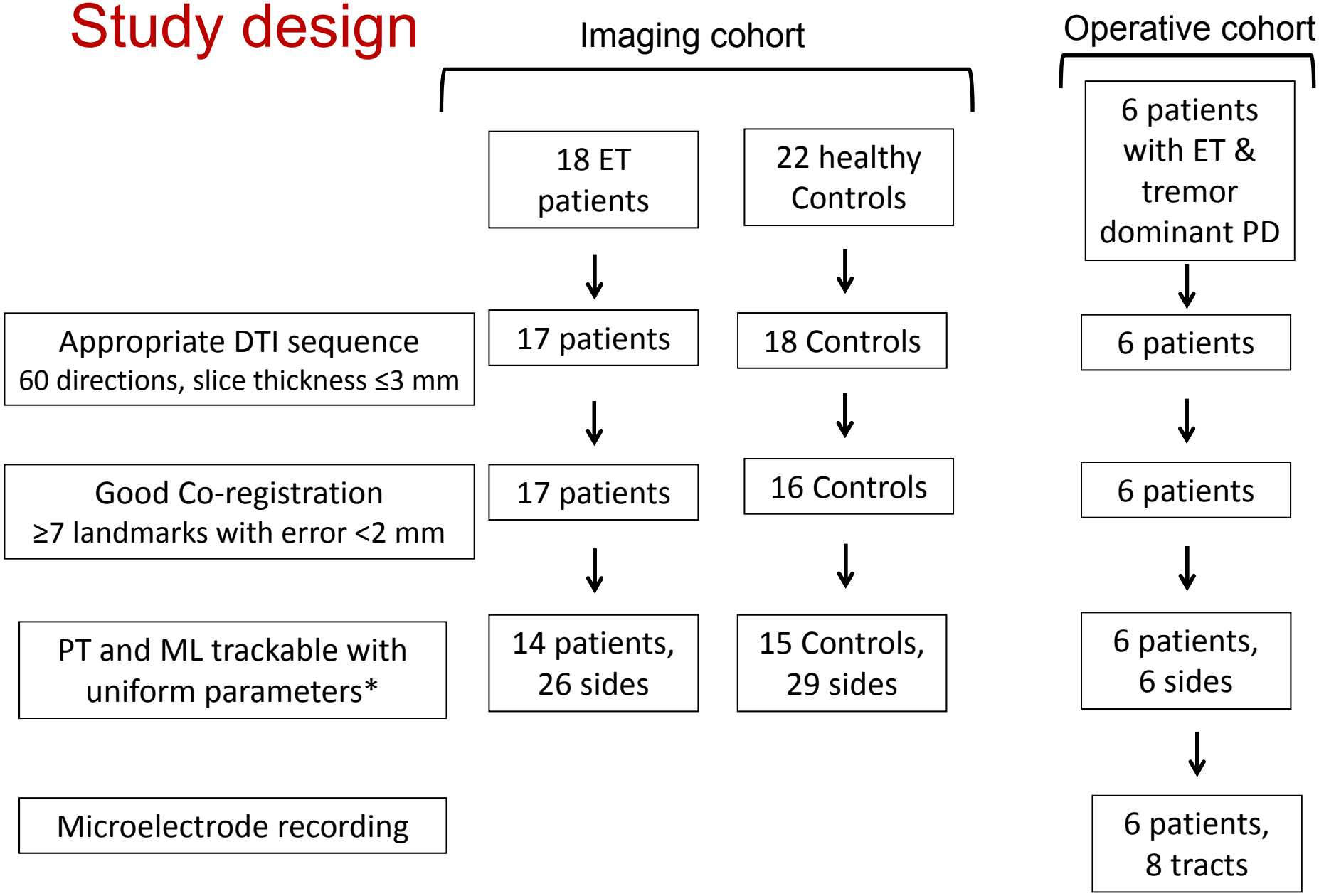


Stereotactic targeting

- Export images to Framelink
- Coregistration of DTI with operative planning
- Calculate frame-based coordinates

Mov Dis 2016 (in press)

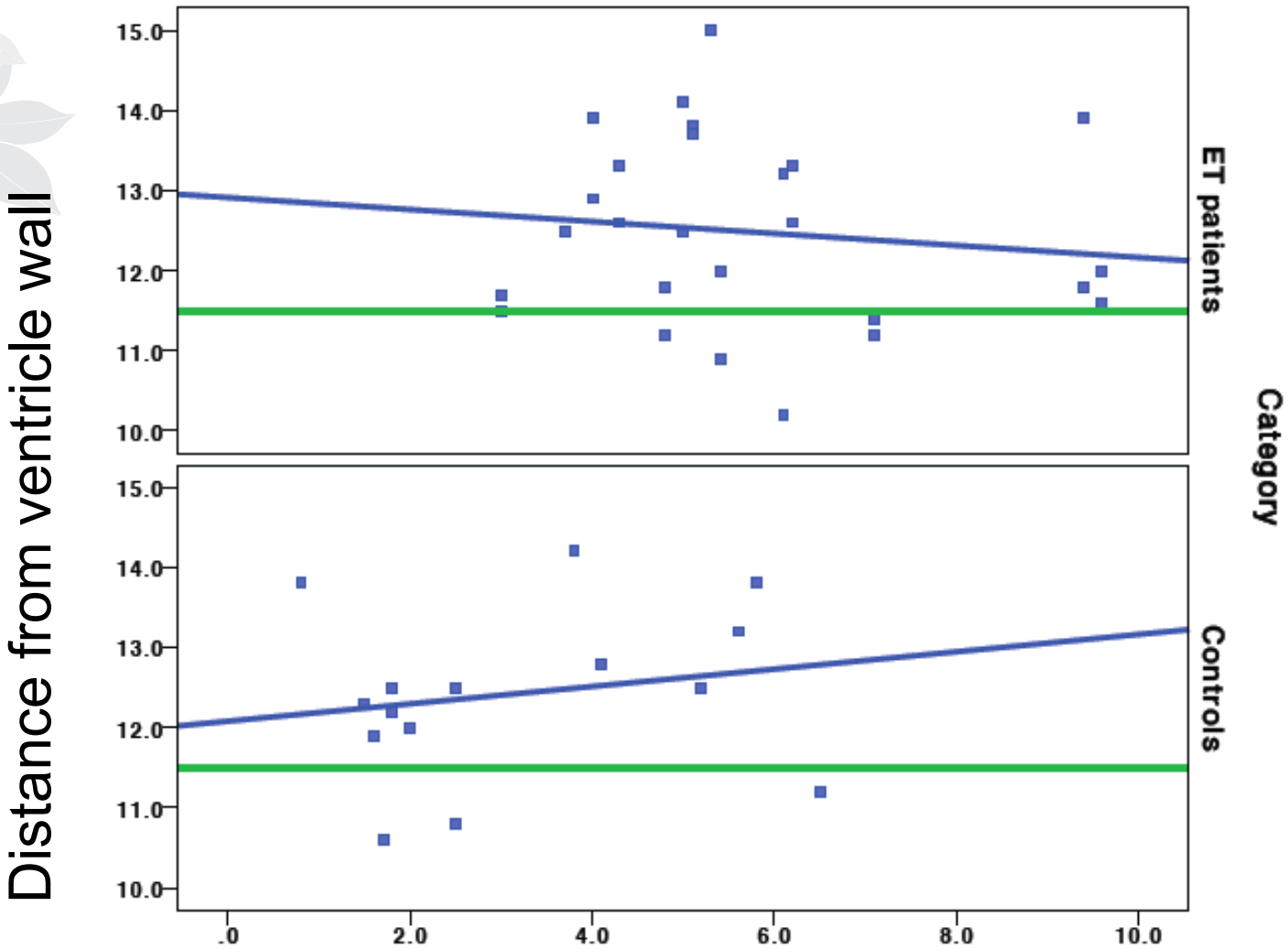
Study design



*FA stop value= 0.2, seed density =1, tracking angle = 45^0 & 60^0 for PT and ML respectively

T-VIM anterior coordinate - Imaging cohort

Variables	Standard targeting	DTI based targeting	P value
Anterior coordinate	6.7 ±0.3	8.5 ±1.1	0.000
Ratio	25%	32% ±4%	0.000
Lateral coordinate			
Distance from midline	15	15.03 ±1.3	NS
Distance from ventricle wall	11.5	12.5 ±1.2	0.000

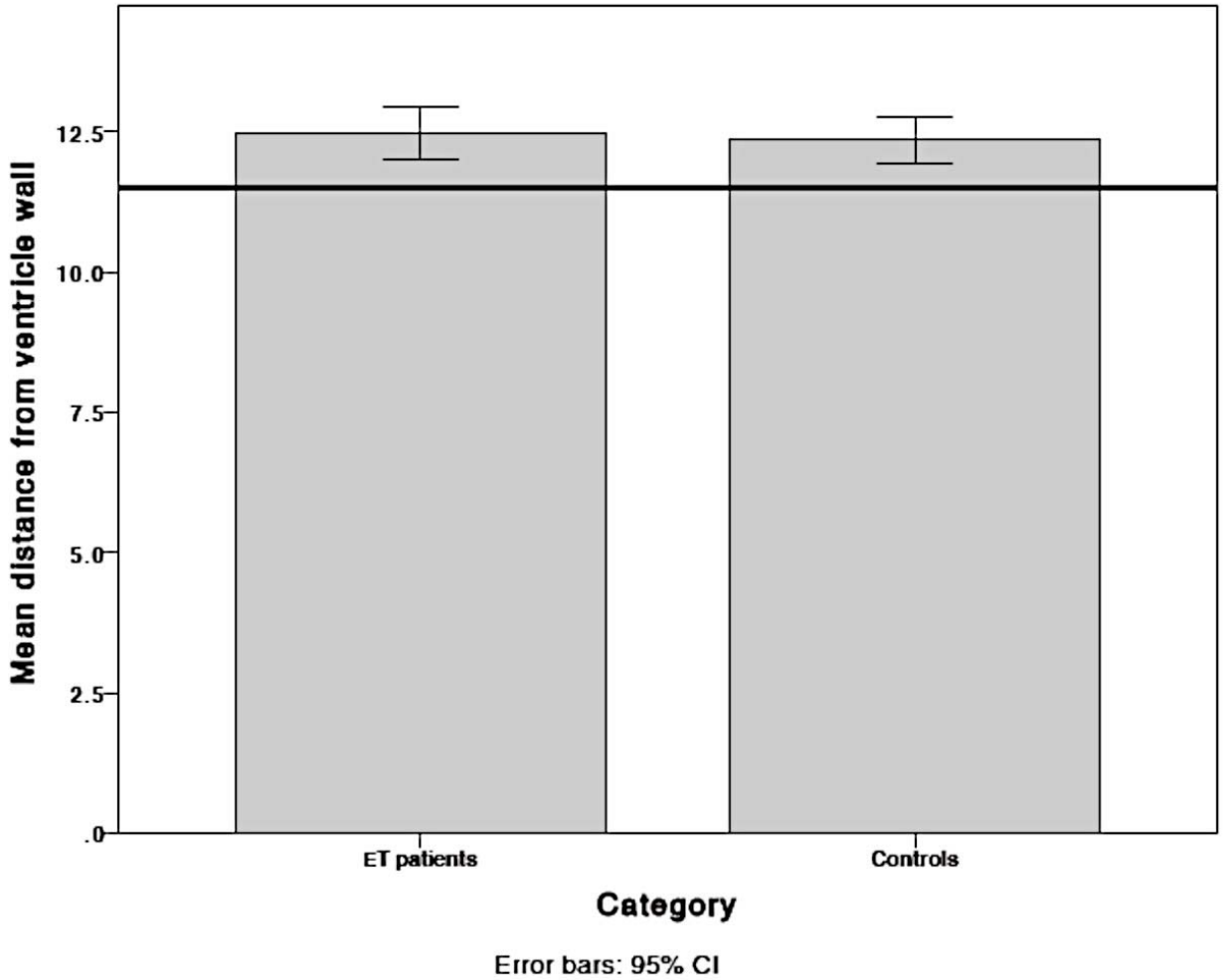


Size of third ventricle

DTI based distance from ventricle wall

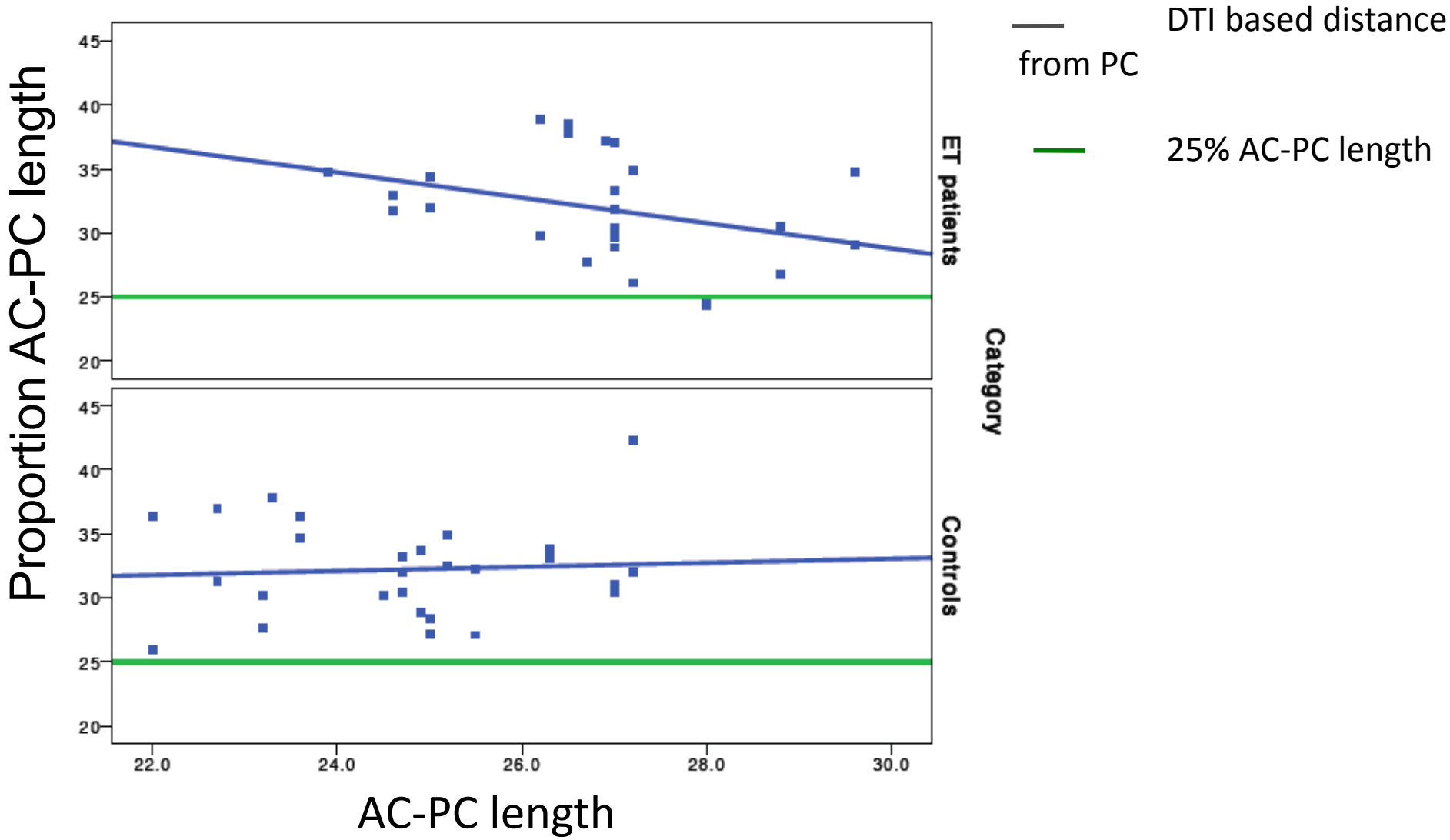
Standard distance from ventricle wall

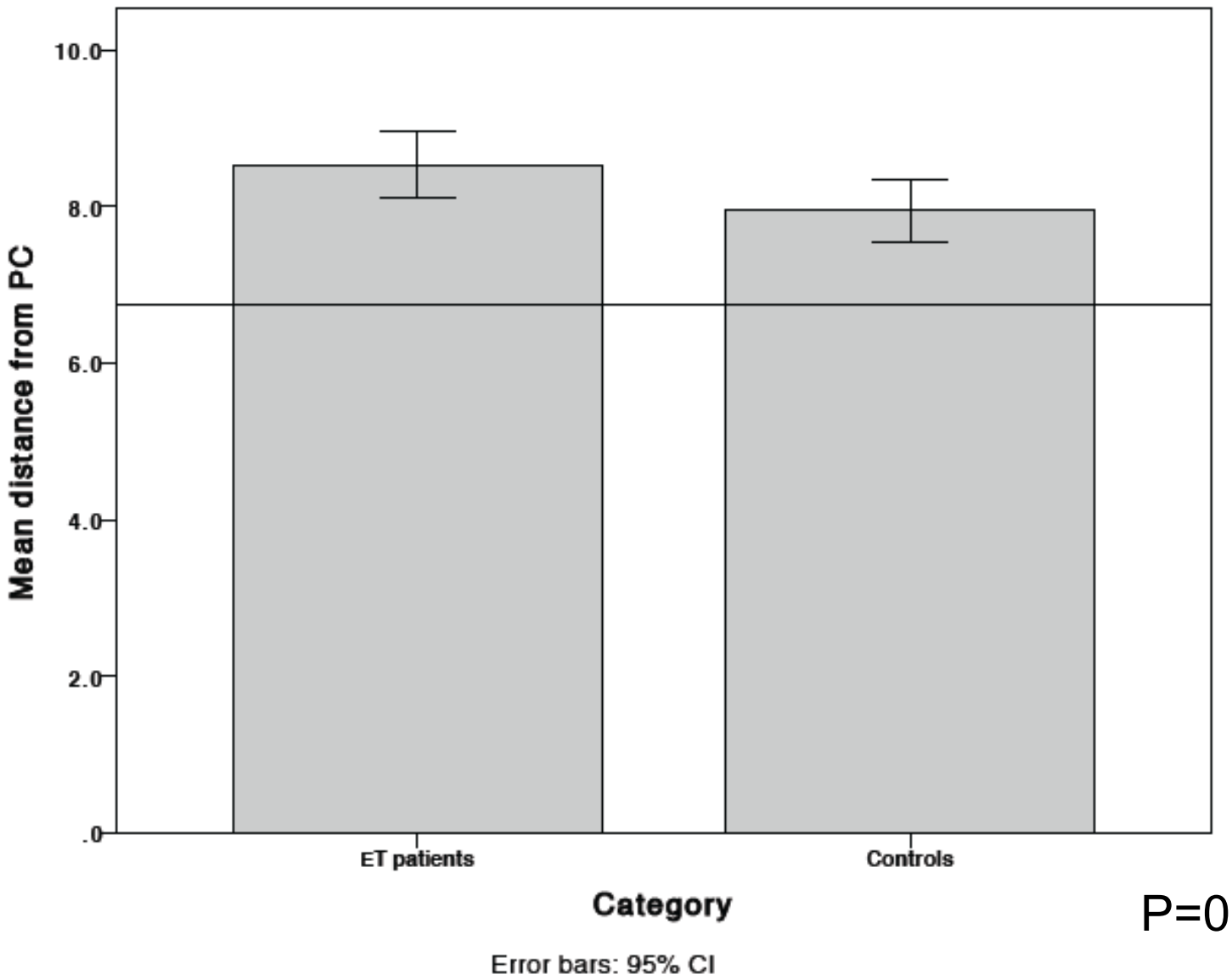
T-VIM lateral coordinate - Imaging cohort



P=0.69

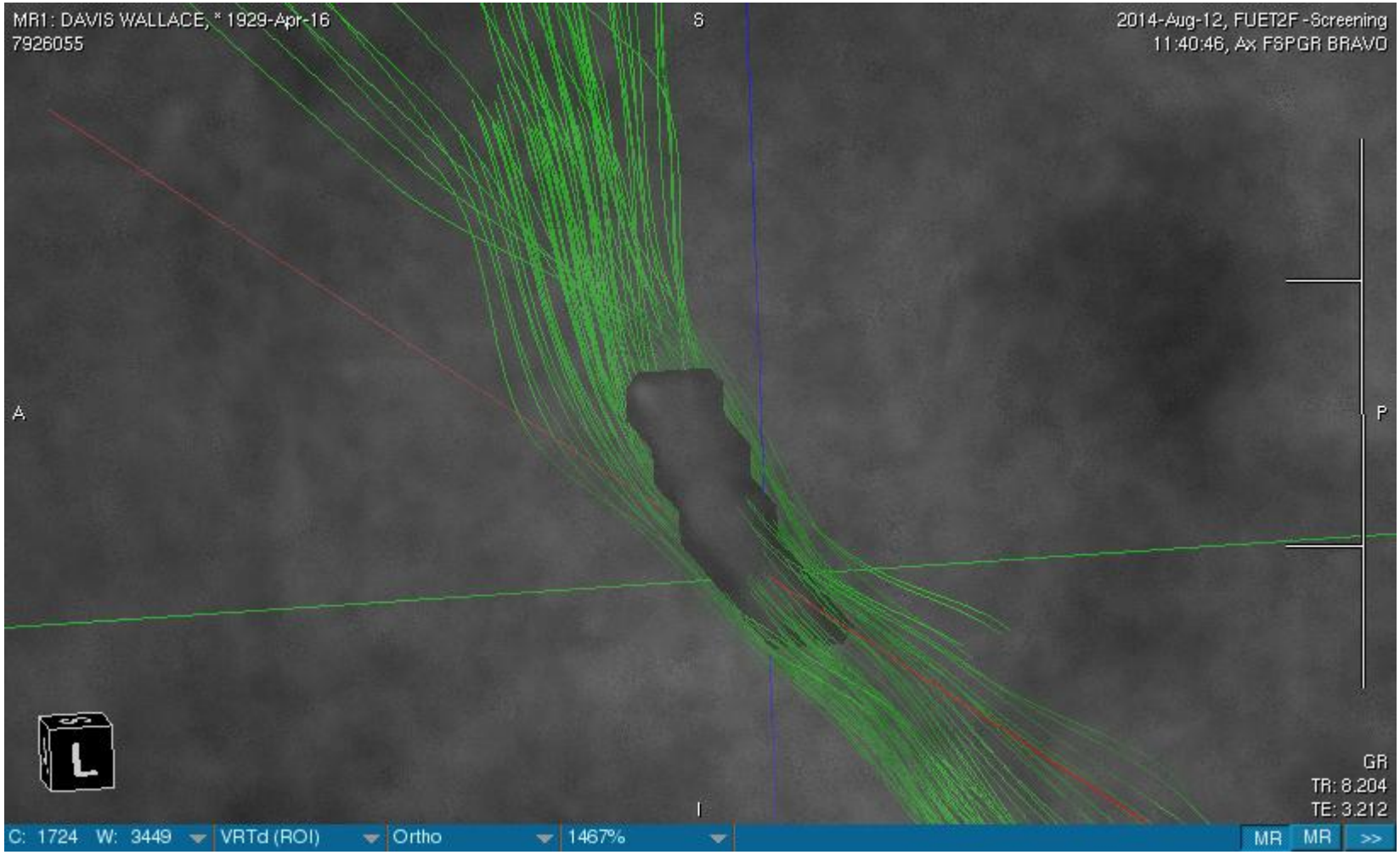
T-VIM anterior coordinate - Imaging cohort




10.0
8.0
6.0
4.0
2.0
.0
Mean distance from PC
ET patients
Controls
Category
Error bars: 95% CI

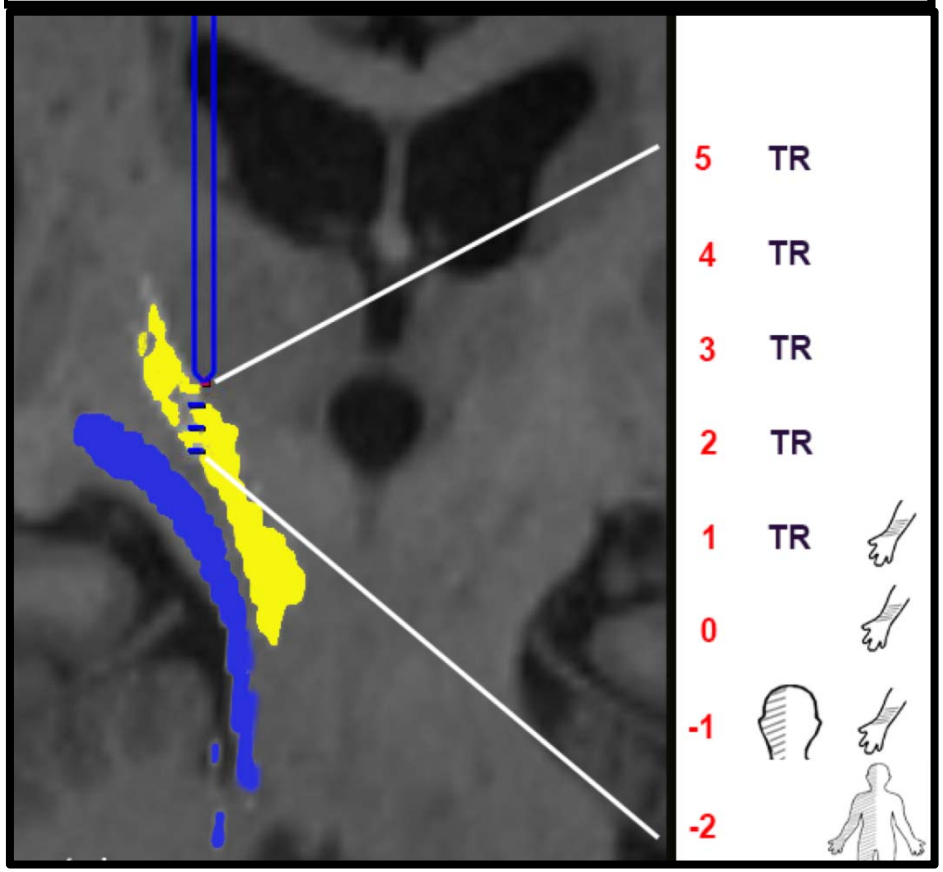
P=0.048

Comparison with Guyot's method

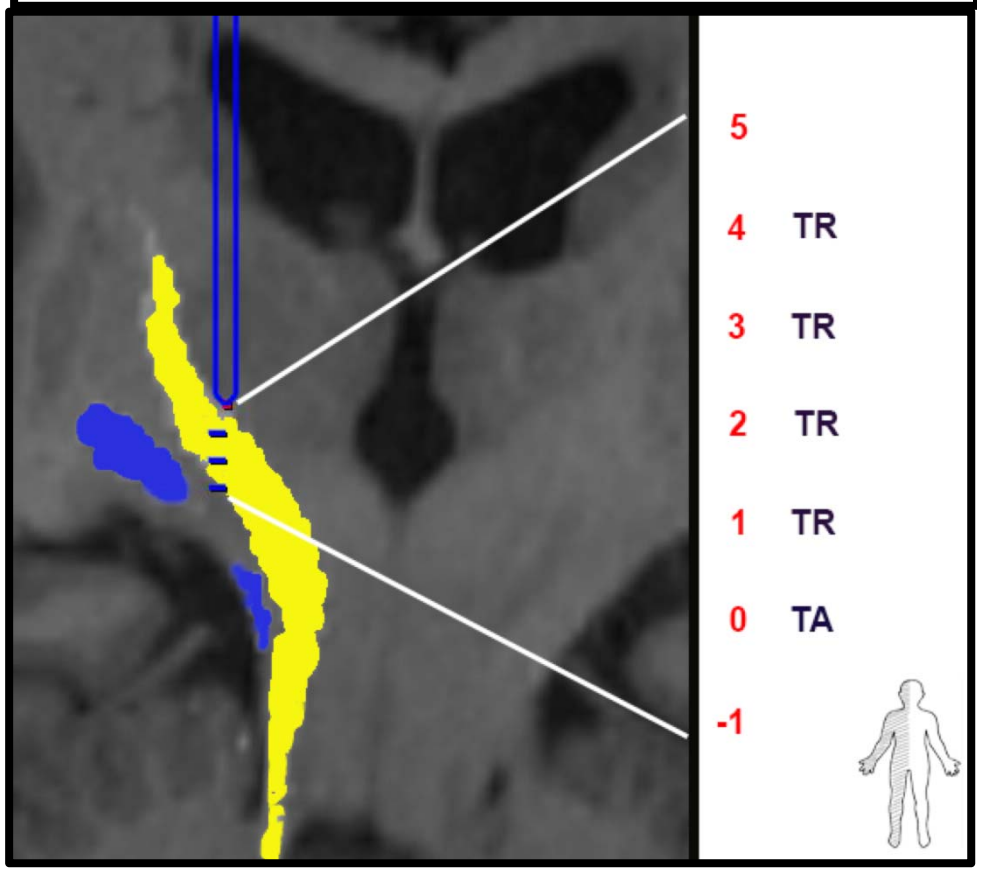


T-VIM validation - Operative cohort

Track 1, 6 mm anterior to PC

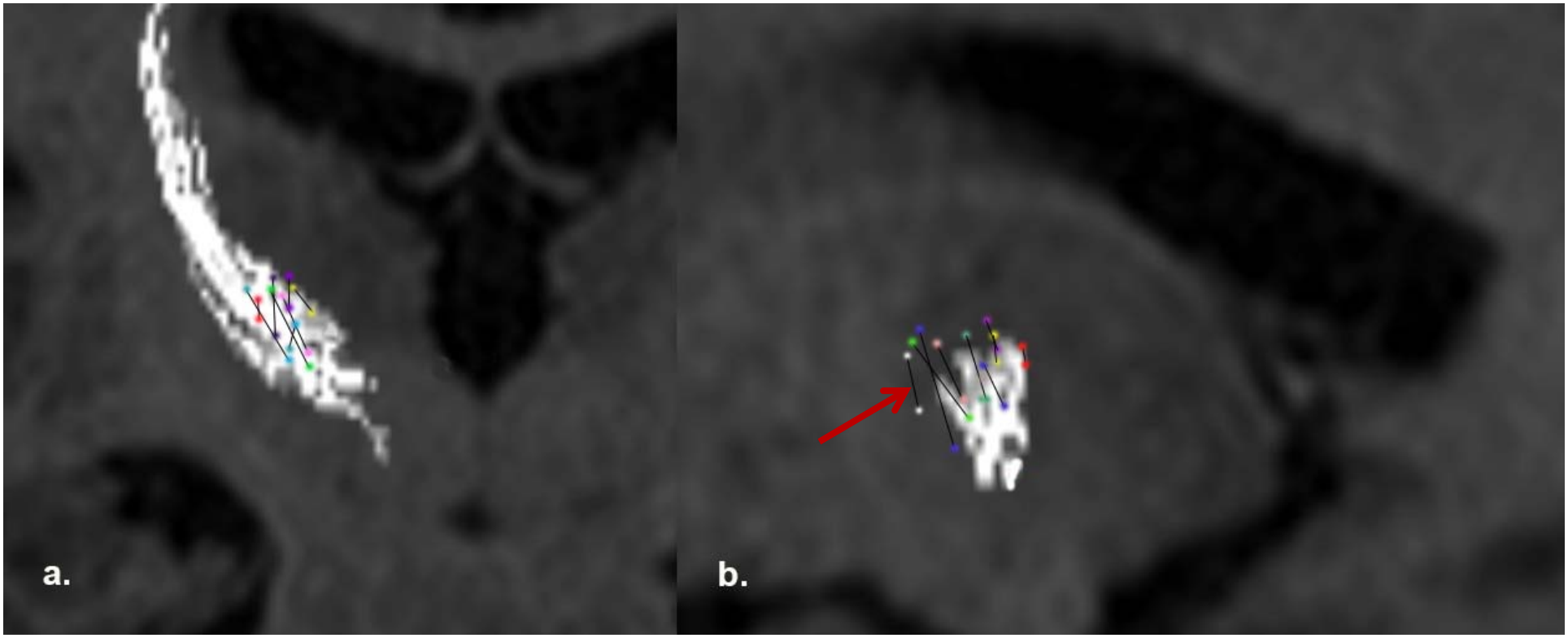


Track 2, 8 mm anterior to PC



The Euclidian distance between surgically identified VIM and T-VIM 1.6±1.1 mm)

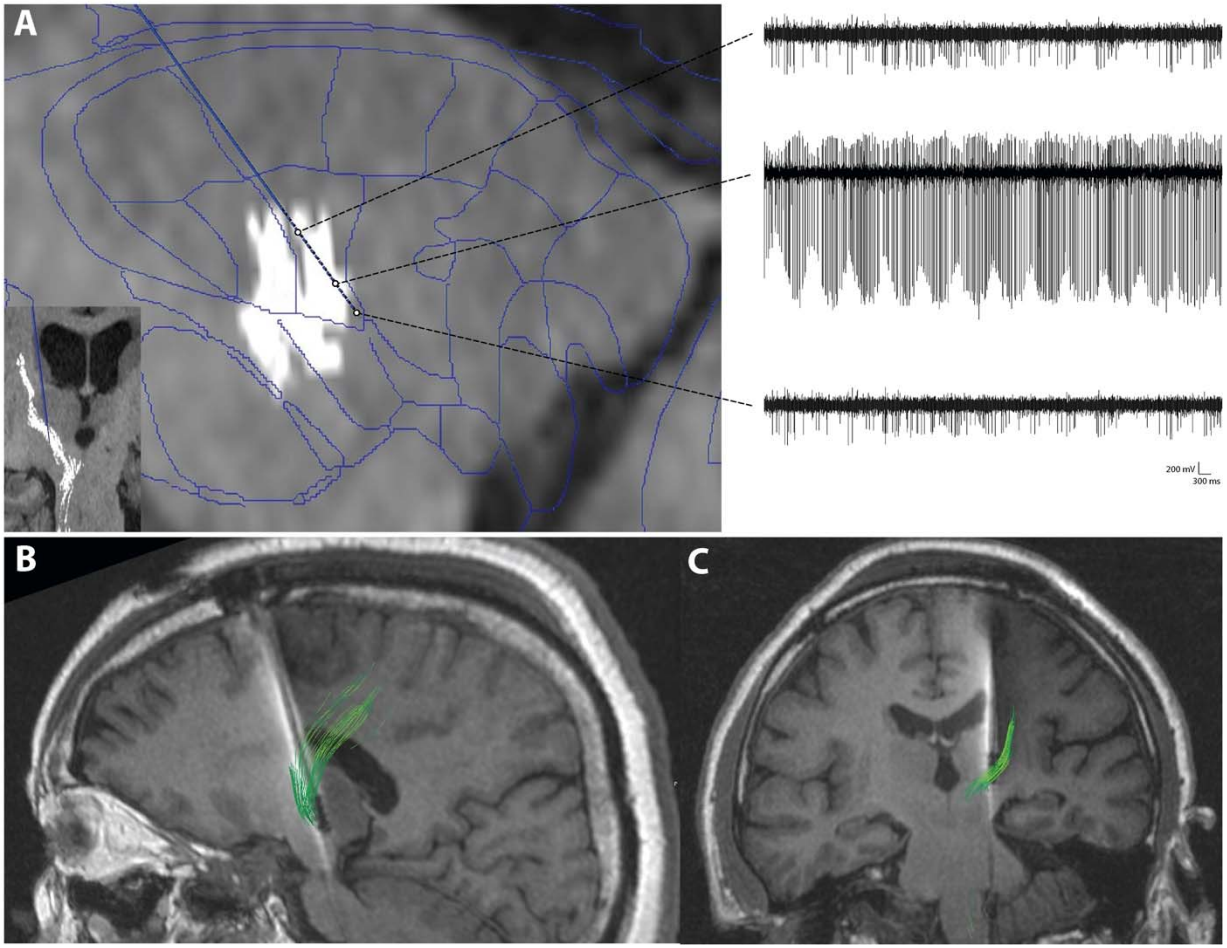
Sites of tremor efficacy correspond with T-VIM



9 trajectories in 6 patients

- 8 trajectories with tremor improvement – within T-VIM
- 1 trajectory without tremor improvement – anterior to T-VIM

Electrophysiology correlates of T-VIM



JNS 2016 (in press)

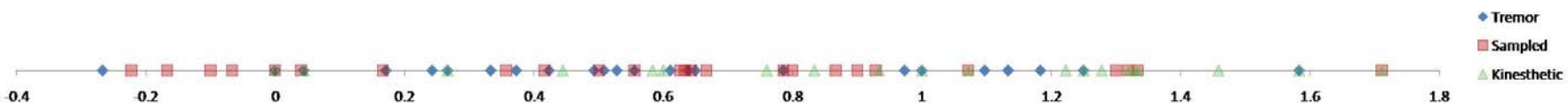
Electrophysiology correlates of T-VIM

- 6 patients
  - 9 microelectrode recording tracks
  - 73 cells recorded (kinesthetic cells, n= 20 and tremor cells n= 26)
  - 27 cells analyzed with spike analysis
    - 18 within T-VIM, 5 dorsal and 4 cells ventral to T-VIM
- Length of VIM trajectory normalized across subjects on a scale of 0 to 1
  - 1 corresponds to the top of T-VIM
  - 0 corresponds to the bottom of T-VIM

JNS 2016 (in press)

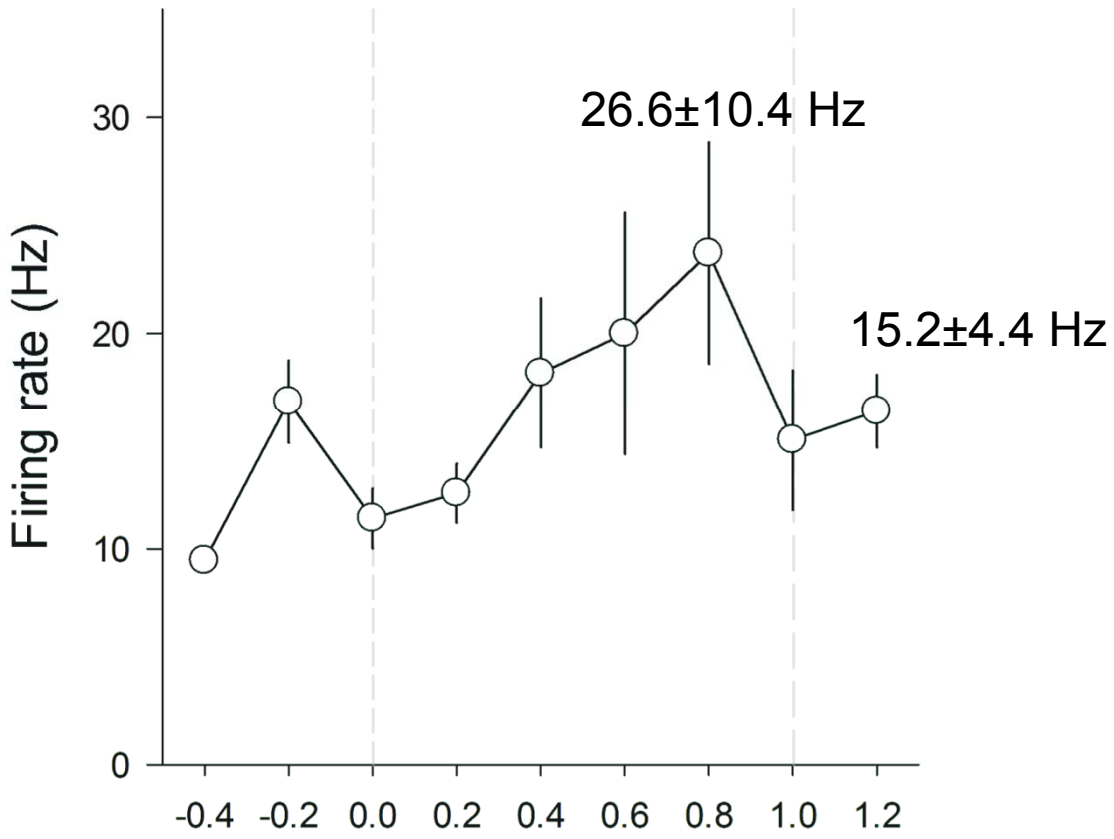
Electrophysiology correlates of T-VIM

- Distribution of cells was significantly different
  - Kinesthetic cells in the dorsal T-VIM (mean normalized depth = 0.95±0.49) versus tremor cells in the ventral T-VIM (mean normalized depth = 0.63±0.44, two-sample t-test, *p* = .03)



JNS 2016 (in press)

Electrophysiology correlates of T-VIM



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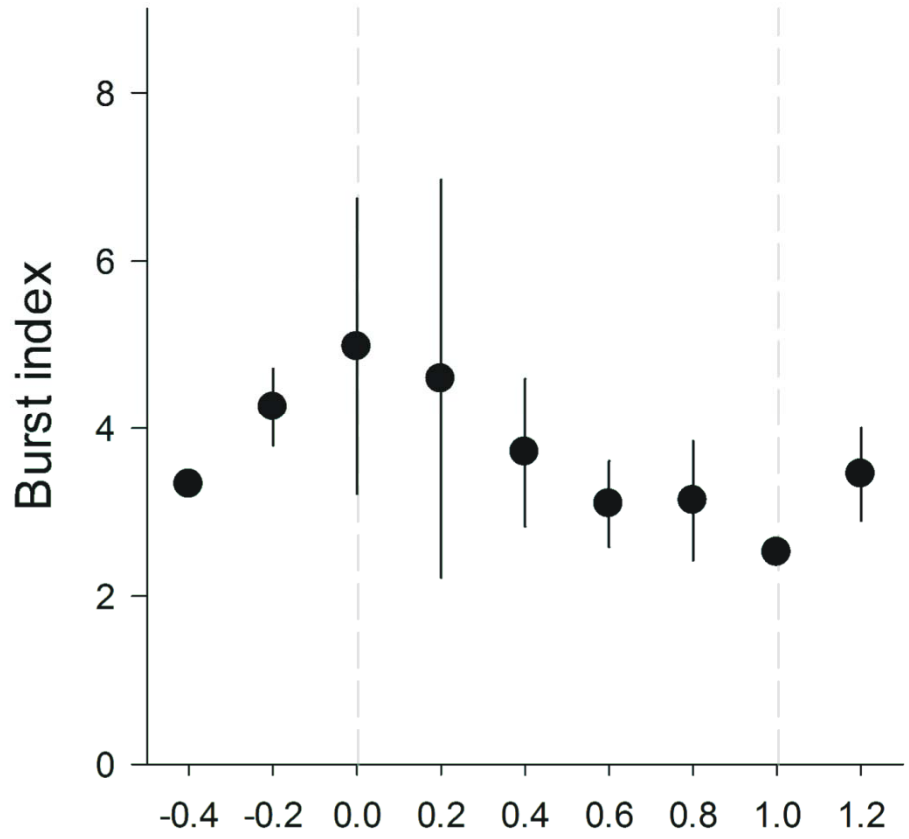
Electrophysiology correlates of T-VIM



Cells recorded towards the bottom of T-VIM have a higher burst index (one-way ANOVA, $p < .001$)

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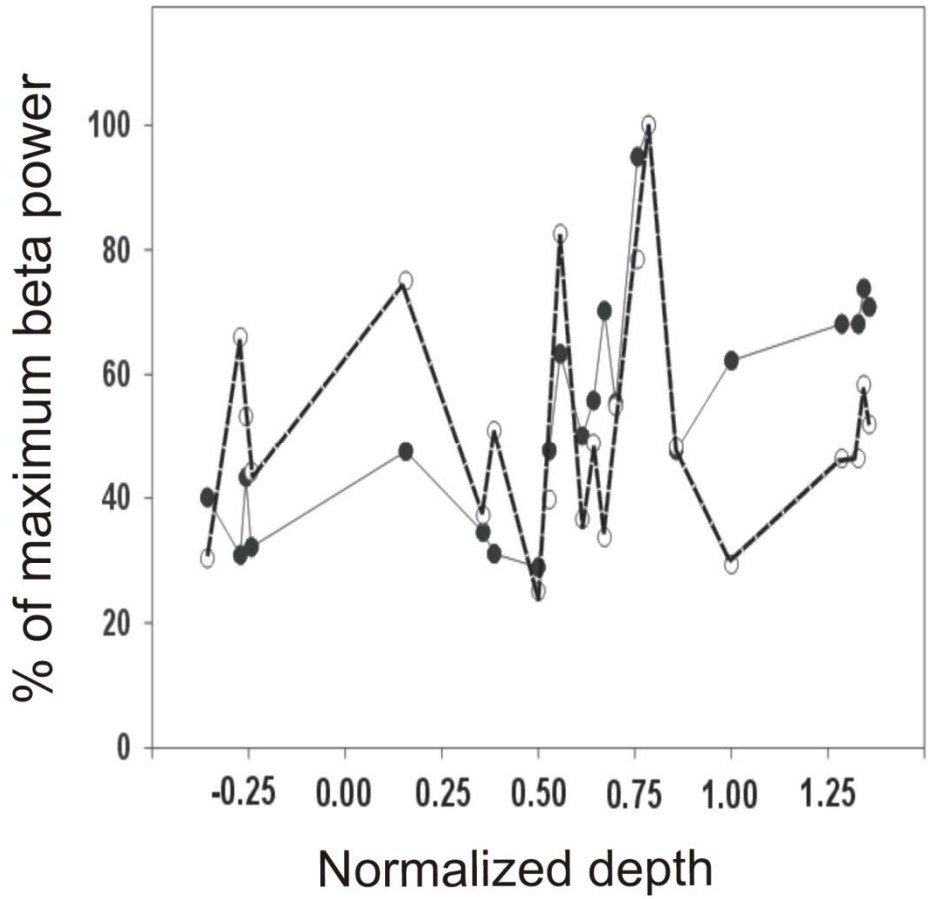
Electrophysiology correlates of T-VIM



Trend towards higher β-power in dorsal T-VIM (correlation (R^2) between β-power and normalized depth = 0.35, p = .08)

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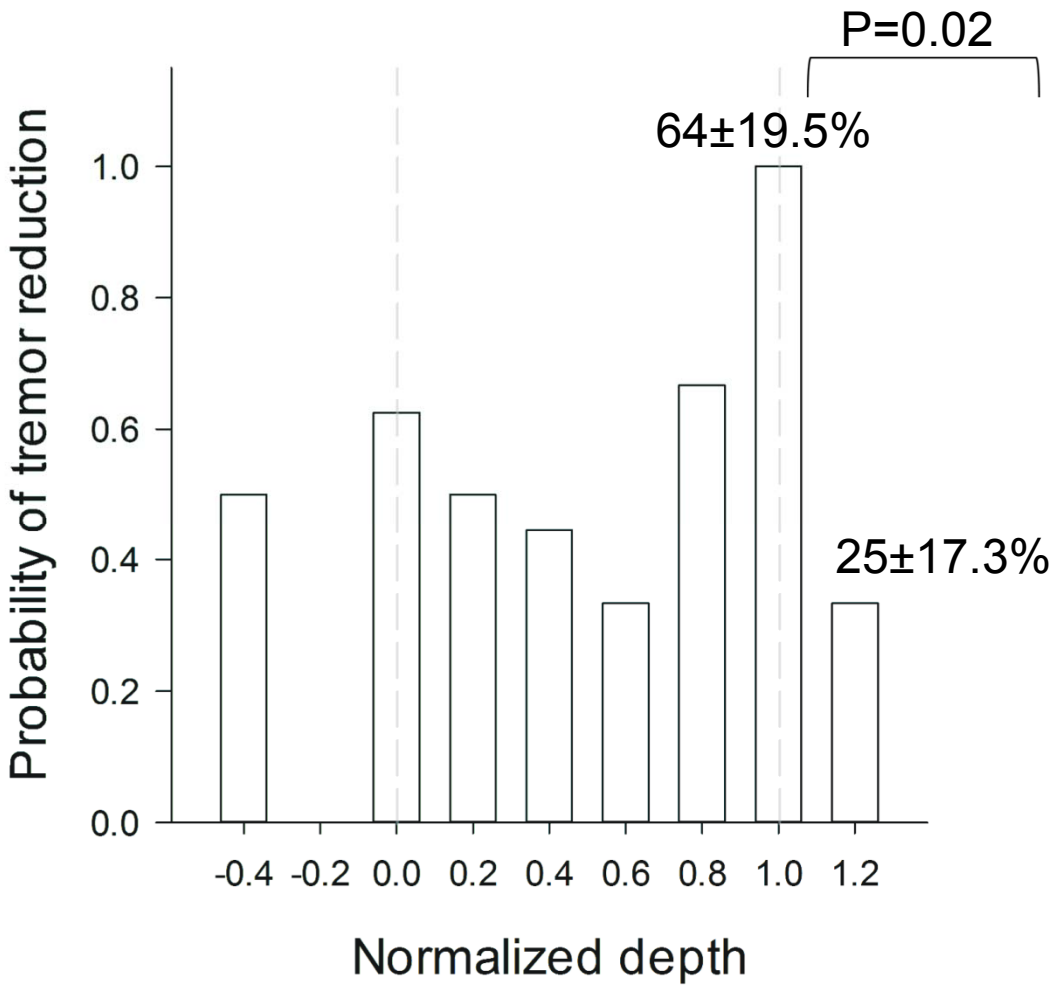
Electrophysiology correlates of T-VIM



Tremor reduction
(4 point tremor scale)

0% - 0 point
<50% - 1 point
≥50% - 2 points
100% - >2 points

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Future direction

- Clinical outcomes associated with T-VIM targeting
  - Tremor outcomes
  - Side effect profiles
  - Correlation with long-term durability
  - Targeting tremor somatotopy
- Neuroimaging markers for efficacious network modulation for other indications
  - Parkinson's disease - Globus pallidus (Gpi)
  - Epilepsy - Anterior nucleus (AN)

Initial results of T-VIM sonication

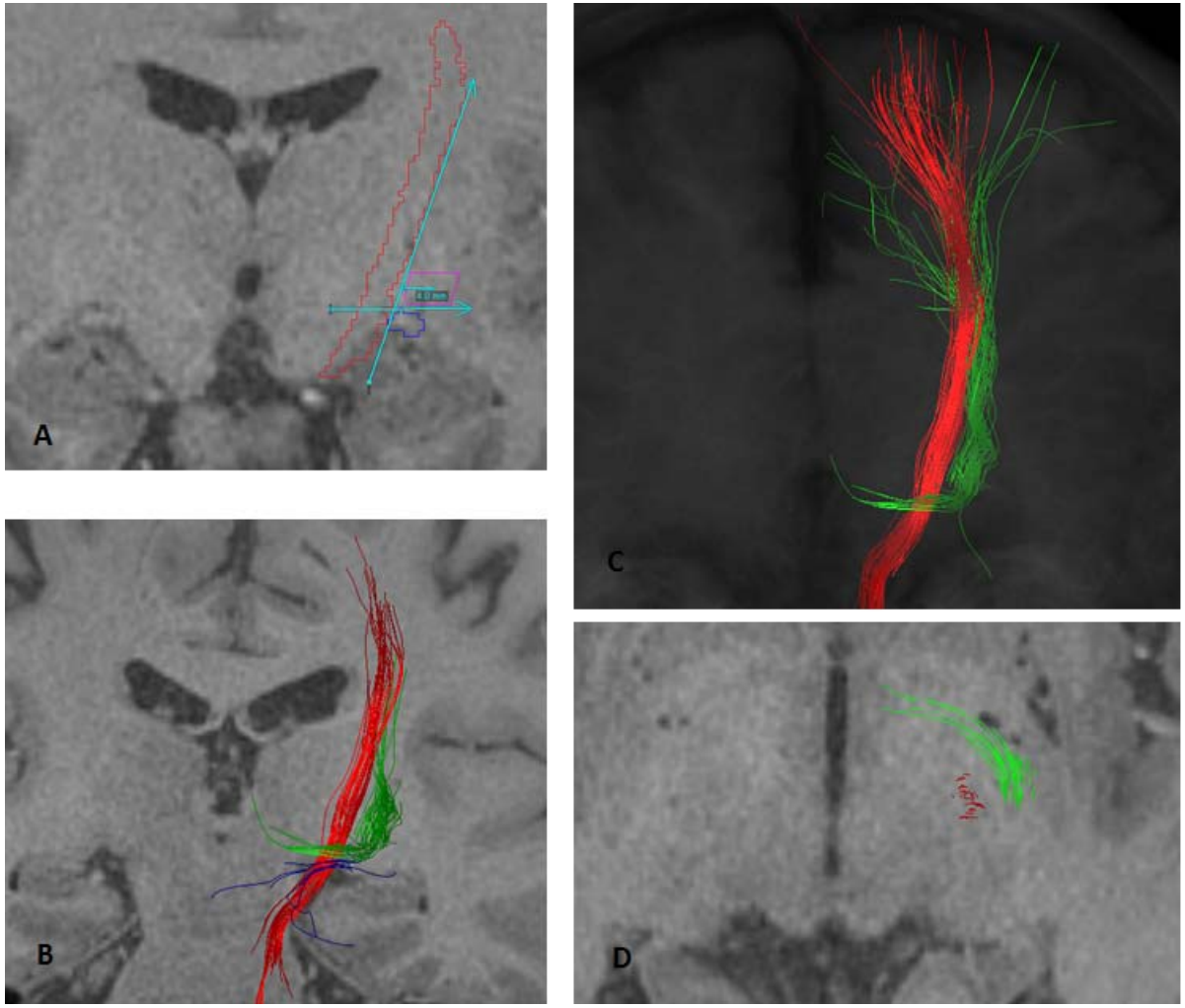
- 7 patients with ET
- Intraoperative clinical efficacy
  - 10 second therapeutic sonication (>55 °C)
  - >50% tremor reduction
- Side effect profile
  - No side effects related to pyramidal tract lesion
  - No side effects related to medial lemniscus lesion
- Surgical procedure
  - Operative time – Sonication time 81.6±3.3 minutes
  - Number of sonications – 13.4±8.9
  - Need for target optimization – only for tremor topology
    - No instances of changes in target location due to side effects

Initial results of T-VIM sonication in ET

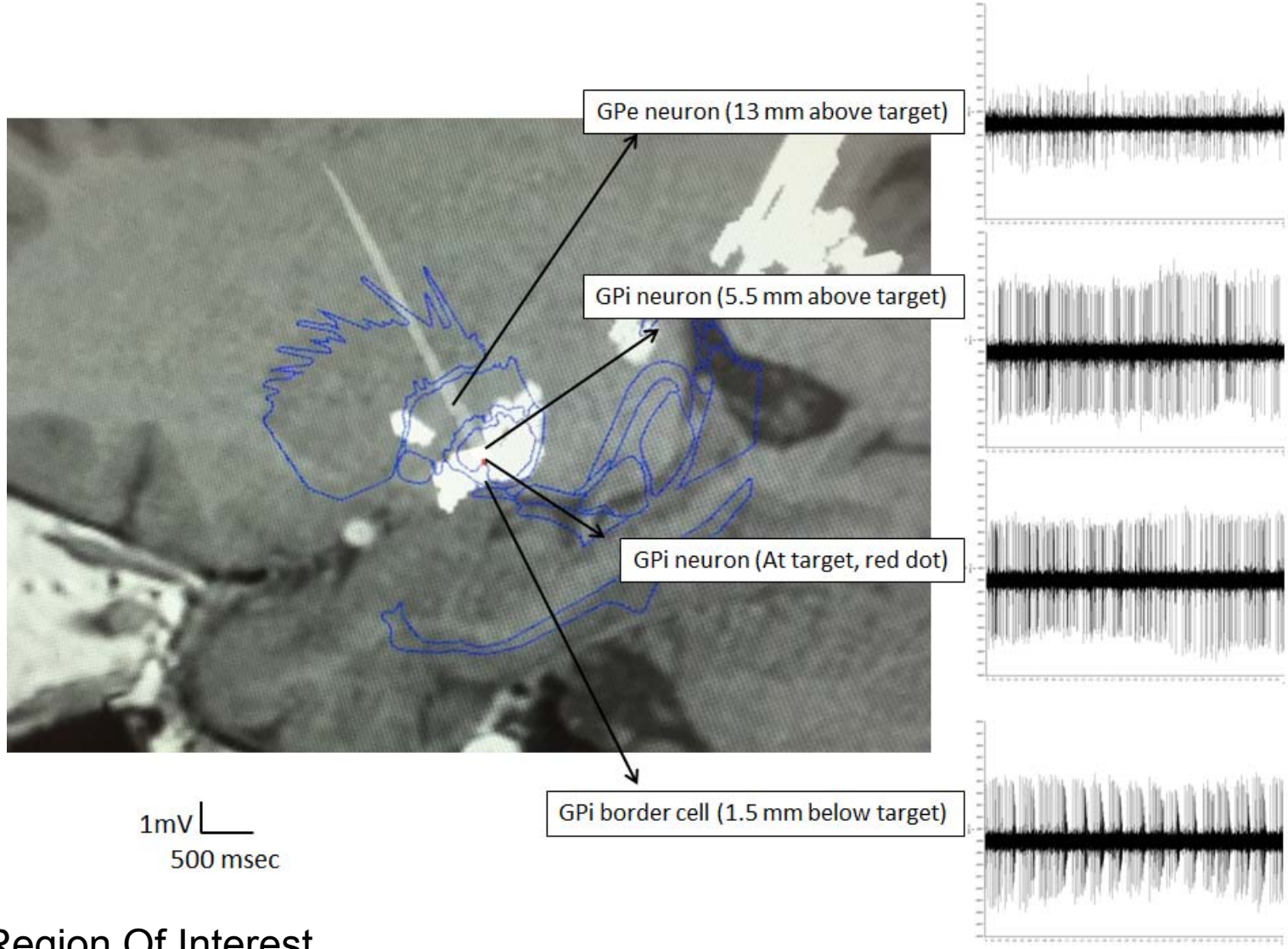
Demographics Age (in yrs) /Gender	Distance T-VIM & lesion epicenter (in mm)	Distance standard target & lesion epicenter (in mm)	Pre op CRST	Post op CRST (1 month)
71/Male	1.8	.2	45	16
75/Female	0.7	3.5	50	22
92/Female	0.9	6.1	88	60
77/Male	0.5	1.3	76	29
72/Male	1.3	5.8	65	30
62/Male	0.2	3.2	51	30
59/Female	.04	4.5	-	-
	0.7±0.6*	3.6±2.1*	62.1±15.5#	31.2±15.2#

* $p = 0.012$ # $p = 0.005$

Tractography-based GPi targeting for modulation of motor networks

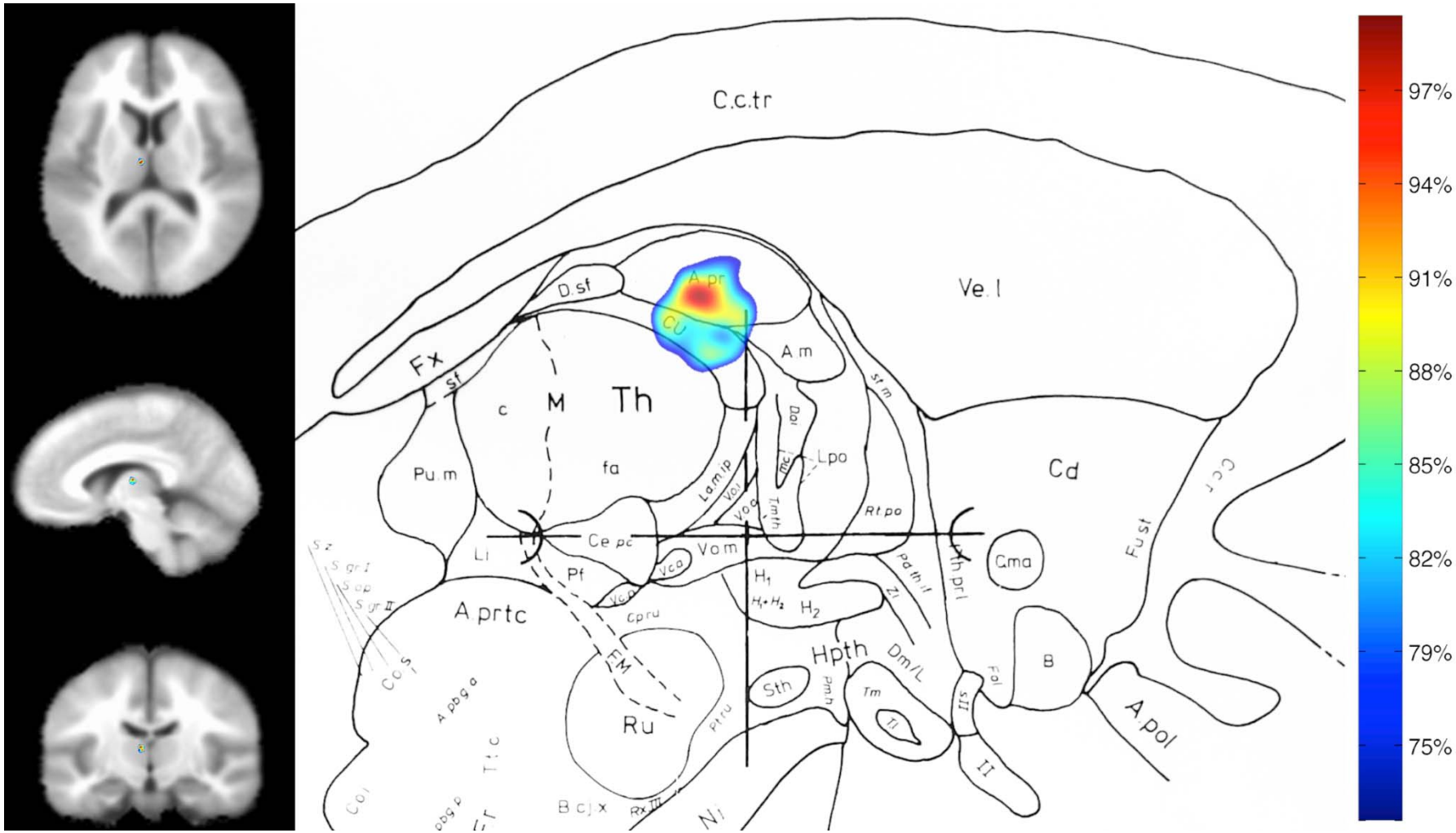


Structural connectivity of GPi ROI - Biomarker of GPi electrophysiology



ROI – Region Of Interest

Modulation of epilepsy network - Efficacious stimulation target within AN



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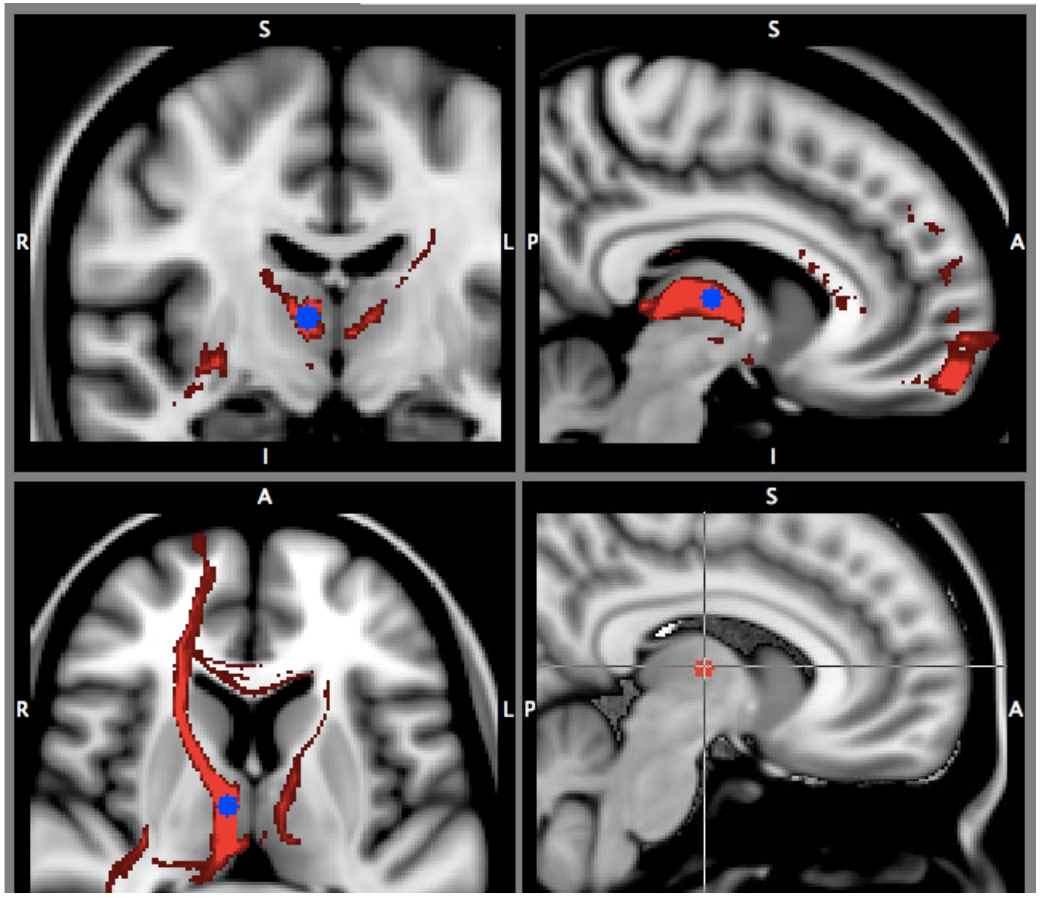
Structural connectivity of AN ‘hotspot’



Manuscript in preparation

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