"What's Shaking with Essential Tremor Nowadays?"

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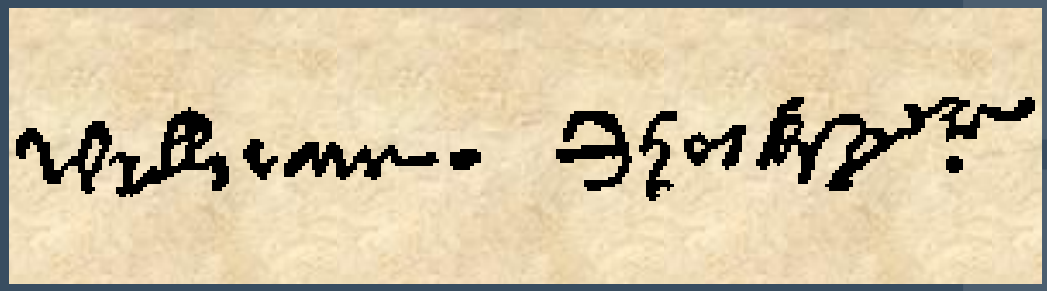
- 10 November 2023

Purpose

- Recognize important reasons why an Essential Tremor diagnosis should be considered in patients
- Recognize history and examination findings which lead to a diagnosis of Essential Tremor
  - To appreciate the nuances between different tremor types
  - To appreciate the important clinical clues that reliably separate tremors (essential tremor versus Parkinson's disease)
- To understand that numerous treatment strategies (medical, surgical and technological) exist for essential tremor

Tremor: Historical Perspectives

- Oldest medical condition mentioned in literature
- Bible – Psalms 99:1
  - “The Lord is king; let the peoples tremble!”
    - Attributed to King David (1040 – 970 BC)
- Shakespeare
  - “the palsy, and not fear, provokes me” History of Henry VI, Part II
  - “The fear whereof doth make him shake and shudder” Venus and Adonis



What is Tremor?

- Most common movement disorder
- Rhythmic oscillatory movement of agonist and antagonist muscles
- Tremors can reflect a “normal” function of the body
  - Shivering
  - Shaking when enraged or frightened
  - Comforting mechanism – stereotypy
  - DM patients with hypoglycemia
  - Alcoholics entering DTs

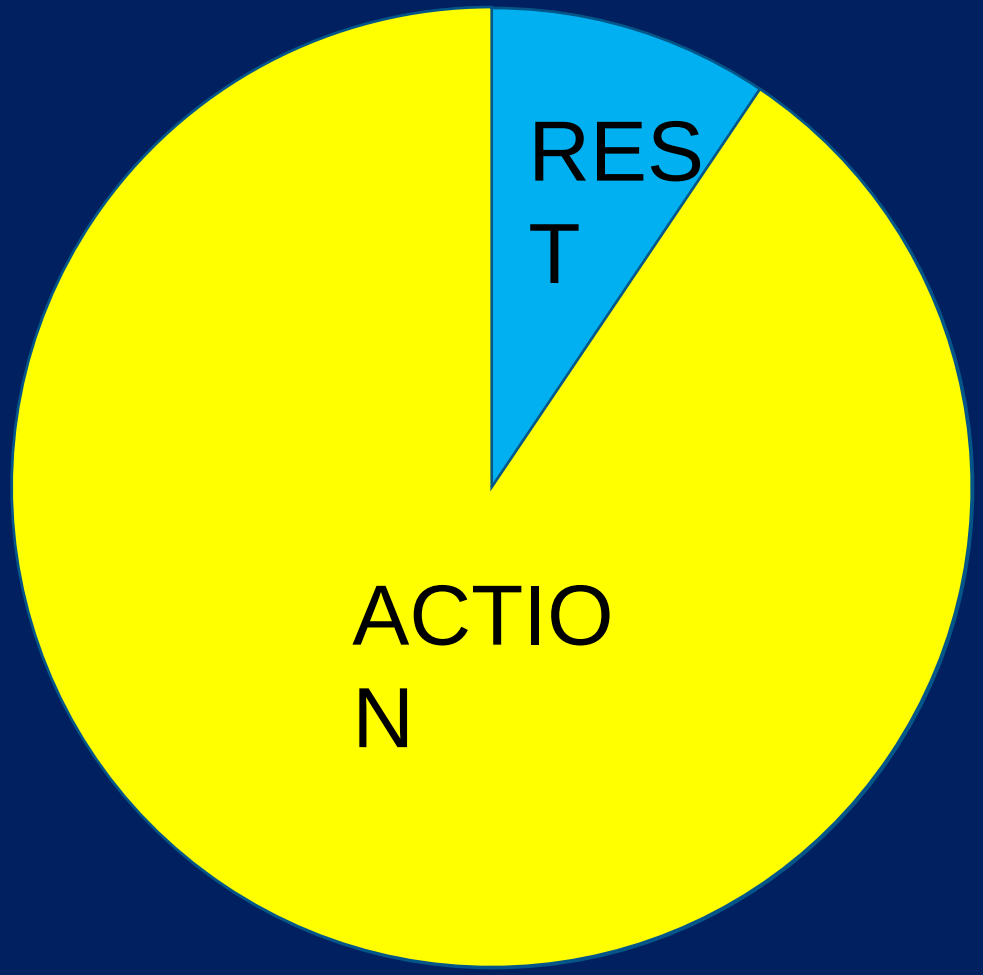
Classification and Characteristics of Tremor

Type of tremor	*Frequency*	*Amplitude*	*Occurrence*	*Examples*
Rest tremor	Low to medium (3 to 6 Hz)	High; decreases with target-directed movement	Limb supported against gravity; muscles are not activated	Parkinson's disease; drug-induced parkinsonism (neuroleptics; metoclopramide [Reglan])
Action tremor	—	—	Any voluntary muscle contraction	
Postural tremor	Medium to high (4 to 12 Hz)	Low; increases with voluntary movement	Limb maintains position against gravity	Physiologic tremor; essential tremor; metabolic disturbance; drug or alcohol withdrawal
Kinetic tremor				
Simple kinetic	Variable (3 to 10 Hz)	Does not change with target-directed movement	Simple movements of the limb	—
Intention	Low (< 5 Hz)	Increases with target-directed movement	Target-directed movement	Cerebellar lesion (stroke, multiple sclerosis, tumor); drug-induced (lithium, alcohol)
Isometric tremor	Medium	Variable	Muscle contraction against stationary objects	Holding a heavy object in one hand
Task-specific tremor	Variable (4 to 10 Hz)	Variable	Occurs with specific action	Handwriting tremor; musician's tremor

REST

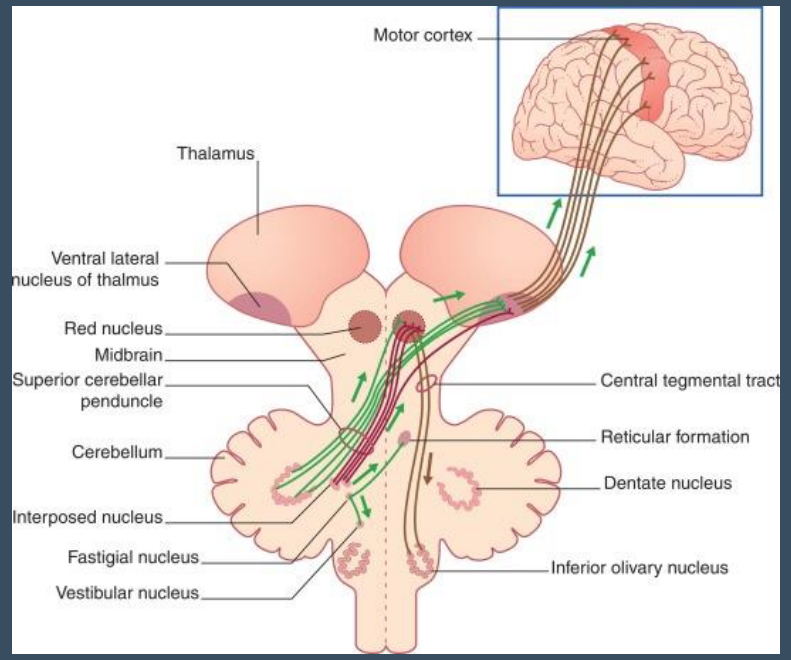
ACTIO
N

Proportion of Rest Tremor to Action Tremor



Pathology of Essential Tremor

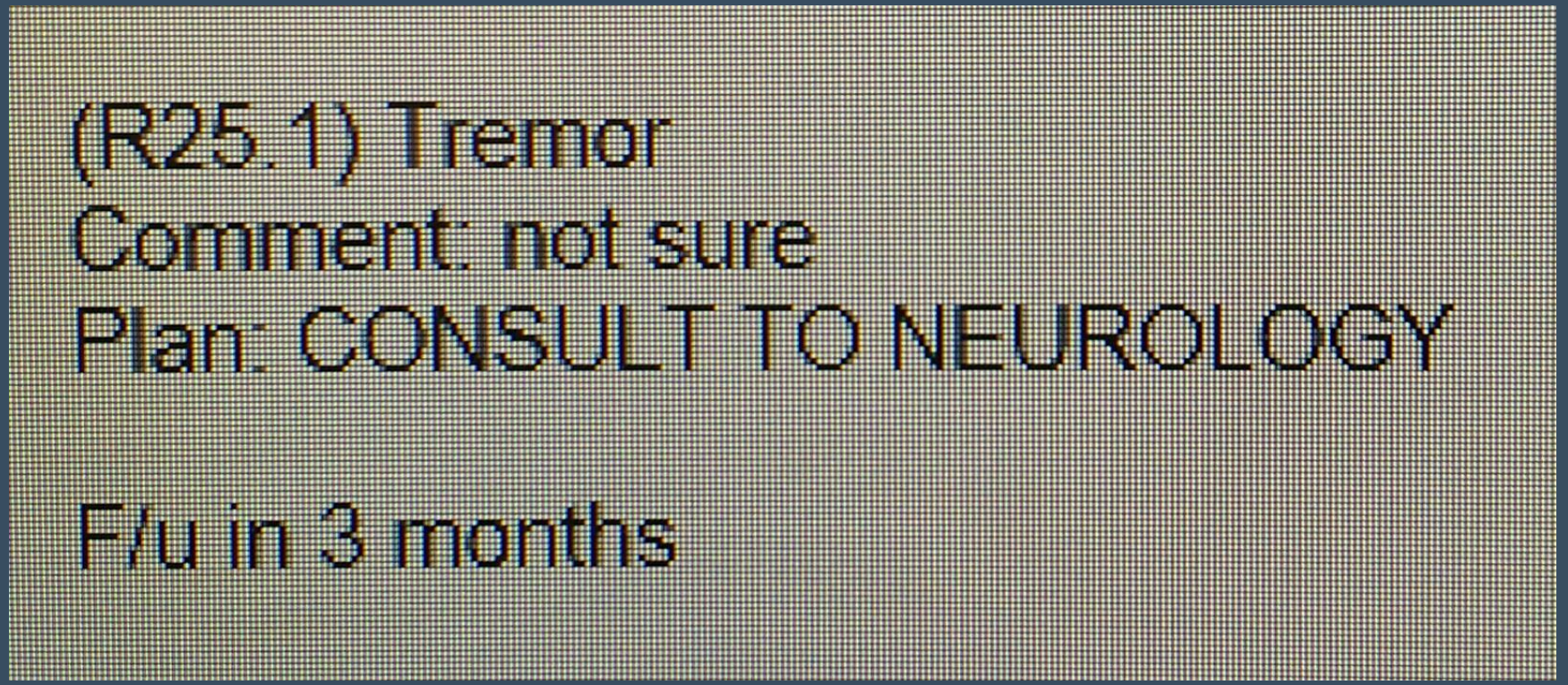
- The cerebellum and/or cerebellothalamocortical pathways are involved
- Neuroimaging (HCT and MRI) tend to be normal



How Does Essential Tremor Get Treated?

Or

Why Should I Go to A Movement Disorder Neurologist?


(R25.1) Tremor
Comment: not sure
Plan: CONSULT TO NEUROLOGY
F/u in 3 months

Differentiating Parkinson disease and essential tremor

Clinical features	Parkinson disease tremor	Essential tremor
Age at onset	>50	Bimodal 2nd and 6th decade
Gender	M≥W	M=W
Family history	>25 percent	>50 percent
Asymmetry	+++	+
Frequency	4 to 6 Hz	4 to 10 Hz
Character	At rest	Postural, kinetic
	Supination-pronation	Flexion-extension
Distribution	Hands, legs, chin, tongue	Hands, head, voice
Associated features	Bradykinesia, rigidity, gait difficulty, postural instability, micrographia	Deafness, dystonia, parkinsonism

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Criteria for diagnosis of essential tremor

Core criteria	Secondary criteria
Bilateral action tremor of the hands and forearms (but not rest tremor)	Long duration (>3 years)
Absence of other neurologic signs, with the exception of cogwheel phenomenon	Positive family history
May have isolated head tremor with no signs of dystonia	Beneficial response to alcohol

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UpToDate®

Family History

- 50% of patients will have 1st degree relative with ET
- LINGO1 (*Leucine rich repeat and Ig domain containing 1*) has been linked to ET – not all patients have gene nor do all people with gene get ET

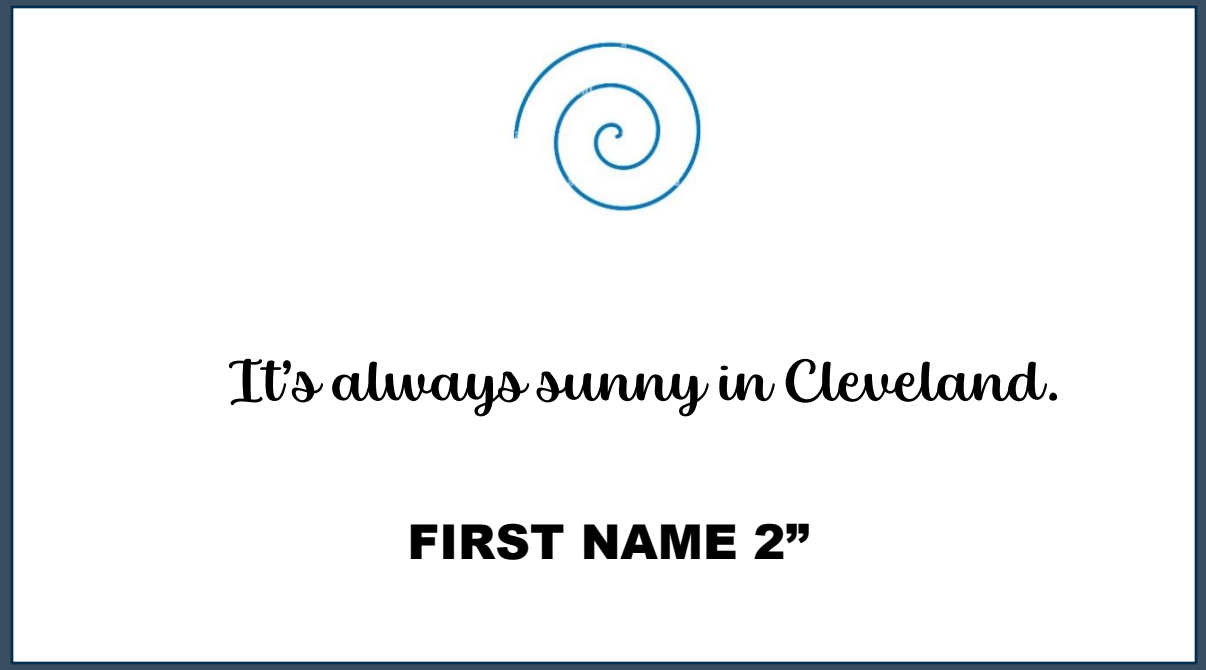
Medications that Cause Tremor

- Steroids
- Valproic Acid (VPA): Depakote, Depakene
- Asthma treatment: albuterol & theophylline
- Mood stabilizers: lithium carbonate & VPA
- Heart medications: amiodarone & procainamide
- Chemotherapy: thalidomide & cytarabine
- Immunosuppressant: cyclosporine
- Antidepressants: TCAs and SSRIs
- Epinephrine
- Stimulants: Weight loss medication (tiratricol), caffeine and amphetamines
- Thyroid replacement: excessive levothyroxine

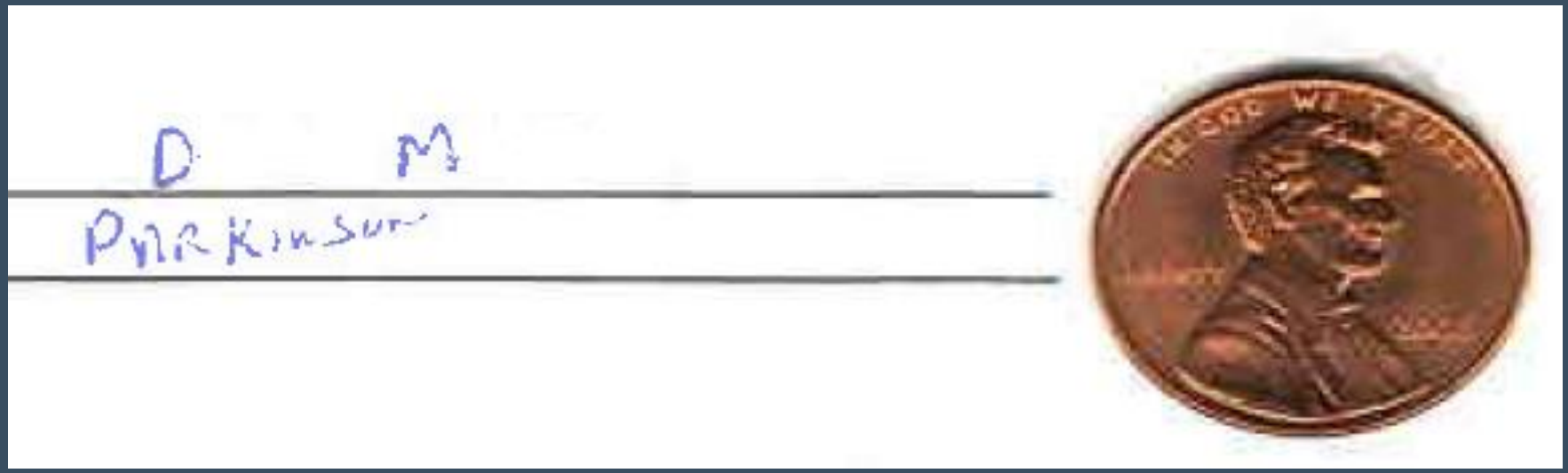
Emotional Activation

Handwriting in the Diagnosis of ET

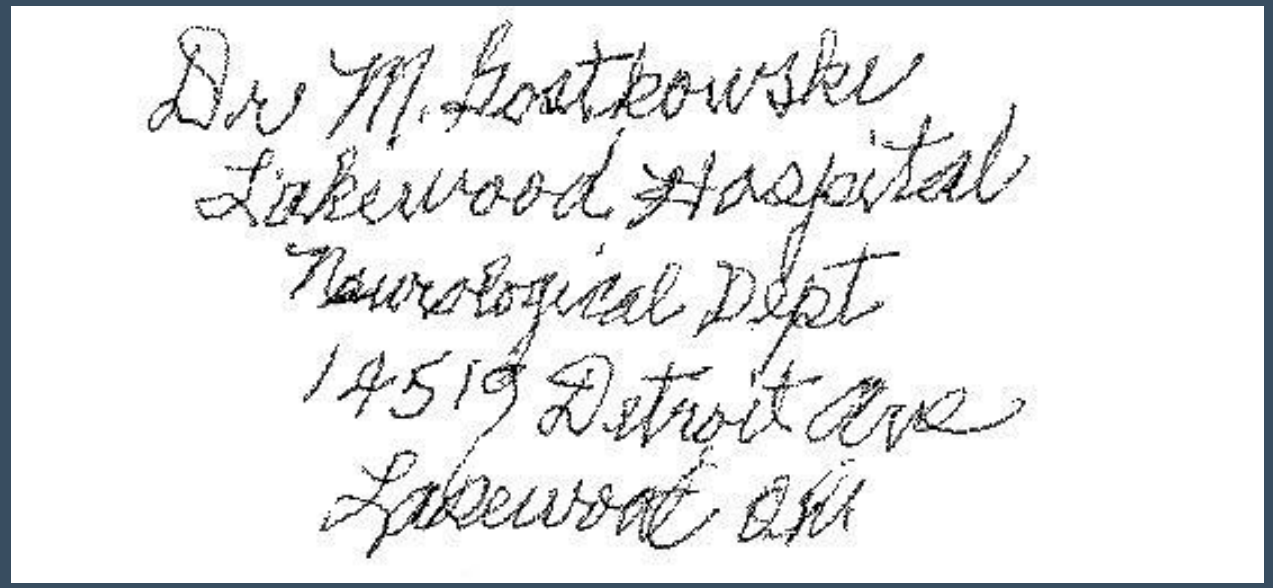
- This is a valuable tool
- It is quick and simple



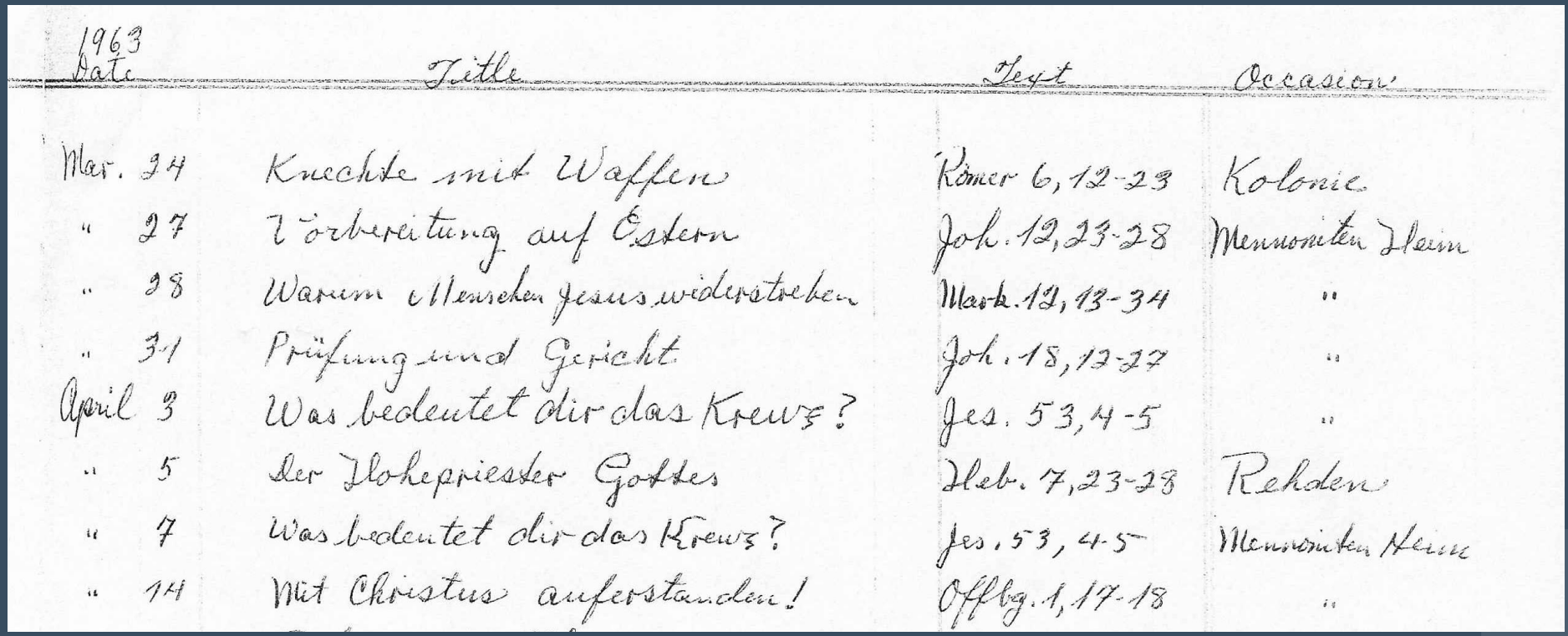
Handwriting in PD



Handwriting in ET



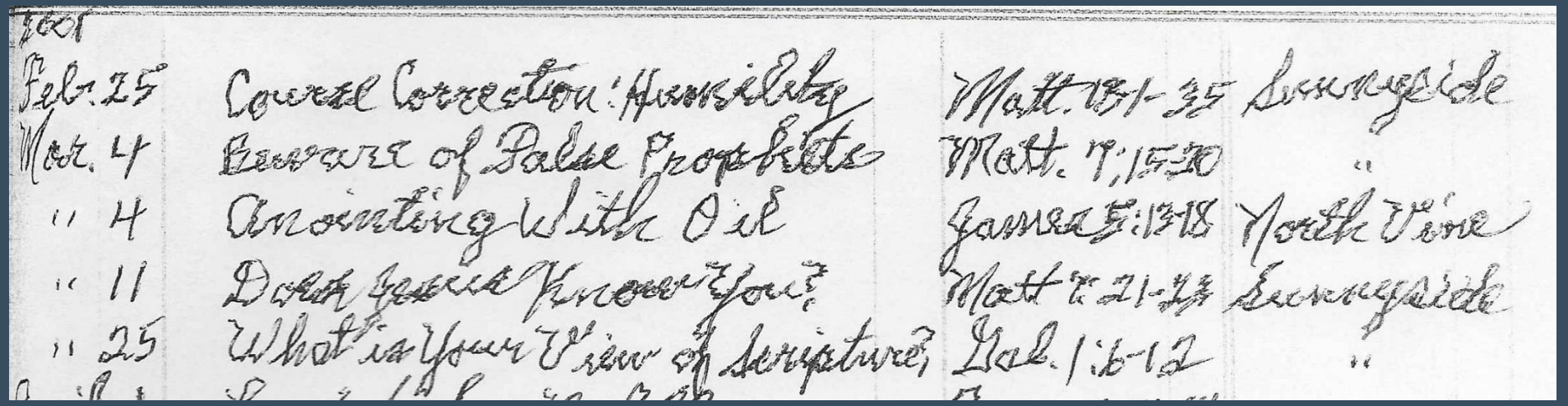
Handwriting for Diagnosis



1963 Date	Title	Text	Occasion
Mar. 24	Knechte mit Waffen	Römer 6, 12-23	Kolonie
" 27	Vorbereitung auf Ostern	Joh. 12, 23-28	Mennoniten Heim
" 28	Warum Menschen Jesus widerstreben	Mark. 12, 13-34	"
" 31	Prüfung und Gericht	Joh. 18, 12-27	"
April 3	Was bedeutet dir das Kreuz?	Jes. 53, 4-5	"
" 5	Der Hohepriester Gottes	Heb. 7, 23-28	Rehden
" 7	Was bedeutet dir das Kreuz?	Jes. 53, 4-5	Mennoniten Heim
" 14	Mit Christus auferstanden!	Offbg. 1, 17-18	"

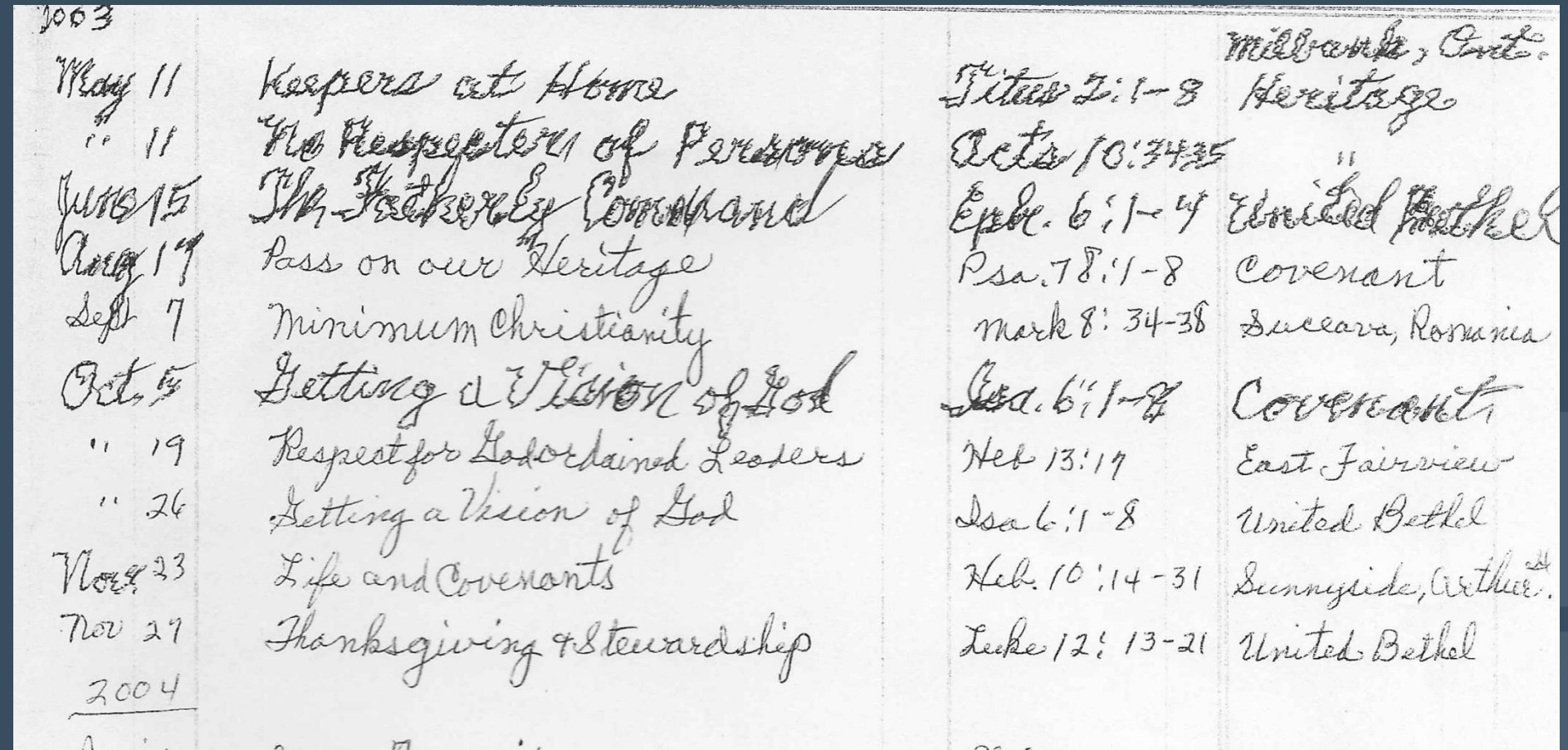
Date	Title	Text	Place
1984			
Sept. 30	Respect for My Parents	Eph. 6:1-3	East Fairview
Oct. 7	Financial Sowing & Reaping	2 Cor. 9:6-9	East Fairview
" 14	Integrity and Truthfulness	Acts 5:1-11	East Fairview
" 21	Nearer!	Mark 4:1-20	East Fairview
" 28	Which Way Am I Headed?	Luke 9:57-62	East Fairview
Nov. 3	Incarnate Love	Phil. 2:5-8	Bellwood Mem Chapel
" 4	Justification By Faith	Rom. 3:19-28	East Fairview

1992			
Jan. 5	First Things First	Matt. 6:19-34	East Fairview
" 19	Divorce and Remarriage	Matt. 19:3-12	East Fairview
" 26	Honourable Marriage	Heb. 13:4	East Fairview
Feb. 16	The Church at Pergamos	Rev. 2:12-17	East Fairview



2001

Feb. 25	Covered Correction: Humility	Matt. 18:1-35	Sunnyside
Mar. 4	Beware of False Prophets	Matt. 7:15-20	"
" 4	Anointing With Oil	James 5:13-18	North View
" 11	Does Jesus Know You?	Matt 7:21-23	Sunnyside
" 25	What is Your View of Scripture?	Gal. 1:6-12	"



2003

			Millbrook, Ont.
May 11	Keepers at Home	Titus 2:1-8	Heritage
" 11	The Responsibility of Parents	Deut 10:34-35	"
June 15	The Fathers Command	Eph. 6:1-4	United Bethel
Aug 17	Pass on our Heritage	Psa. 78:1-8	Covenant
Sept 7	Minimum Christianity	Mark 8:34-38	Suceava, Romania
Oct. 5	Getting a Vision of God	Isa. 6:1-8	Covenant
" 19	Respect for God ordained Leaders	Heb 13:17	East Fairview
" 26	Getting a Vision of God	Isa 6:1-8	United Bethel
Nov 23	Life and Covenants	Heb. 10:14-31	Sunnyside, Arthur.
Nov 27	Thanksgiving & Stewardship	Luke 12:13-21	United Bethel

2004

Lifelong Untreated Essential Tremor

DATscan

- 123i-FP-CIT single photon emission tomography
- Distinguishes patients with parkinsonian disorders from essential tremor (ET), drug-induced parkinsonism (DIP) and non-parkinsonian disorders
- SWEDD – scans without evidence of dopaminergic deficit

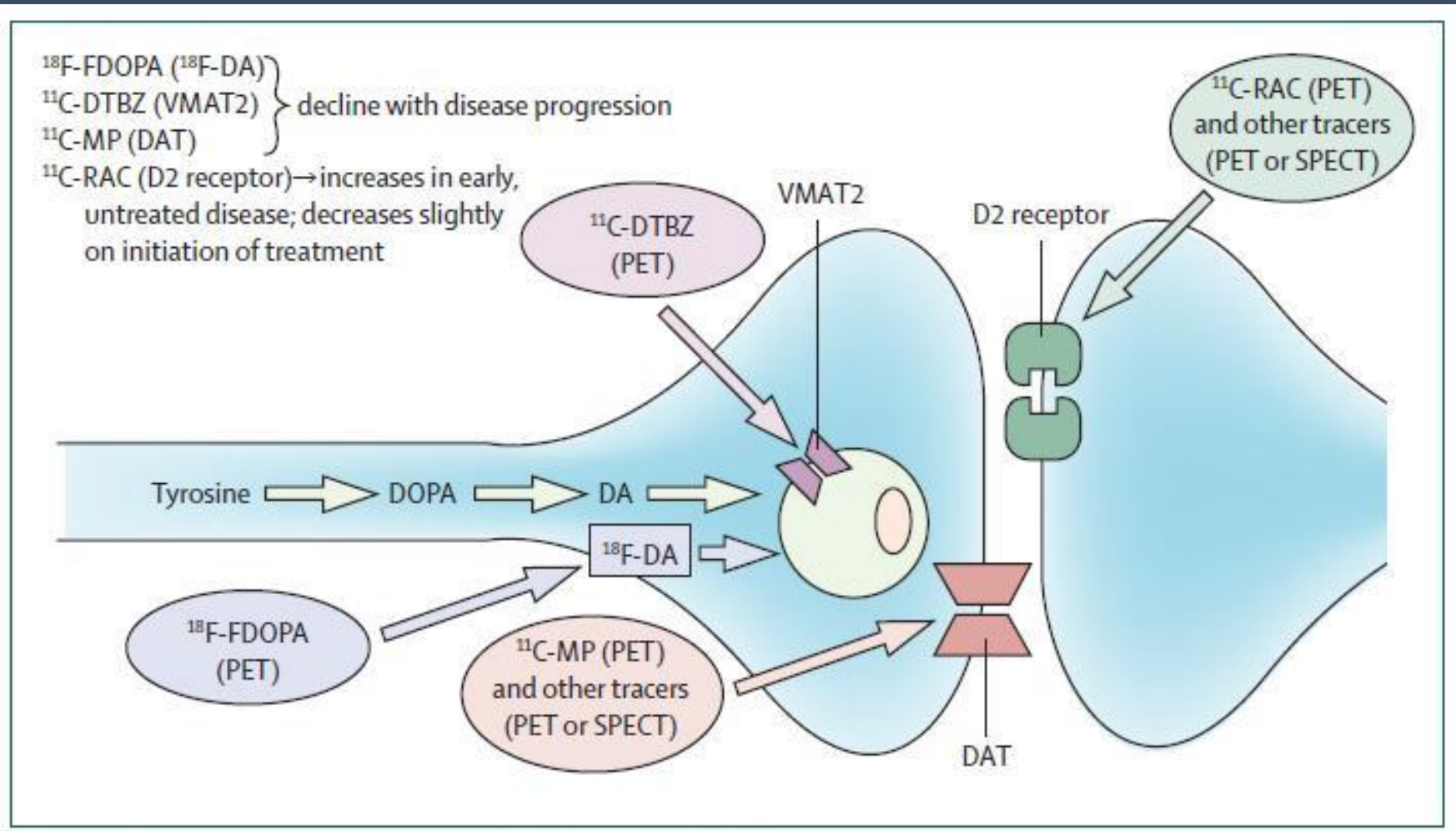


***Figure 1*: Dopaminergic nerve terminal labelled by radiotracers**

^{18}F-fluoro-L-dopa (^{18}F-FDOPA) is decarboxylated to ^{18}F-dopamine (^{18}F-DA) and stored in synaptic vesicles in a manner analogous to levodopa. The vesicular monoamine transporter type 2 (VMAT2) is labelled by ^{11}C-dihydrotetrabenazine (^{11}C-DTBZ), and the membrane dopamine transporter (DAT) can be labelled by ^{11}C-methylphenidate (^{11}C-MP) or various other agents suitable for PET or SPECT labelling. Dopamine D2 receptor availability can be labelled by ^{11}C-raclopride (^{11}C-RAC), which is sensitive to synaptic levels of dopamine, or by numerous other agents which might or might not be sensitive to endogenous dopamine, depending on their affinity.

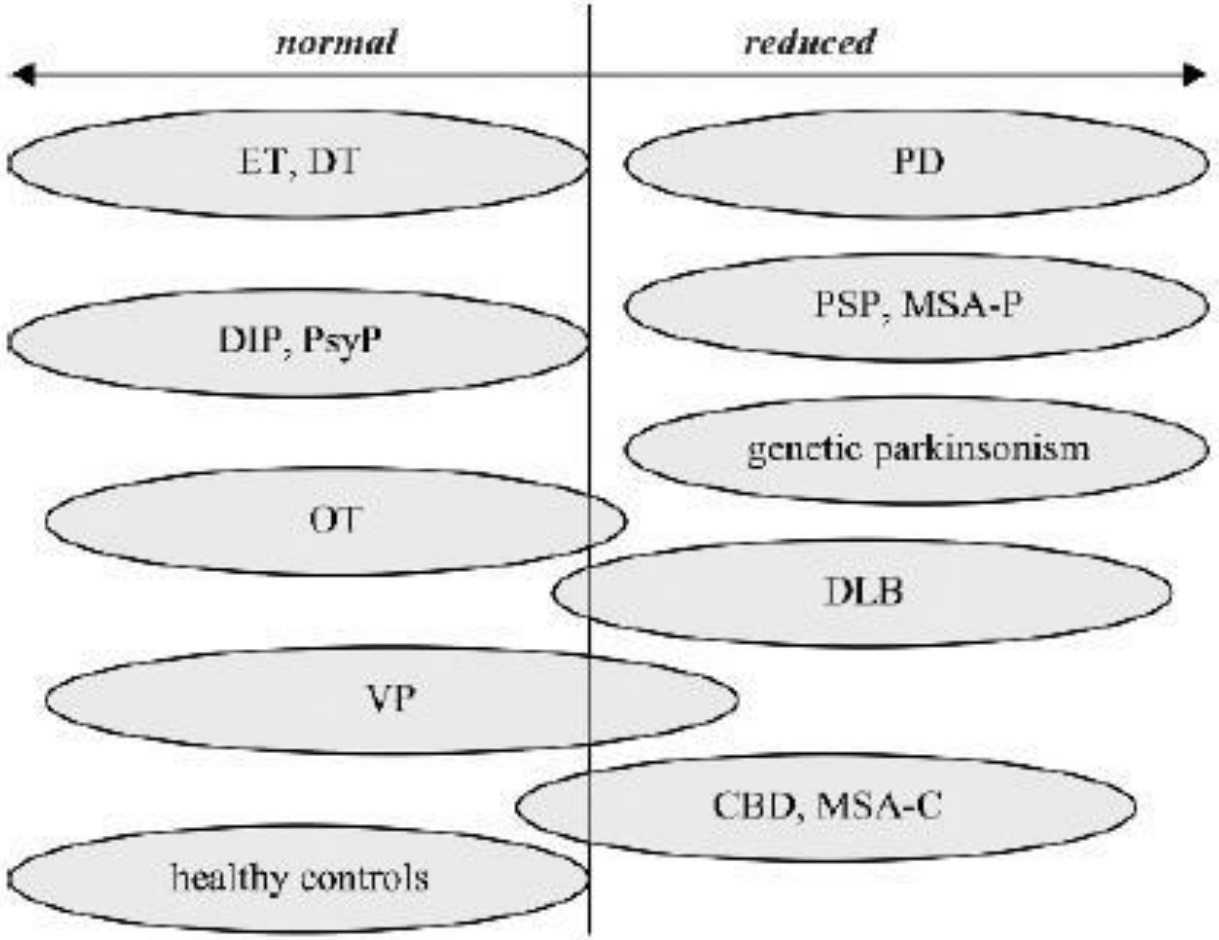
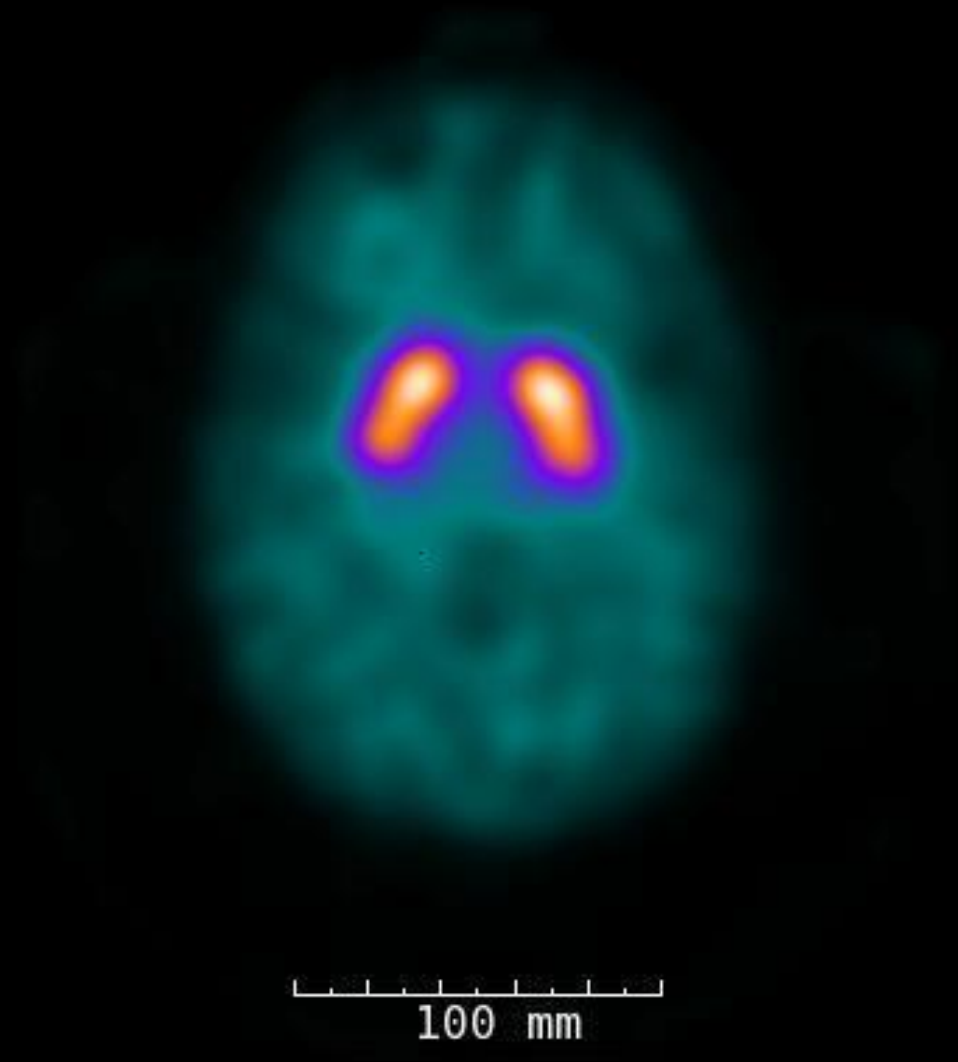
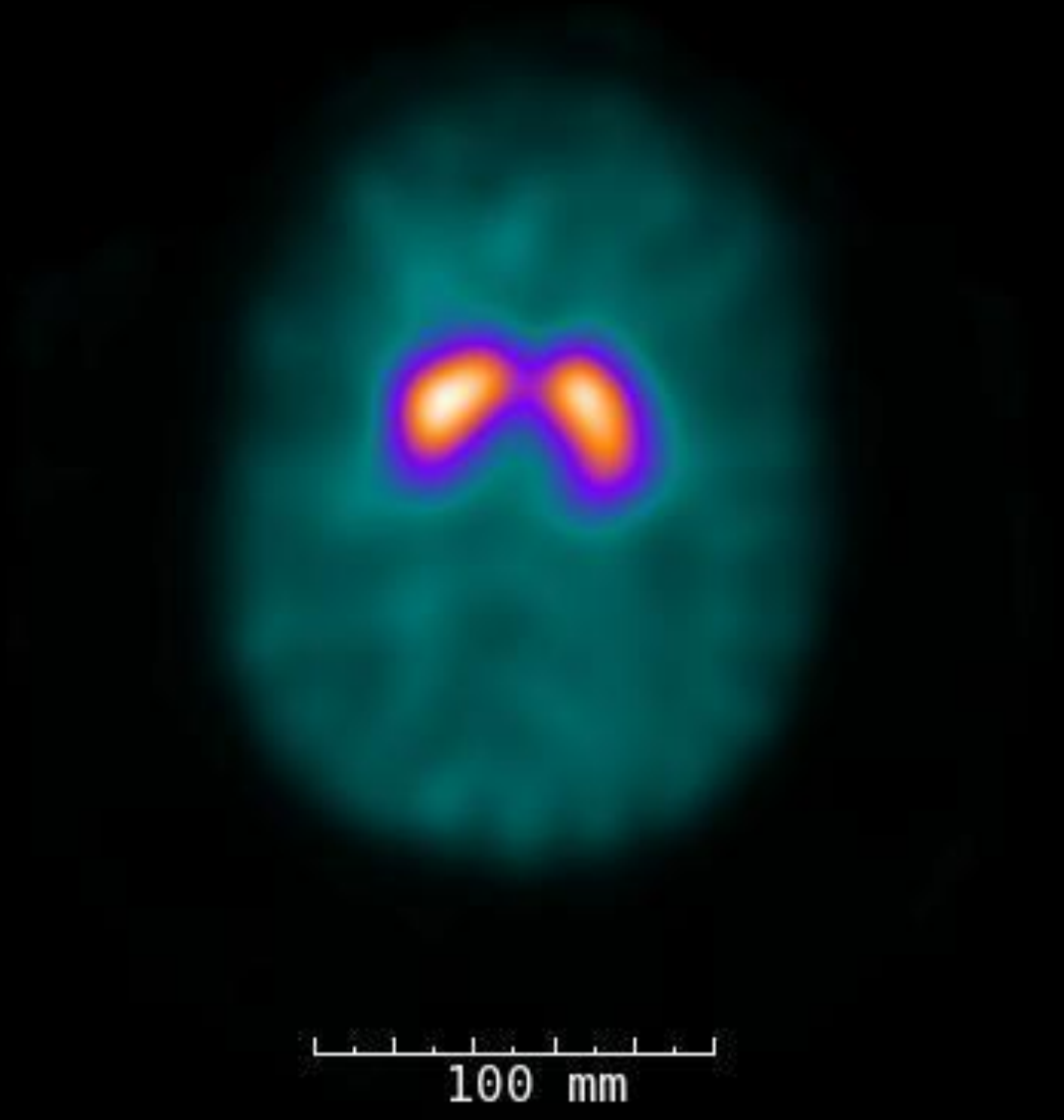


Figure 2 Striatal dopamine transporter binding. CBD, corticobasal degeneration; DIP, drug-induced parkinsonism; DLB, dementia with Lewy bodies; DT, dystonic tremor; ET, essential tremor; MSA-C, multiple system atrophy-cerebellar; MSA-P, multiple system atrophy-parkinsonism; OT, orthostatic tremor; PD, Parkinson disease; PSP, progressive supranuclear palsy; PsyP, psychogenic parkinsonism; VP, vascular parkinsonism.

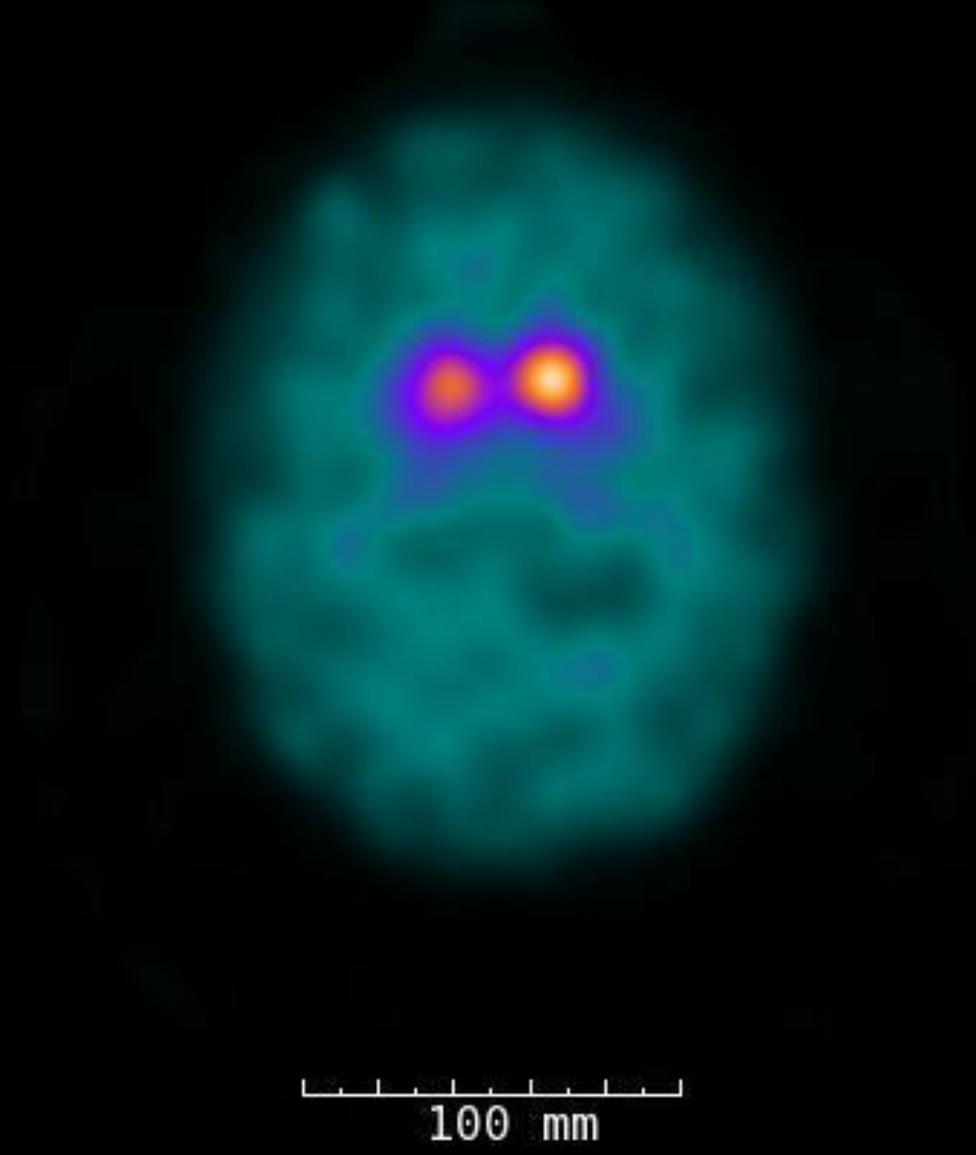
Normal



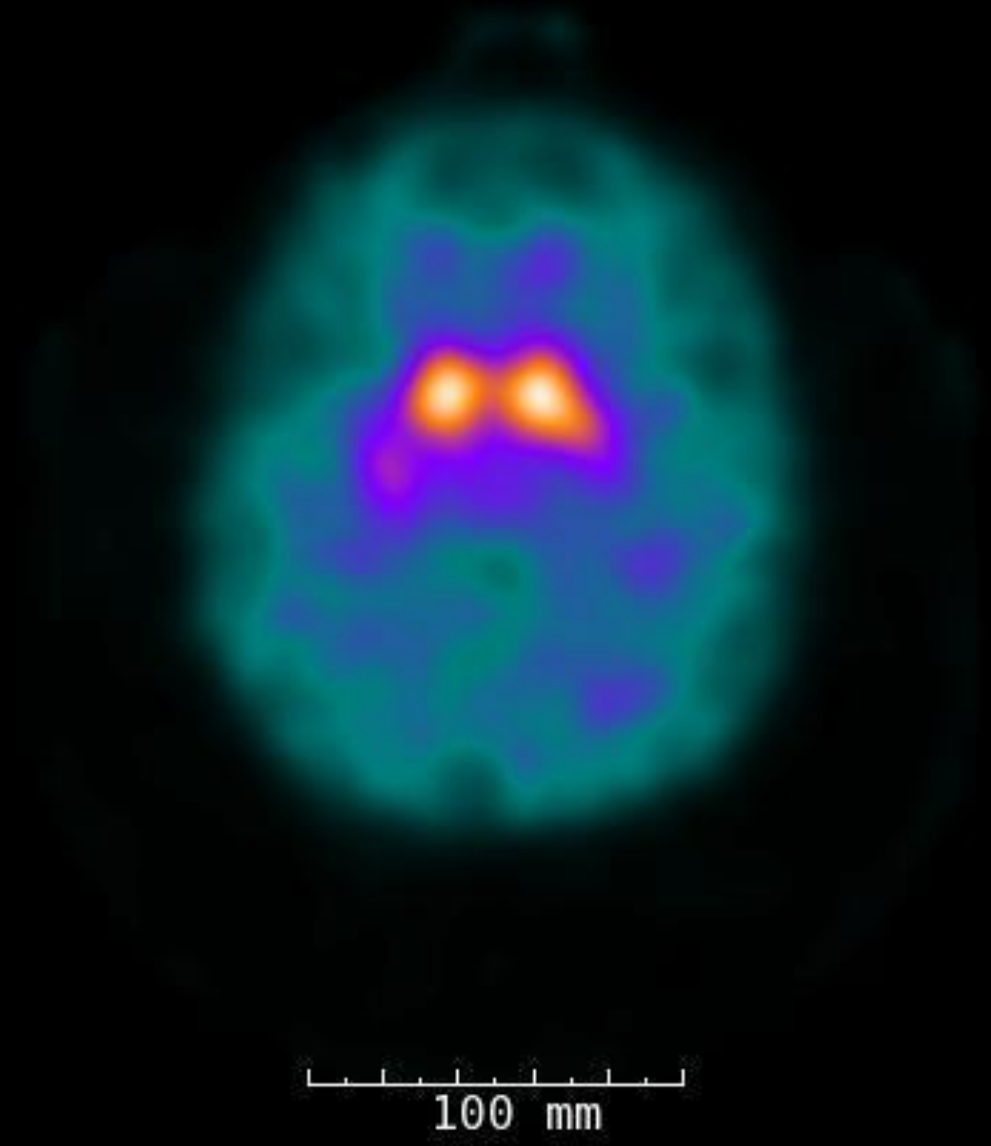
Normal



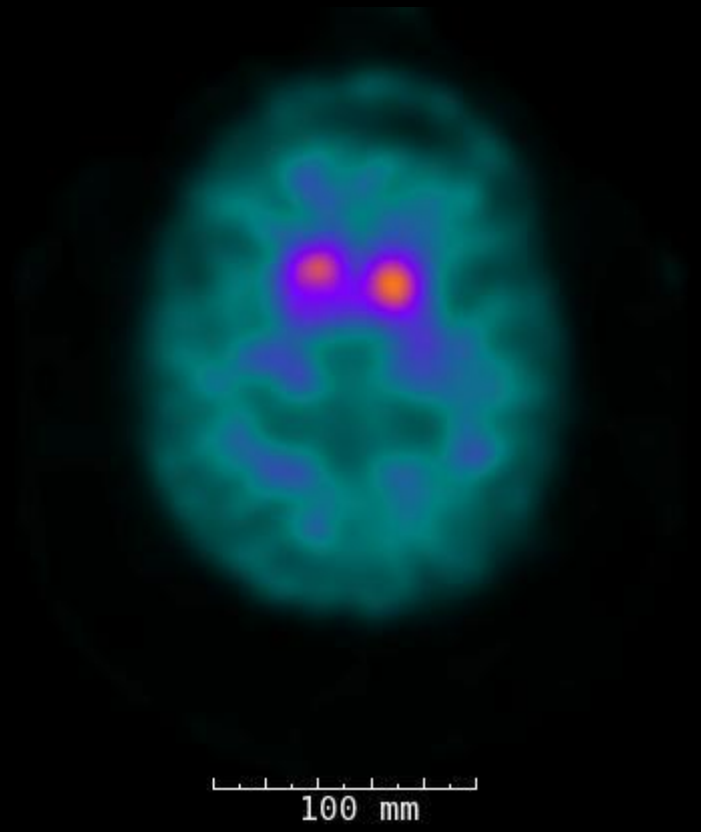
Abnormal



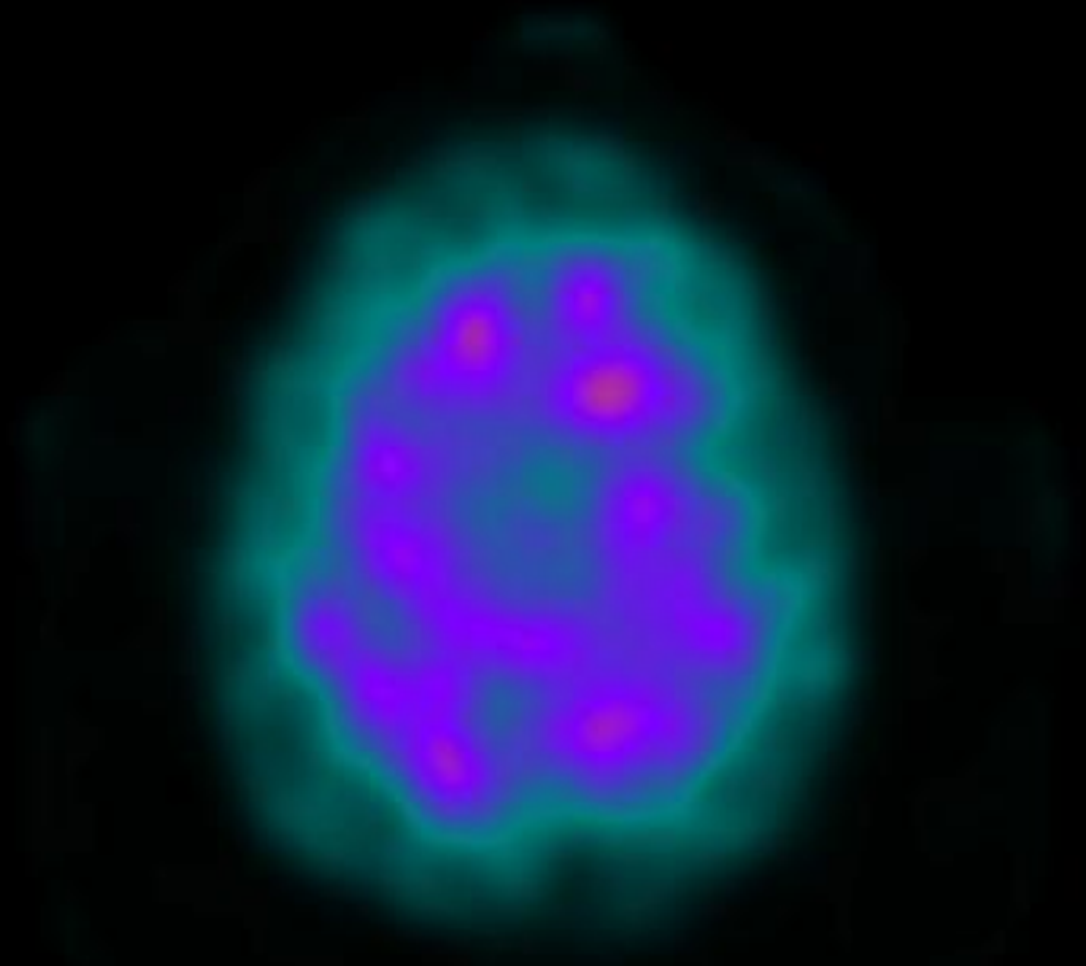
Grade 1 loss



Grade 2 loss



Grade 3 loss



Why is Essential Tremor Important?

Cleveland Clinic

When a person with Parkinson’s disease has a bad tremor, nobody panics, because it's all “part of the disease”

But when someone sees a person with severe essential tremor, well then everyone loses their minds!

Case

- 42 year-old woman – homemaker who also works part-time as hairdresser
- 10-12 year history of dominant left hand tremor with start of tremor in her right hand
- Diagnosed as “early PD” by non-neurologist
- No treatment offered since “medications wear out” – told to enjoy as “much as she could out of life before she died”
- Went to neurologist after she cut her son’s ear lobe with scissors.

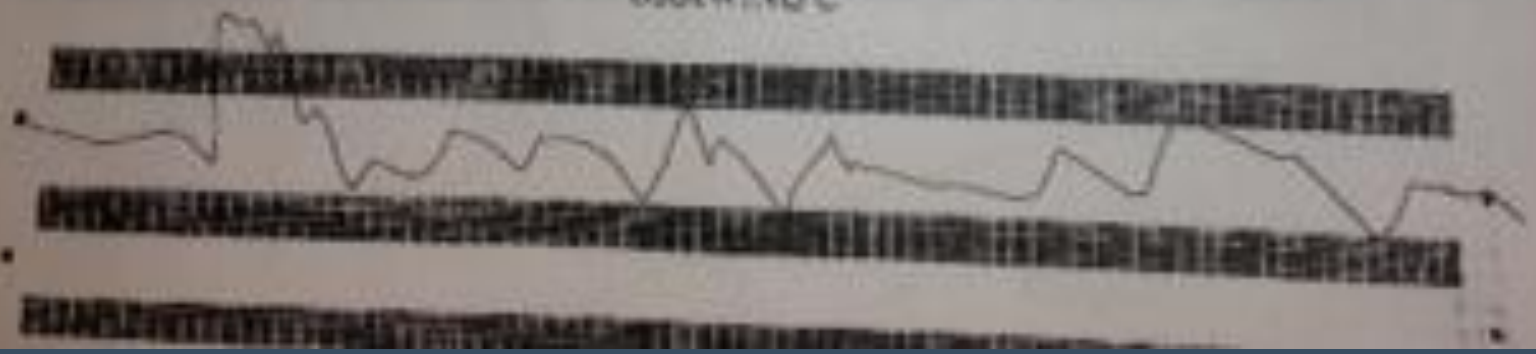
Date

Drawings A, B, and C and mark with the Left Hand / Right Hand

DRAWING A

DRAWING B

DRAWING C



- After initial visit placed on primidone (mysoline) 200mg HS without improvement
- Referred for DBS – right Vim DBS

Date: _____

Drawings A, B, and C and make with the X Left Hand

_____ Right Hand

DRAWING A

DRAWING B

DRAWING C

TABLE 4. *Percentage of patients endorsing individual BDI symptoms, by group*

BDI item no.	Item description	PD	Dystonia	ET	χ^2 Statistic[1]	P value
1	Mood	22	22.9	17.0	0.79	0.67
2	Pessimism	30.8	24.4	29.4	2.25	0.33
3	Sense of failure	11.0	14.5	13.2	0.87	0.65
4	Self-dissatisfaction (anhedonia)	65.0	60.2	54.7	2.42	0.30
5	Guilt	9.0	13.3	11.3	1.44	0.47
6	Punishment	6.8	4.8	5.7	0.48	0.79
7	Self-dislike	16.4	20.5	17.0	0.80	0.67
8	Self-accusations	24.0	24.1	26.4	0.15	0.93
9	Suicidal ideation	10.2	8.4	17.0	2.76	0.25
10	Crying	22.9	19.3	20.8	0.57	0.75
11	Irritability	43.2	48.2	28.3	5.55	0.06
12	Social withdrawal	21.8	21.7	26.4	0.60	0.74
13	Indecisiveness	44.5	31.3	34.0	5.94	0.05
14	Body image change	30.2	38.6	26.4	2.81	0.25
15	Work difficulty	79.1	68.7	60.4	11.05	0.004*
16	Insomnia	60.2	55.4	56.6	0.77	0.68
17	Fatigability	85.0	75.9	77.4	5.07	0.08
18	Decreased appetite	33.9	19.3	26.4	7.26	0.03
19	Weight loss	27.4	27.7	22.6	0.56	0.76
20	Somatic preoccupation	51.4	44.6	28.3	10.27	0.006*
21	Loss of libido	50.3	53.0	50.4	0.45	0.80

Note: The percentage of nonzero scores on the individual items is shown as an indicator of the frequency of these symptoms.

[1]For all χ^2 tests, df = 2 and N = 490.

*Significant at $P < 0.01$.

Miller K, Okun M, et al. Depression Symptoms in Movement Disorders: Comparing Parkinson's Disease, Dystonia and Essential Tremor. Movement Disorders. 22; 5; 2007.

How to Treat Essential Tremor

Natural Products for Essential Tremor

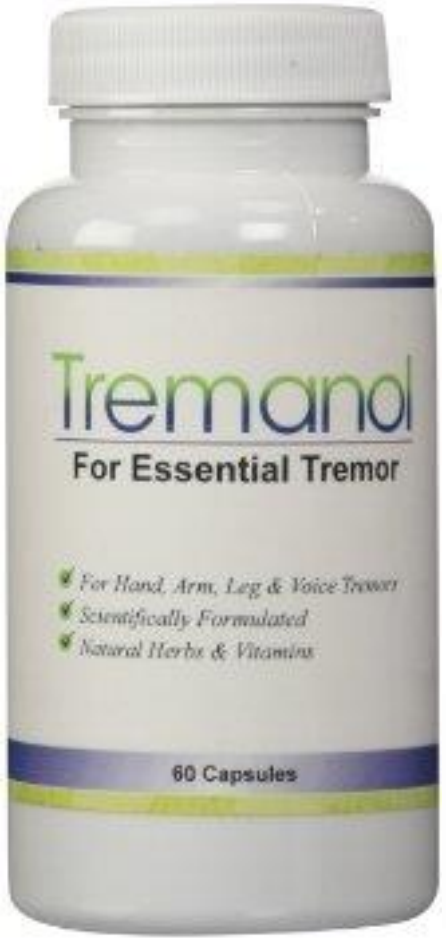


Table 3. Overview of Drugs Commonly Used to Treat ET

Treatment	Level of Evidence	Number of Studies	Cohort Size	Daily Dose	Severity of Adverse Events[a]	Magnitude of Effect
Primidone	A	12	218	≤750 mg	MM (sedation, drowsiness, fatigue, nausea, giddiness, vomiting, ataxia, malaise, dizziness, unsteadiness, confusion, vertigo, ATR)	50% mean improvement by CRS and accelerometry
Propranolol	A	32	533	60-320 mg	MM (reduced arterial pressure, reduced pulse rate, tachycardia, bradycardia, impotence, drowsiness, exertional dyspnea, confusion, headache, dizziness)	50% mean improvement by CRS and accelerometry
Propranolol-LA	A	2	33	80-320 mg	Mild (skin eruption, transient dizziness)	30%-38% improvement by accelerometry
Alprazolam	B	2	46	0.125-3 mg	Mild (fatigue, sedation; potential for abuse)	25%-34% mean improvement in CRS from baseline
Gabapentin	B	3	61	1,200-1,800 mg	Mild (lethargy, fatigue, decreased libido, dizziness, nervousness, shortness of breath)	77% improvement by accelerometry
Topiramate	B	5	335	≤400 mg	Mild (appetite suppression, weight loss, anorexia, parethesias, concentration difficulty)	22%-37% mean improvement in CRS from baseline

[a] Mild: somewhat bothersome; moderate: very bothersome; severe: potentially harmful.
ATR: acute toxic reaction; CRS: clinical rating scale; LA: long-acting; MM: mild-to-moderate.
Source: Reference 9.

- EtOH (ethanol) – “reduces action tremor for up to 5 hours but is habit forming.”

Medications for Essential Tremor

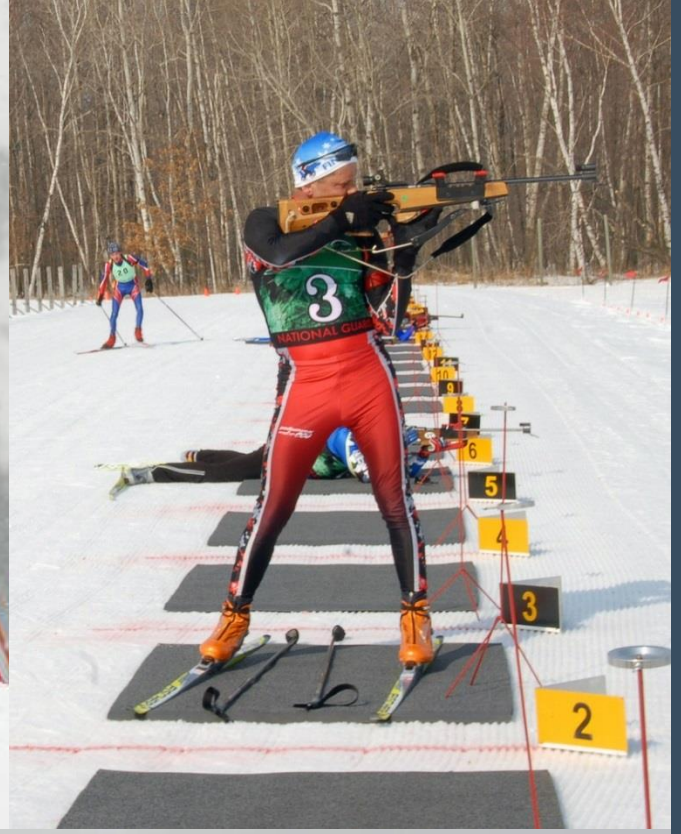
Propranolol - Inderal

Primidone

Klonopin

Topamax


12
4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2


1
2
3
4
5
6
7
8

Anticholinergics

Should be left in 1960s

- Cogentin advertisement, 1965.

DBS in Essential Tremor

DBS PATIENT SELECTION

- Referral to Movement Disorders
- Evaluation in patient management conference
- Tremor interfering with quality of life-eating, drinking, shaving, makeup application, writing, computer/phone use
- Focused ultrasound vs. DBS vs GK VS RF
- Some patients are not open to DBS and/or do not want surgery.
- CT/MRI during evaluation

CANDIDATES FOR SURGERY

- Essential Tremor or Tremor related to Parkinson's Disease
- Skull Density Ratio of 0.4
- Able to stop anticoagulation or antiplatelet therapy
- Able to tolerate supine position with head immobilized for 2-4 hours
- No MRI contra-indications
  - Shunts may be okay.
  - DBS leads not at this time
- Okay with complete head shave
- Unilateral Treatment only

TREATMENT COMPARISON

Table 1 A comparison of surgical outcomes for ET

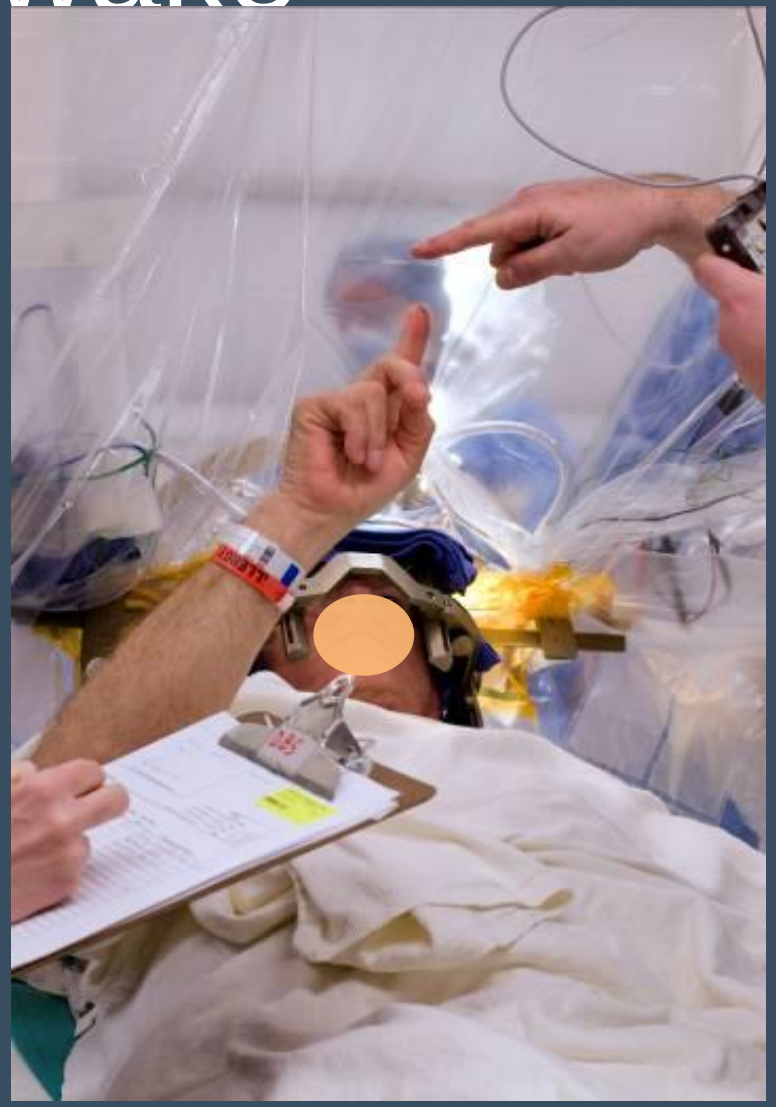
	DBS	FUS	GKRS	RF
Experience	1093 patients since 1998	151 patients since 2013	360 patients since 2007	278 patients since 1986
Level of Evidence, (OCEM)	Level 2	Level 1	Level 4	Levels 2–4
Tremor control, 12-month follow-up	Unilateral: 53.4%–62.8% Bilateral 66%–78%	Unilateral: 35%–75% Bilateral: no data	Unilateral: 48%–63% Bilateral: no data	Unilateral: 74%–90% Bilateral: no data
Tremor control, long-term follow-up	Unilateral: 60%–75% Bilateral 75%	Unilateral: 56%	Unilateral: 3%–63%	Unilateral: 74%–90%
Quality of life improvements	57.9%–82%	37%–73%	65%	47%
Complications (range, transient and permanent)	Unilateral, bilateral			
Dysarthria	11%–39%, 22%–75%	3%	1%–3%	4.6%–29%
Ataxia/gait	9%–17%, 56%–86%	23%	0%–17%	5%–27%
Paraesthesia	5%, 5.9%	14%–25%	1%–9%	6%–42%
Hemiparesis	4.5%, 6.7%	2%–7%	0%–8%	0%–34%

Dallapiazza, 2019

PATIENT MANAGEMENT: DBS vs HIFU

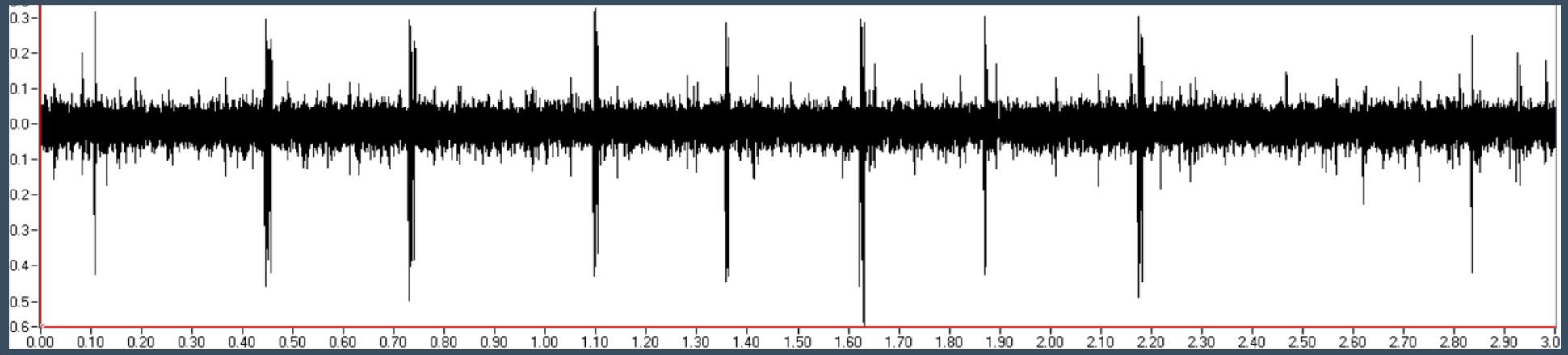
DEEP BRAIN STIMULATION	FOCUSED ULTRASOUND
Younger age	Older age (Recurrence??)
SDR < 0.40	Unlikely to follow up
Bilateral hand control essential	Short recovery
Possible better tremor control/more flexible	Not able to use programmer/recharger
MRI contraindicated (CT only okay)	Brain Atrophy
Long history of success	Malnourished/Scalp/Skin thin
Proven durability	Patient Preference
	Multiple medical co-morbidities
	Cognitive concerns

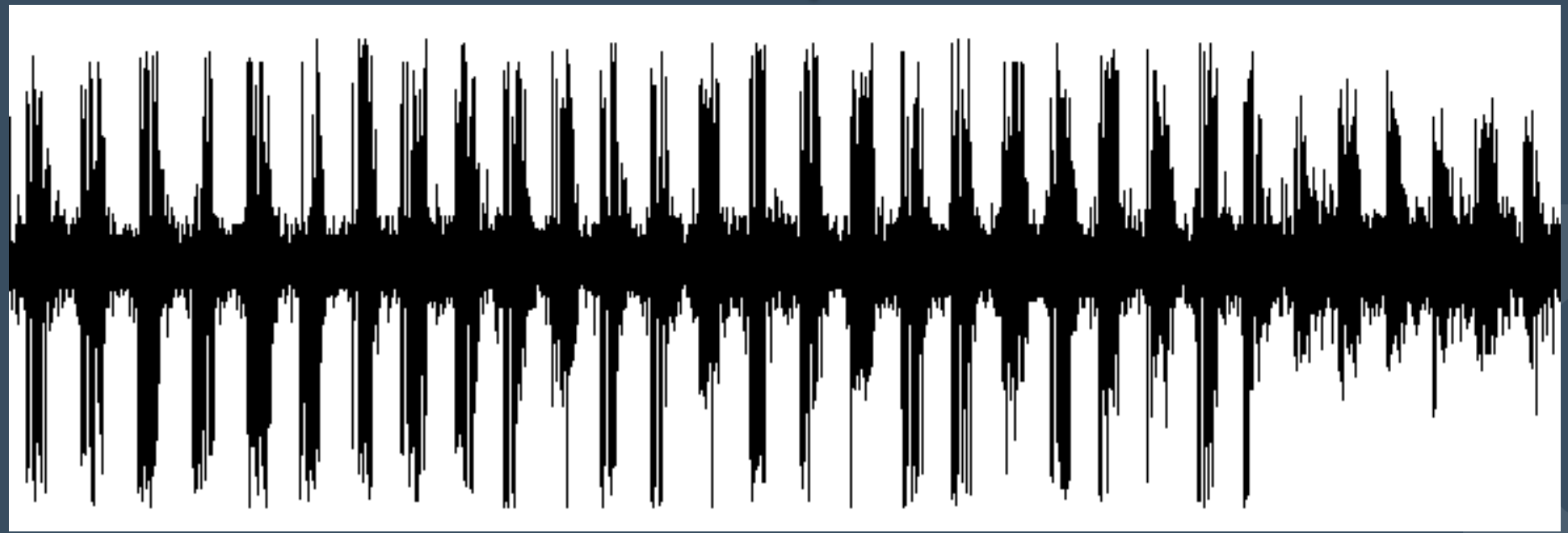
Electrode implant: the patient is awake



Surgical Procedure

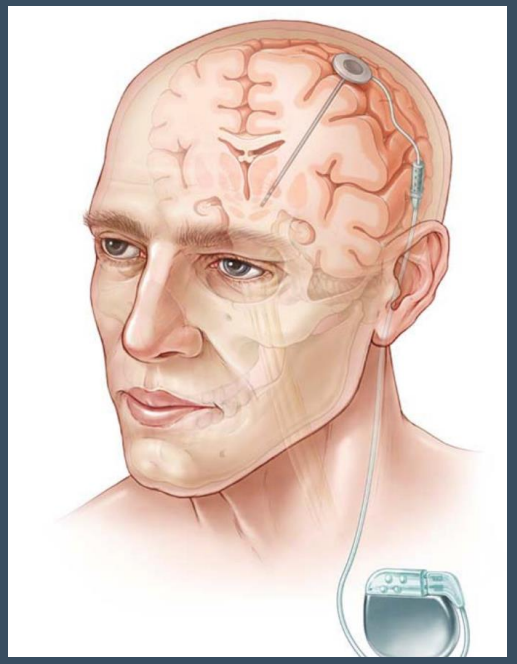
Microelectrode Recording (MER) Vim Thalamus






Microelectrode Recording (MER) Vim Thalamus
SONY
10.19.2013 19:44

BATTERY IMPLANT FOR DEEP BRAIN STIMULATION AND PROGRAMMING



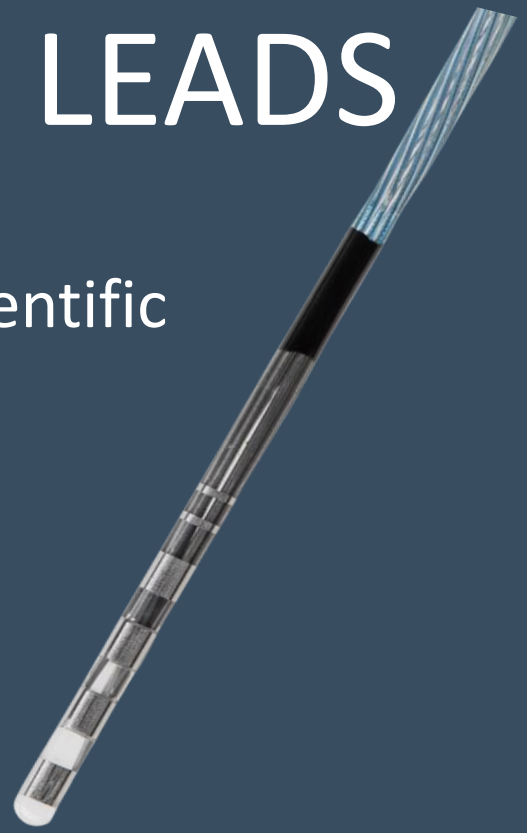
RECHARGEABLE OR NON RECHARGEABLE

CLOSED LOOP OPTION

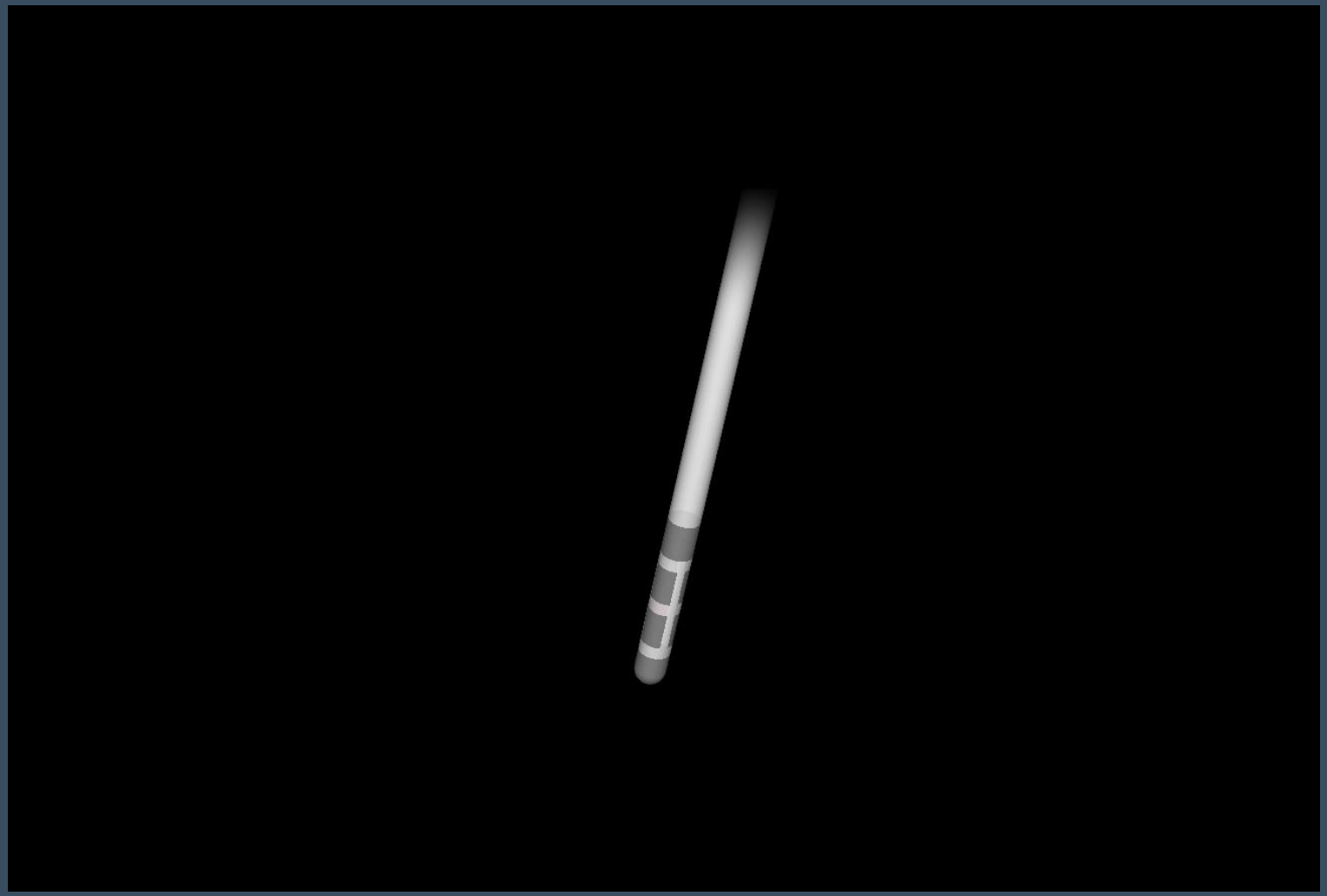
DIRECTIONAL LEADS

Abbott / St. Jude

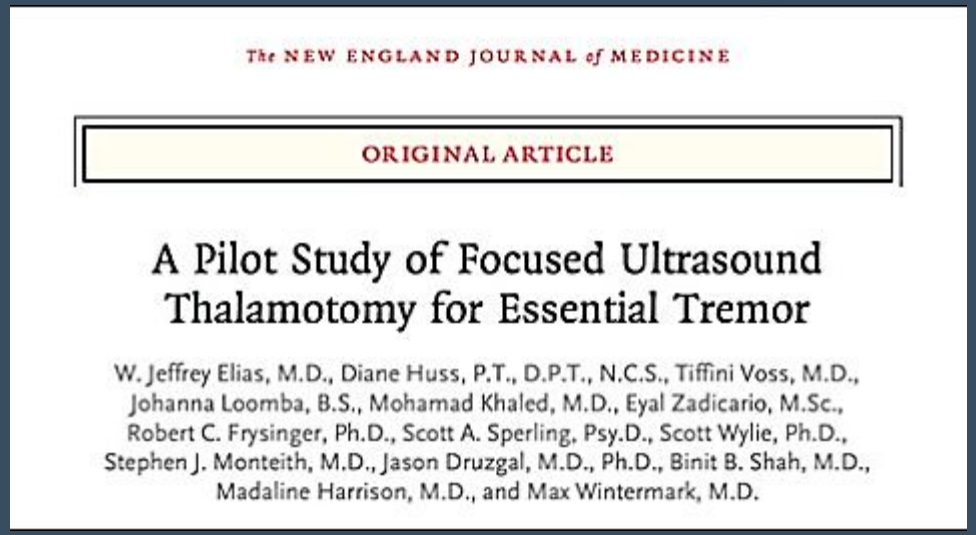
Boston Scientific



Medtronic



Lesioning Options



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Pilot Study of Focused Ultrasound Thalamotomy for Essential Tremor

W. Jeffrey Elias, M.D., Diane Huss, P.T., D.P.T., N.C.S., Tiffini Voss, M.D., Johanna Loomba, B.S., Mohamad Khaled, M.D., Eyal Zadicario, M.Sc., Robert C. Frysinger, Ph.D., Scott A. Sperling, Psy.D., Scott Wylie, Ph.D., Stephen J. Monteith, M.D., Jason Druzgal, M.D., Ph.D., Binit B. Shah, M.D., Madaline Harrison, M.D., and Max Wintermark, M.D.

- Ultrasound
- gamma thalamotomy

COST COMPARISON: DBS vs HIFU (Canadian Dollars)

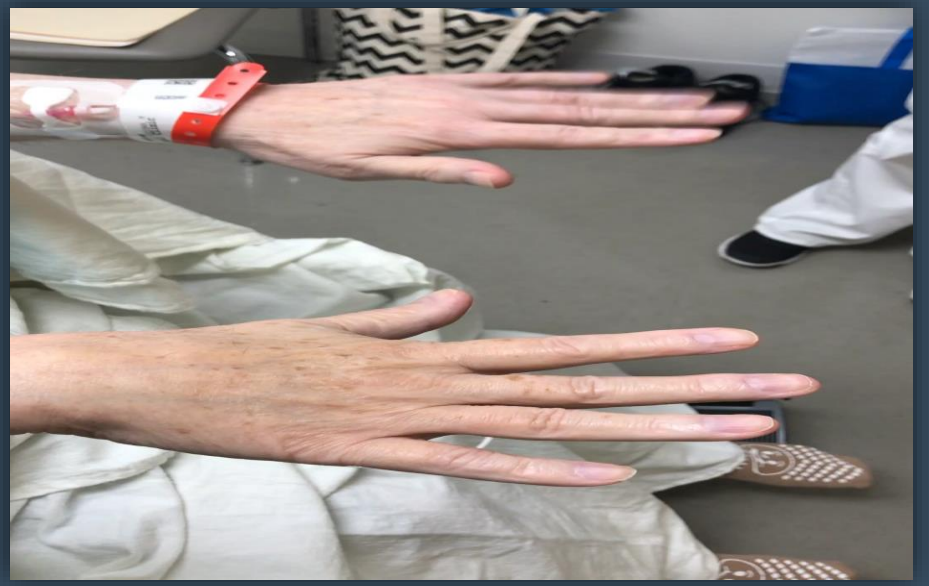
	MRgFUS, Mean (95% CI)	RF, Mean (95% CI)	DBS, Mean (95% CI)
Cost of primary surgery	$19,786	$11,774	$37,366
Cost of monitoring	$814	$814	$3307
Cost of medications	$1096	$1096	$1081
Cost of reoperation	$1731	$1030	–
Cost of managing adverse events	$71	$259	$6306
Cost of battery replacement	—	—	$9463[a]
Total cost	**$23,497($22,044-$25,287)**	**$14,972 ($14,096-$16,051)**	**$57,523($55,507-$59,772)**
Life-years	4.63	4.63	4.63
QALYs	3.70(3.48-3.89)	3.63(3.42-3.82)	3.96(3.75-4.14)
ICER ($ per QALY gained)			
MRgFUS versus RF			**$119,607**
DBS versus MRgFUS			**$130,850**

SLIGHTLY LESS EFFECTIVE BUT MUCH LESS EXPENSIVE THAN DBS

Li, 2019

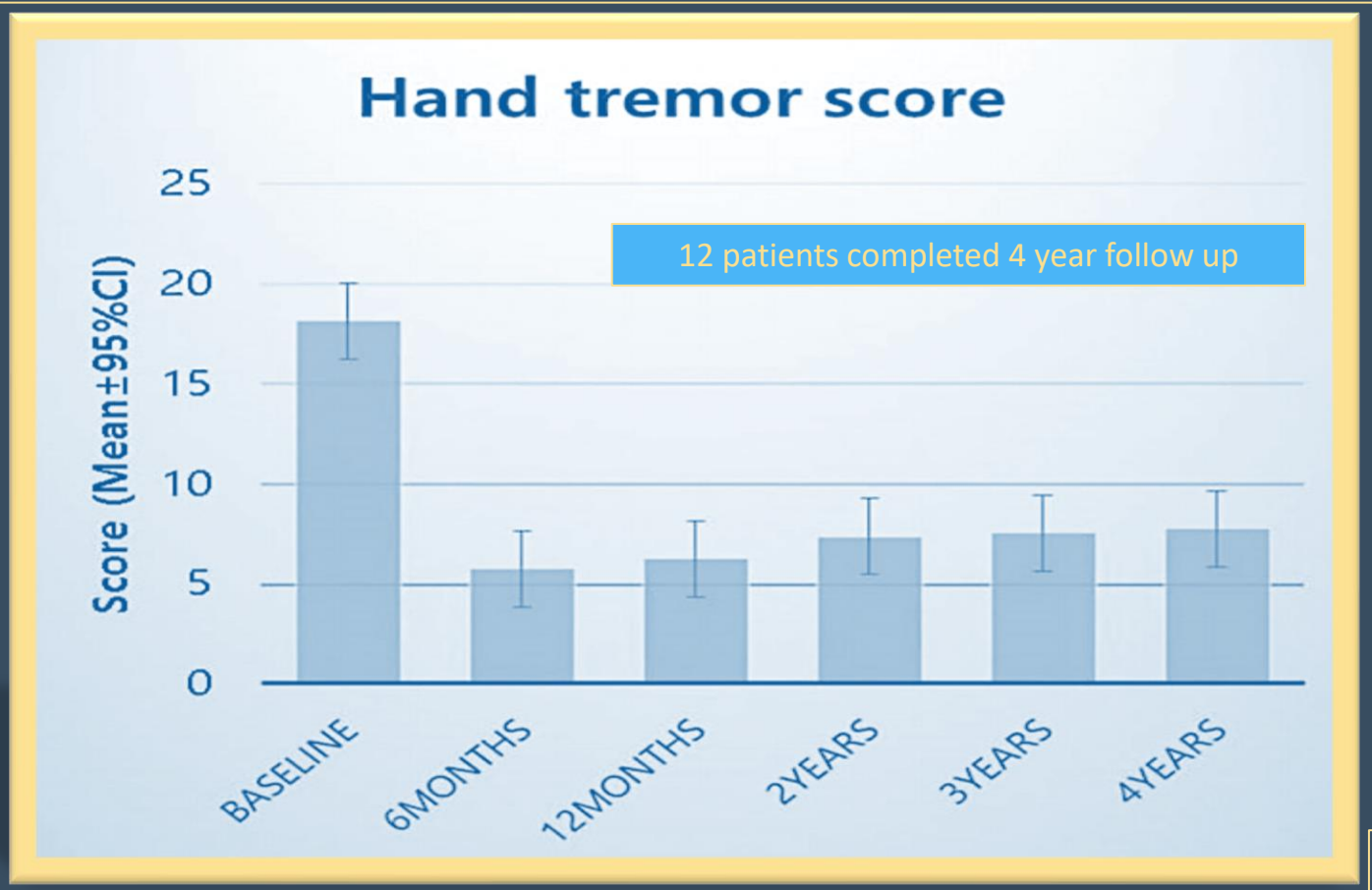
BEFORE

AFTER



MRI GUIDED FOCUSED ULTRASOUND: DURABILITY

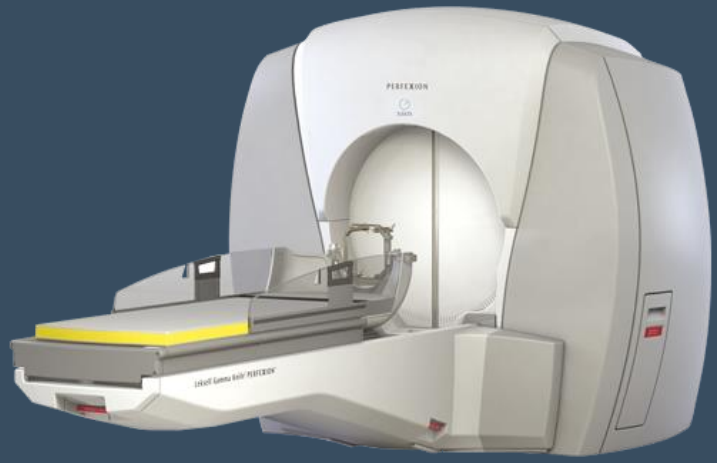
CLINICAL RATING SCALE OF TREMOR (0-32)



Park, 2019

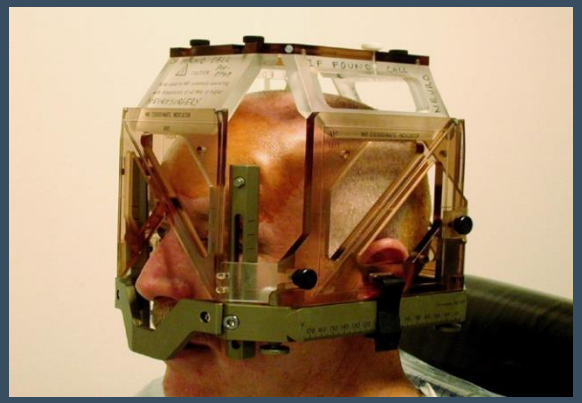
Gamma Knife Radiosurgery

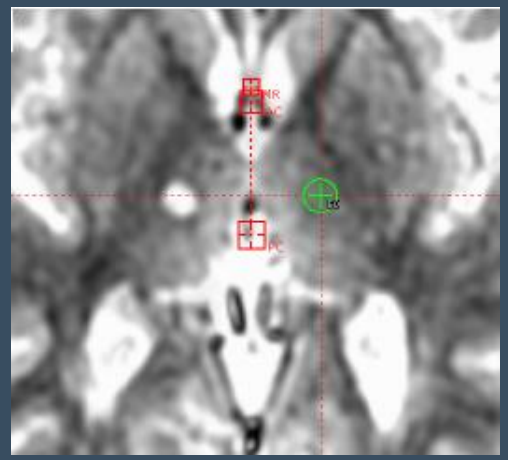
- No incisions needed
- Uses low dose radiation beams called gamma rays
- Targets cells in thalamus that cause tremor
- Creates a lesion and tremor improves after 3-6 months



How is Gamma Knife Done?

- Outpatient procedure
- Frame is placed
- CT scan is obtained
- Surgeon and team plan the treatment
- 90 minute procedure time in the GK





Symptom improvement after Gamma Knife

- 80% of patients have at least 50% improvement in arm and leg tremor
- Can improve head and voice tremor with a lesion on both sides
  - Second side GK must be done at least 12 months later

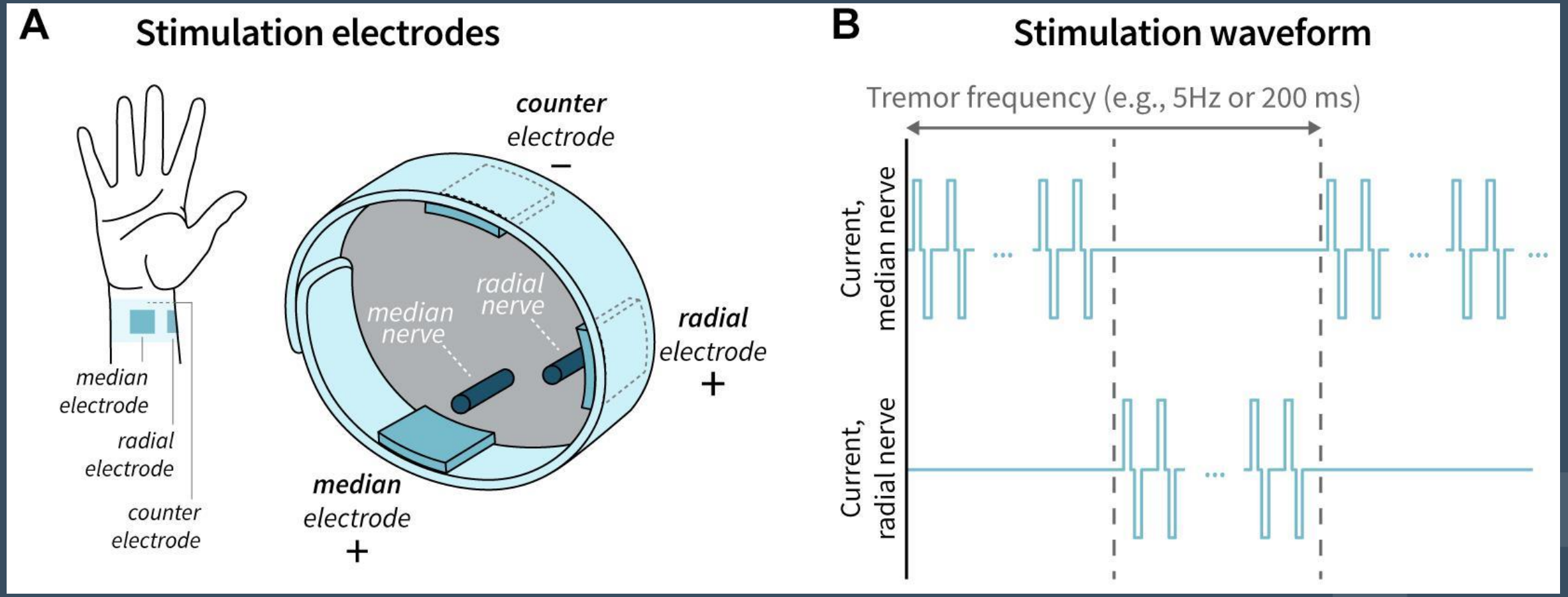
Procedural Risks

- 2-3% Numbess or weakness on half of body
- 2-3% Speech impairment
- 1% Recurrent tremor

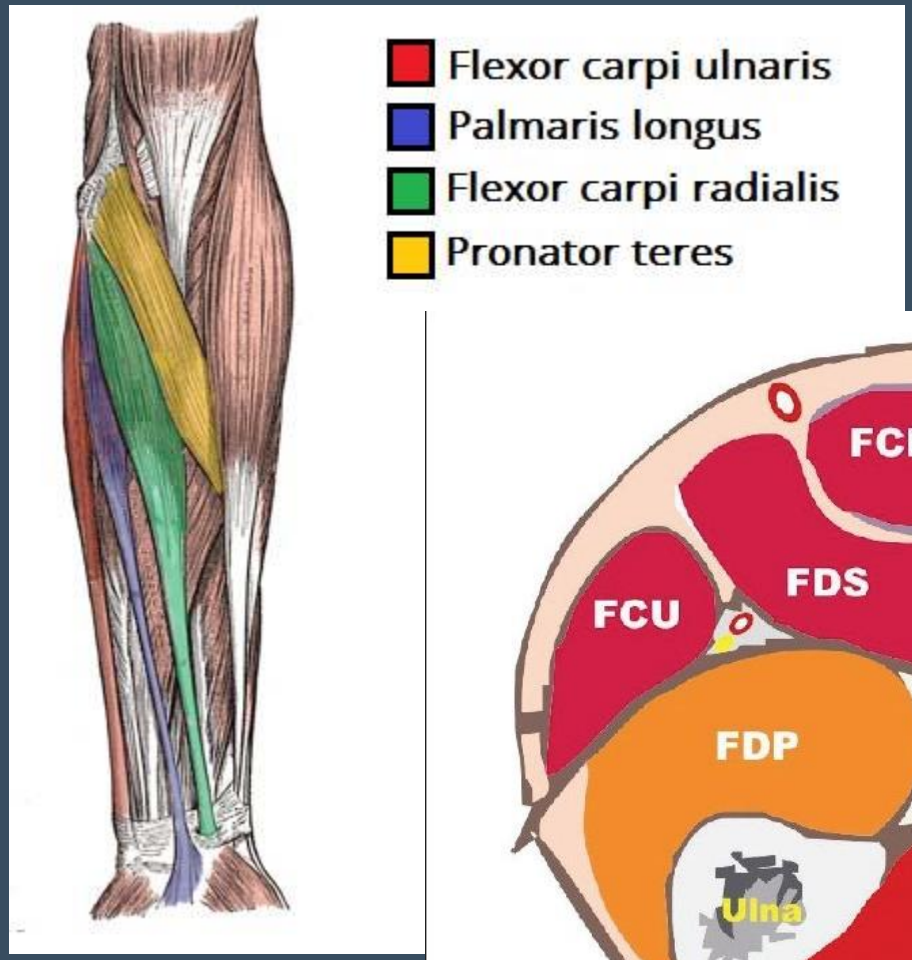
NOTE: side effects of procedure may occur in delayed fashion (6 months post treatment) and may be temporary

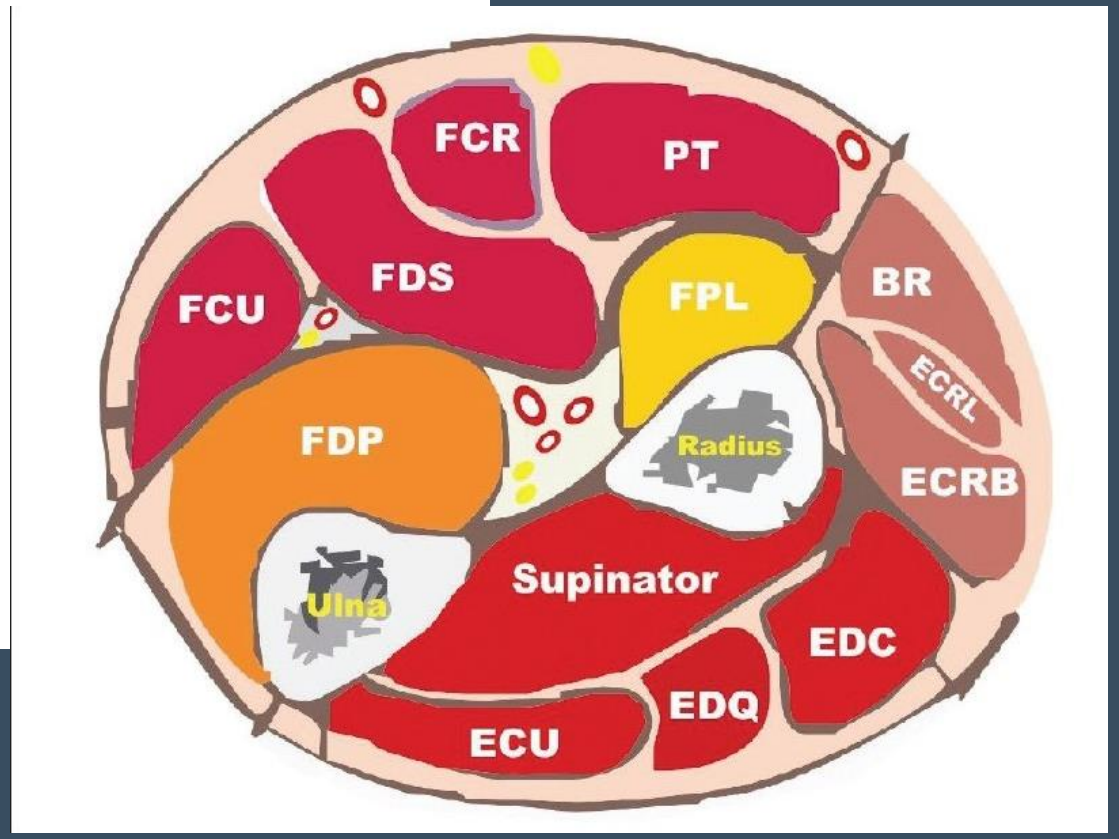
Cala

- Cala kIQ
  - kIQ, pronounced “kick,” stands for Kinetic [movement] + IQ [smart]
  - the only FDA-cleared, wearable device that delivers effective therapy for action hand tremor in people with essential tremor and Parkinson’s disease.
  - TAPS (Transcutaneous Afferent Patterned Stimulation) therapy


A
Stimulation electrodes
median electrode
radial electrode
counter electrode
counter electrode
−
radial electrode
+
median electrode
+
median nerve
radial nerve
B
Stimulation waveform
Tremor frequency (e.g., 5Hz or 200 ms)
Current, median nerve
Current, radial nerve

Botulinum toxin for ET





Personal observations

- Botulinum toxin injections are an "Art" as much as a "Science"
- Head injections are easier to get paid – listed as cervical dystonia
- Limb injections due to the nature of the forearm muscles lead to weakness.
- Ultrasound guidance can very helpful in localizing specific muscle fibers and bundles.