Tremor and Wilson's Disease



Michael S. Okun, MD

Distinguished Professor of Neurology

Medical Advisor, Parkinson's Foundation

Director, Norman Fixel Institute for Neurological Diseases



Is it palatal tremor or myoclonus?

- Ask Rabbi of תְּנוּעָה ‘movement and medicine’

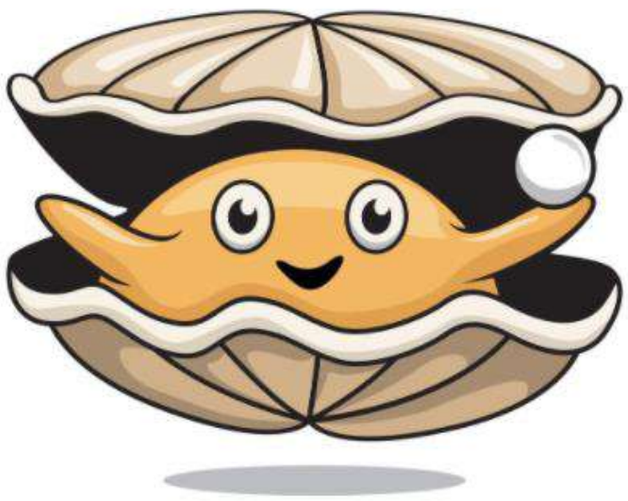


Maimonides (Moshe Ben Maimon) (1138–1204)
12th-century Spanish-North African Talmudist, philosopher, and law codifier

NIH Support

- UH3 NS18-023 Defining Targets for Tic Detection and Suppression in Tourette Syndrome Deep Brain Stimulation NS18-023
- R01NS131342 Thalamic DBS and Voice Tremor
- U01 Automated Image Differentiation of Parkinson's
- R25NS108939 University of Florida R25 Early Research Program for Neurology and Neurosurgery Residents
- R01NS096008 The Human Thalamocortical Network in Tourette Syndrome
- R01NR014852 Mobile Decision Support System for Nurse Management of Neuromodulation Therapy
- R21NS072897 Neural Correlates of Tourette Syndrome
- R21NS119849 Balance and Gait in Essential Tremor
- R34MH080764 Scheduled and Responsive Brain Stimulation for the Treatment of Tourette Syndrome

The ‘cypher’ for my talk



Clinical Pearl



New Paper



‘Hot’ Paper

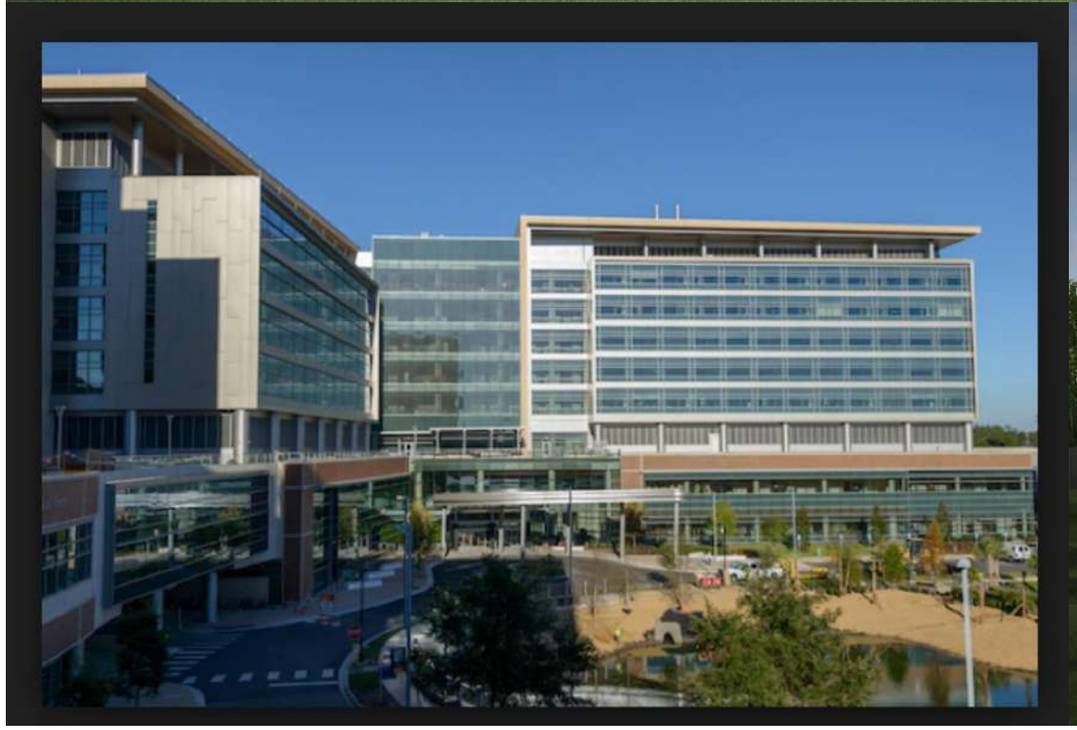
‘Fixel Institute’ Campus for Neurological Diseases at UF Health

Social Media: @MichaelOkun

Blog: www.pdplan.org









What’s new in tremor?

Movement Disorders

REVIEW

Update on Medical Treatments for Essential Tremor: An International Parkinson and Movement Disorder Society Evidence-Based Medicine Review

Deepa Dash, MD,[1] Verónica Bruno, MD, MPH, FRCPC,[2] Petra Schwingenschuh, MD,[3] Kelly E. Lyons, PhD,[4] Eng-King Tan, MD,[5] Claudia M. Testa, MD, PhD,[6] Santiago Perez Lloret, MD, PhD,[7,8] Bettina Balint, MD,[9] João Costa, MD, PhD,[10] Rob M.A. de Bie, MD, PhD,[11] Monty A. Silverdale, MD, PhD,[12] Ai Huey Tan, MD, PhD, FRCP (Edin),[13] and Tiago A. Mestre, MD, PhD[14*]

TABLE 1 *Summary of findings and efficacy conclusions of included interventions in the MDS-EBM review on medical treatments for essential tremor*

Intervention	RCT (n)	Treated (n)	Tremor severity (versus placebo)	Risk of bias	Precision	Consistency	Directness	Level of the evidence in favor of or against the intervention	Efficacy conclusion
Propranolol	4	71	Improved	High	Imprecise	Consistent	Direct	Low	Insufficient evidence
Primidone	3	60	Improved	High	Imprecise	Consistent	Direct	Low	Insufficient evidence
Topiramate	4	172	Improved	High	Imprecise	Consistent	Direct	Low	Insufficient evidence
Alprazolam	1	22	Improved (functional)	High	Imprecise	Unknown	Direct	Very low	Insufficient evidence
Botulinum toxin type A	4	140	Improved	High	Imprecise	Inconsistent	Direct	Very low	Insufficient evidence
Perampanel	1	22	Improved	High	Imprecise	Unknown	Direct	Very low	Insufficient evidence
Acetazolamide	1	22	Not improved	High	Imprecise	Unknown	Direct	Very low	Insufficient evidence
Flunarizine	1	17	Improved	Low	Imprecise	Unknown	Direct	Low	Insufficient evidence
Gabapentin	1	25	Improved	High	Imprecise	Unknown	Direct	Very low	Insufficient evidence
Levetiracetam	2	27	Not improved	High	Imprecise	Consistent	Direct	Low	Insufficient evidence
Mirtazapine	1	16	Not improved	High	Imprecise	Unknown	Direct	Very low	Insufficient evidence
Phenobarbitone	3	45	Not improved	High	Imprecise	Inconsistent	Direct	Very low	Insufficient evidence
Pregabalin	3	46	Not improved	High	Imprecise	Consistent	Direct	Low	Insufficient evidence
Progabide	1	10	Not improved	High	Very imprecise	Unknown	Direct	Very low	Insufficient evidence
Trazodone	2	24	Not improved	High	Imprecise	Consistent	Direct	Low	Insufficient evidence
Zonisamide	1	10	Not improved	High	Imprecise	Unknown	Direct	Very low	Insufficient evidence

Abbreviations: MDS-EBM, International Parkinson and Movement Disorder Society Evidence-Based Medicine; RCT, randomized controlled trial.

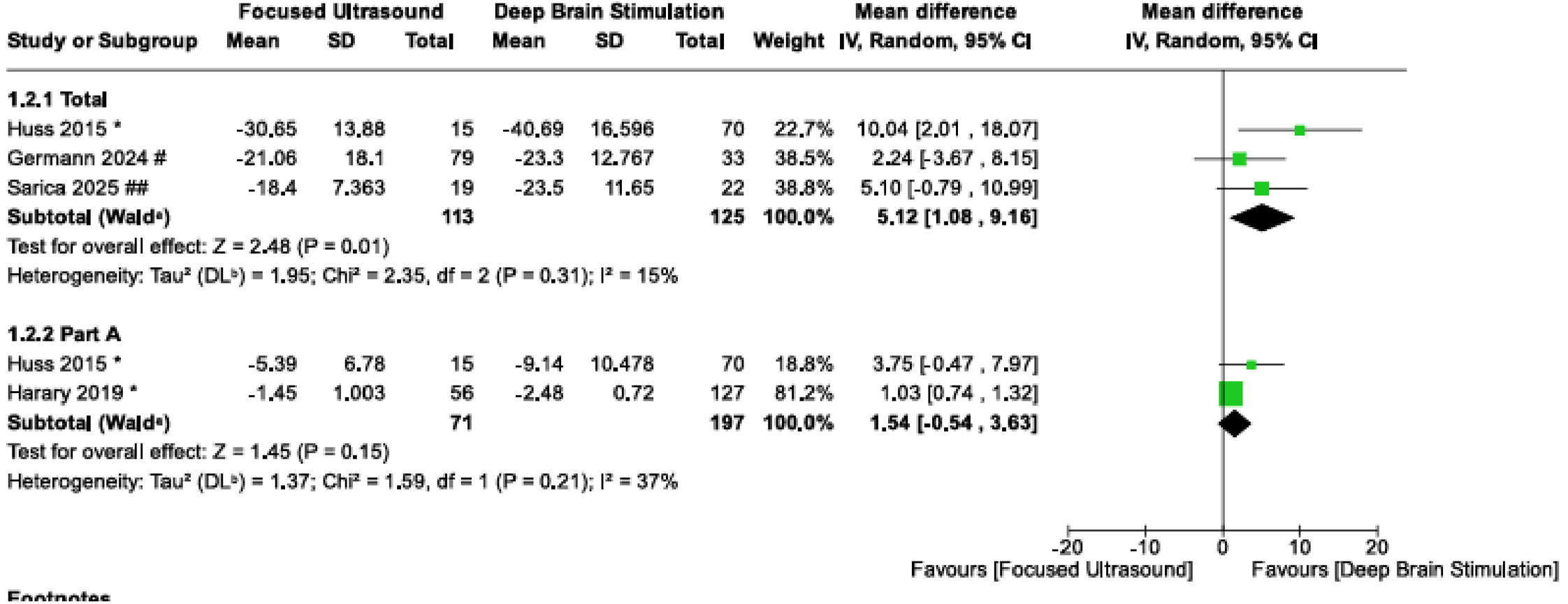
Neurosurgical Review

Neurosurgical Review (2026) 49:264
https://doi.org/10.1007/s10143-025-04076-x

RESEARCH

Deep brain stimulation and magnetic resonance–guided focused ultrasound for essential tremor: a meta-analysis of effectiveness and safety

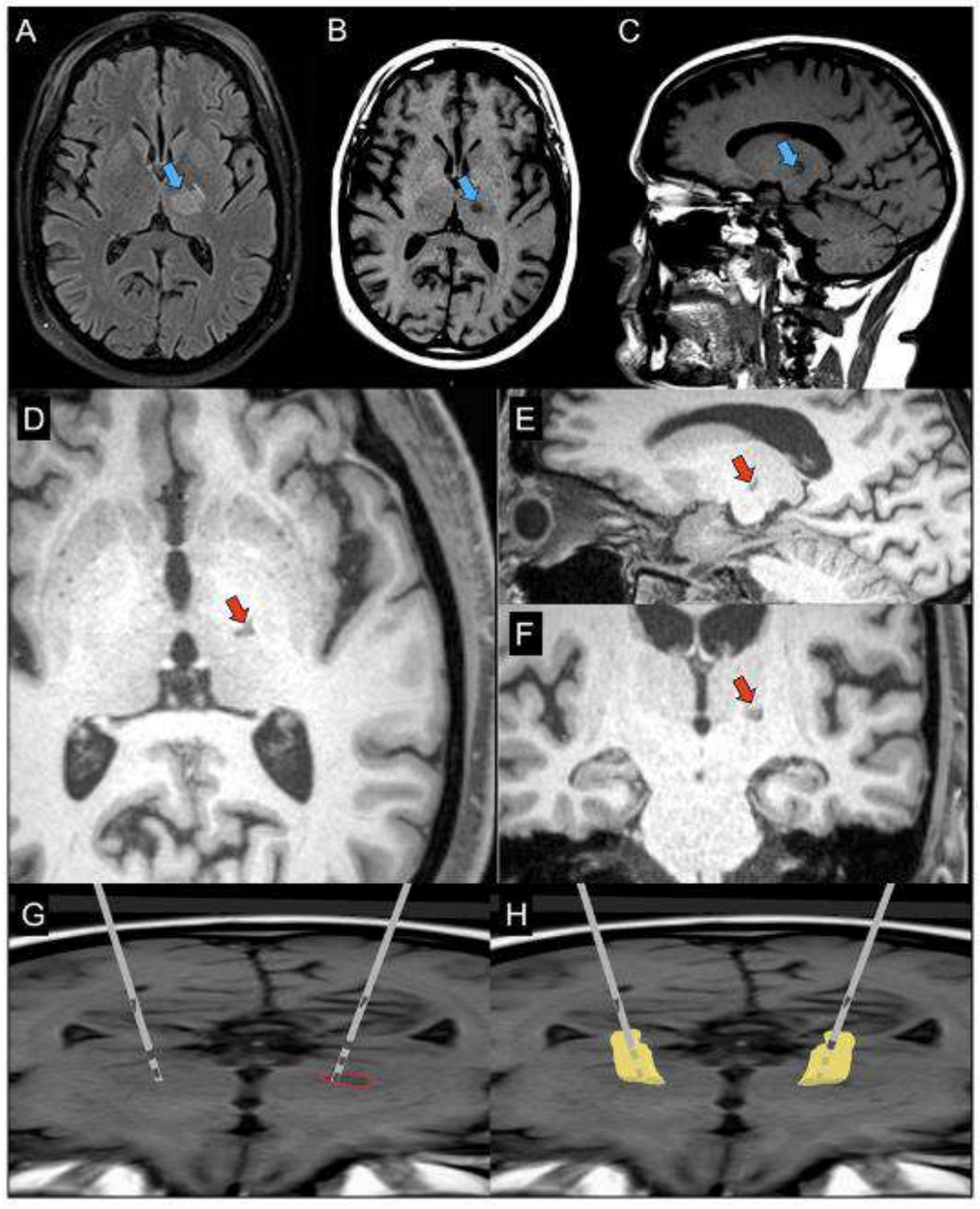
Haneen Sabet[1] · Abdallah Abbas[2] · Esraa Y. Salama[3] · Abrar AbuHamdia[4] · Mohamed El-Moslemani[2] · Majed Aldehri[5,6] · Ibrahim Alnaami[7]



Footnotes

Tremor
and Other Hyperkinetic Movements

Tremor Recurrence in MR-Guided Focused Ultrasound Thalamotomy for Essential Tremor: DBS vs. Re-lesion



- Tremor recurrence after focused ultrasound not equal original procedure failed; it may reflect progression of a chronic neurological condition.

- In this case, staged bilateral VIM DBS provided durable tremor control after tremor returned following an initially successful focused ultrasound procedure.

- Therapeutic DBS stimulation was achieved even within a previously lesioned thalamic target, suggesting that focused ultrasound and DBS may complement one another over time.

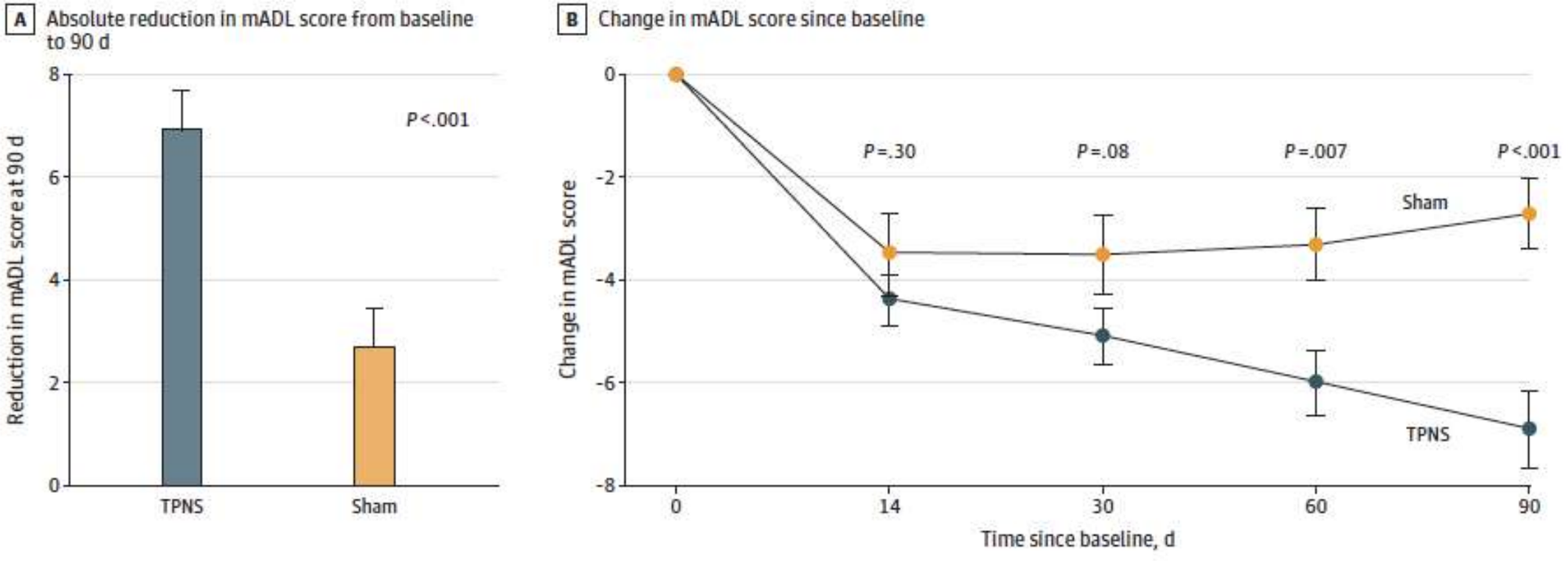
JAMA Neurology

JAMA Neurology | Original Investigation

Transcutaneous Peripheral Nerve Stimulation for Essential Tremor
A Randomized Clinical Trial

William G. Ondo, MD; Wen Lv, MD; Xiaodong Zhu, MD, PhD; Yongsheng Hu, MD; Stuart H. Isaacson, MD; Yuan Yuan, MD; Alberto J. Espay, MD; David Kreitzman, MD; Sheng-Han Kuo, MD; Salima Brillman, MD; Holly A. Shill, MD; Kelly E. Lyons, PhD; Zhi Yang, PhD; Qi Zhao, PhD; Zhen Zhang, PhD; Rajesh Pahwa, MD

Figure 2. Change in Modified Activities of Daily Living (mADL) Score Over Time



AAN 2026: Essential Tremor Response Maintained with Ulixacaltamide

21 Apr 2026 | Neurology | View All News



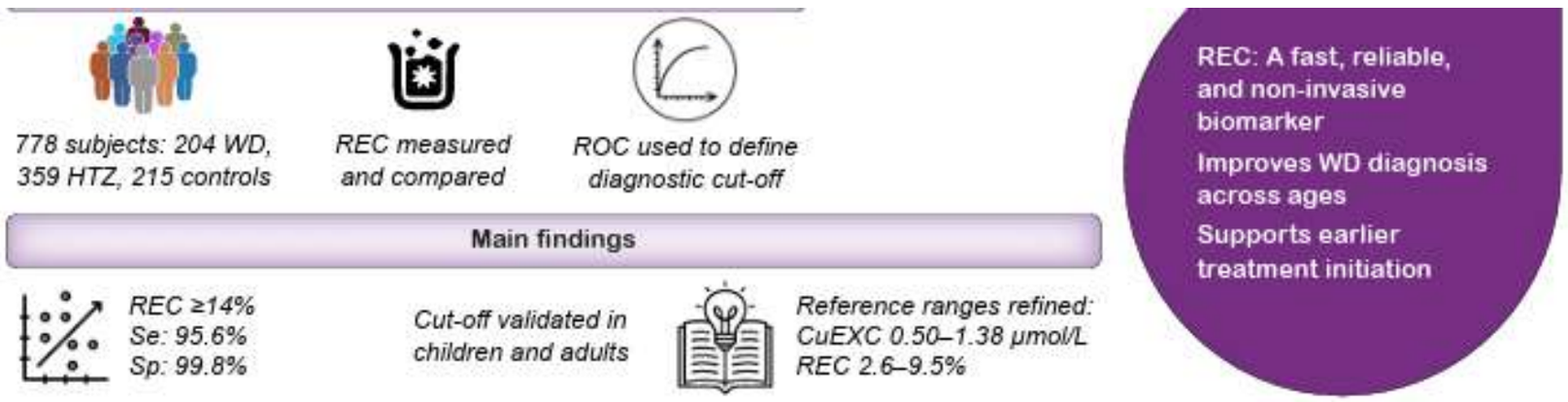
- n=238 participants
- Met primary outcome
- T-type calcium channel modulation

JHEP Reports
Innovation in Hepatology
EASL

Relative exchangeable copper: A highly specific and sensitive biomarker for Wilson disease diagnosis

Authors

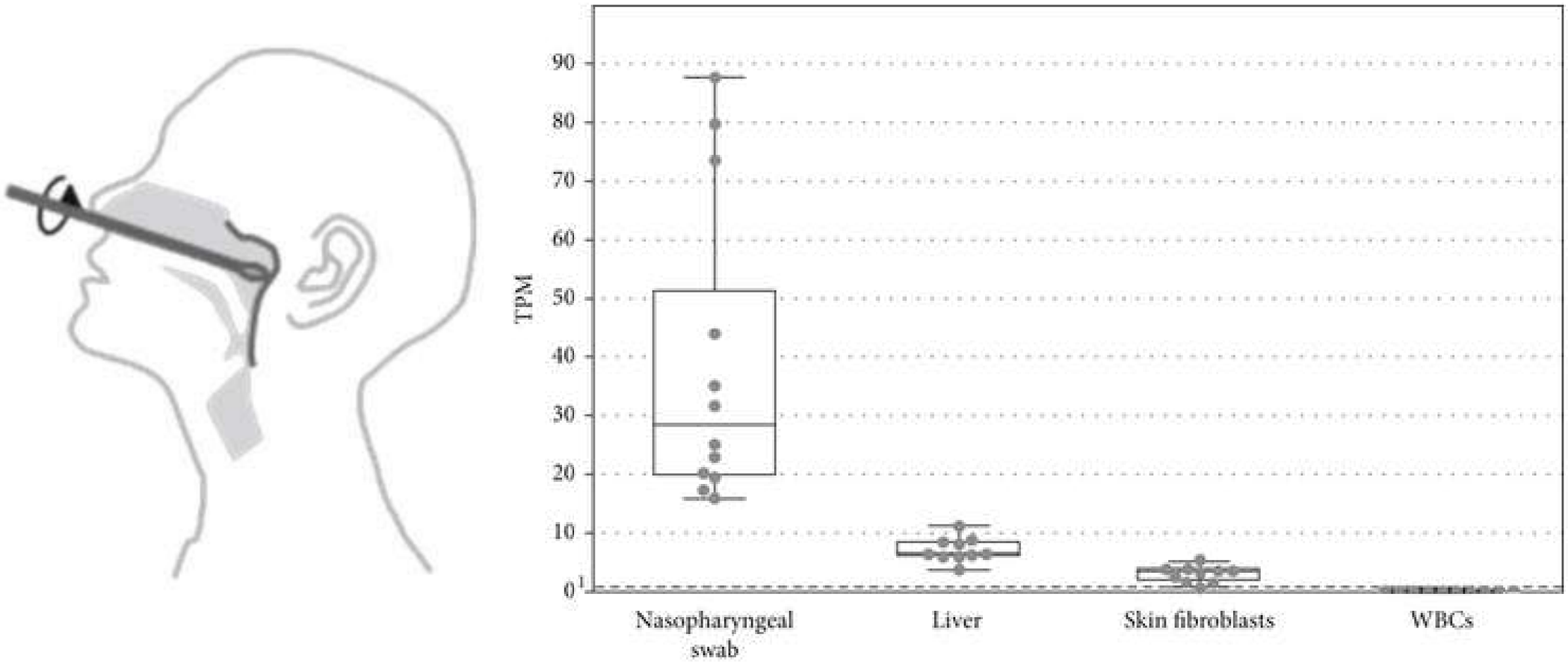
Nouzha Djebrani-Oussedik, Clément Desjardins, Mickaël Alexandre Obadia, …, Joël Poupon, Dominique Debray, Aurélia Poujois



- Ultrafiltration followed by direct Cu quantification
- CuEXC rapid and reliable estimate
- Circumvents the use of more complex and time-consuming techniques, such as Cu speciation

Human Mutation

Analyses of *ATP7B* mRNA in Nasopharyngeal Swab Samples Increase Yields of Wilson Disease Molecular Genetic Diagnostics



Wiley
Human Mutation
Volume 2026, Article ID 8416660, 12 pages
https://doi.org/10.1155/humu/8416660

Orphanet Journal of Rare Diseases

RESEARCH

Post-marketing safety signals of Wilson's disease therapies: evidence from FAERS and VigiBase

Hülya Tezel-Yalçın[1], Nadir Yalçın[2*], Karel Allegaert[3,4,5] and Pınar Erkekoğlu[1]

D-Penacillamine

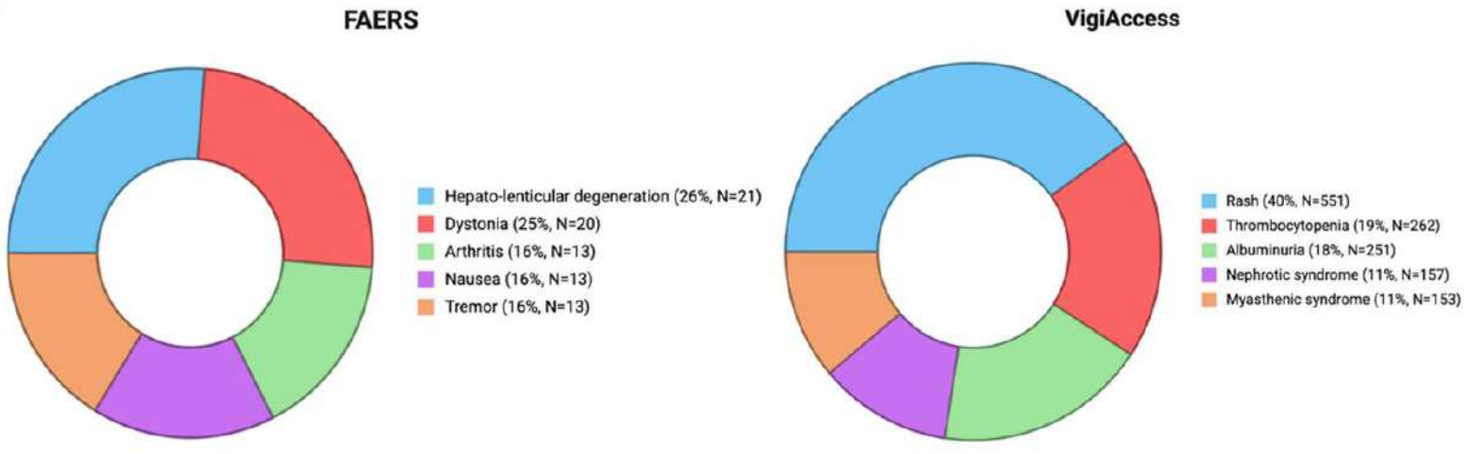


Fig. 10 Most frequently reported ADEs for D-Penicillamine in FAERS and VigiAccess

Trientine

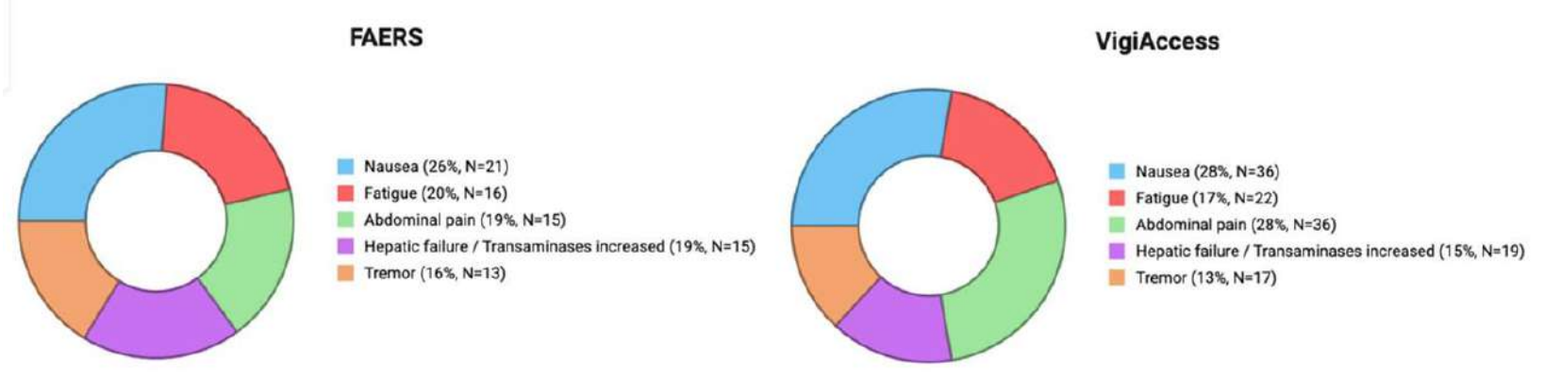


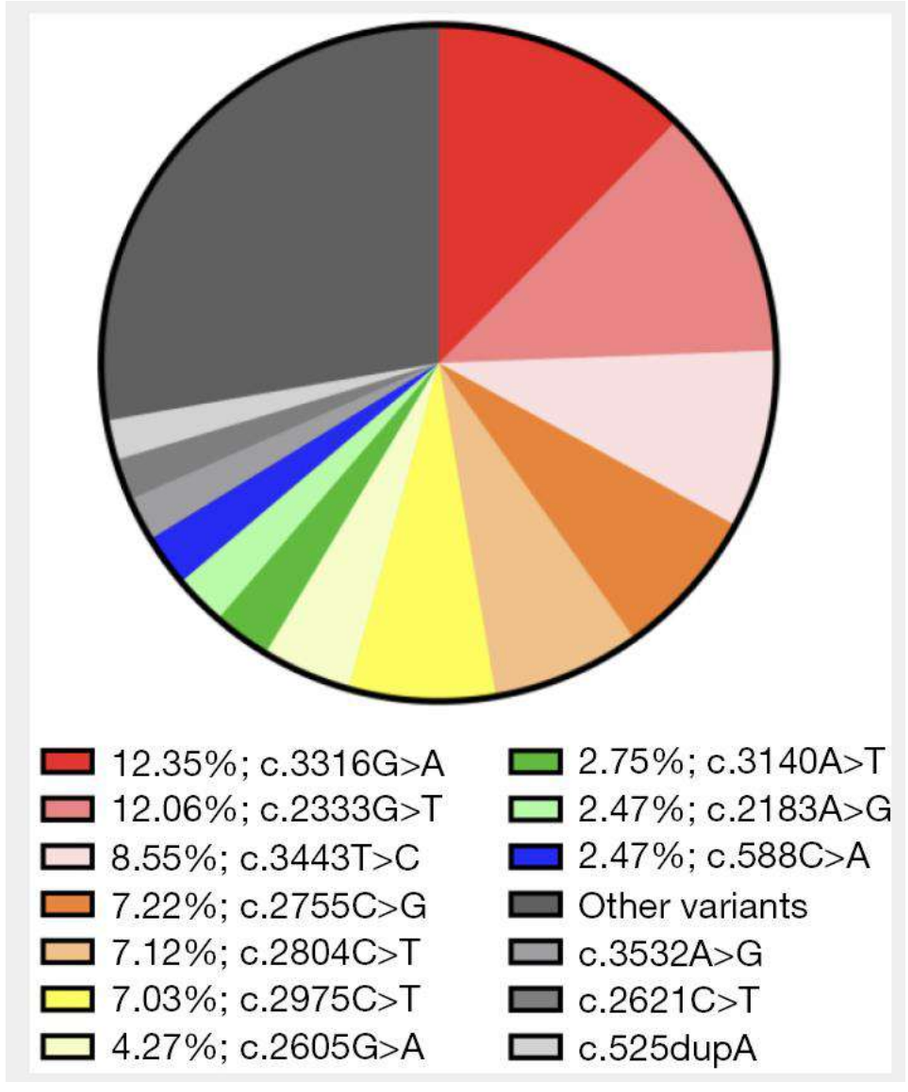
Fig. 11 Most frequently reported ADEs for trientine in FAERS and VigiAccess

JLPM JOURNAL OF LABORATORY AND PRECISION MEDICINE
AN OPEN ACCESS JOURNAL FOR HIGH-QUALITY RESEARCH IN LABORATORY MEDICINE

The results of *ATP7B* gene screening in 38,158 neonates and the clinical and variants characteristics of 14 cases with Wilson's disease

Ou Jiang[1#], Yinchun Zhang[2#], Guiping Liu[3], Yilin Lin[1], Hui Zhou[1], Mengxian Liu[2], Hongying Mi[1]

- 5 newborns were preliminarily diagnosed with WD (composite heterozygous variation)
- The remaining 27 newborns were identified as carriers



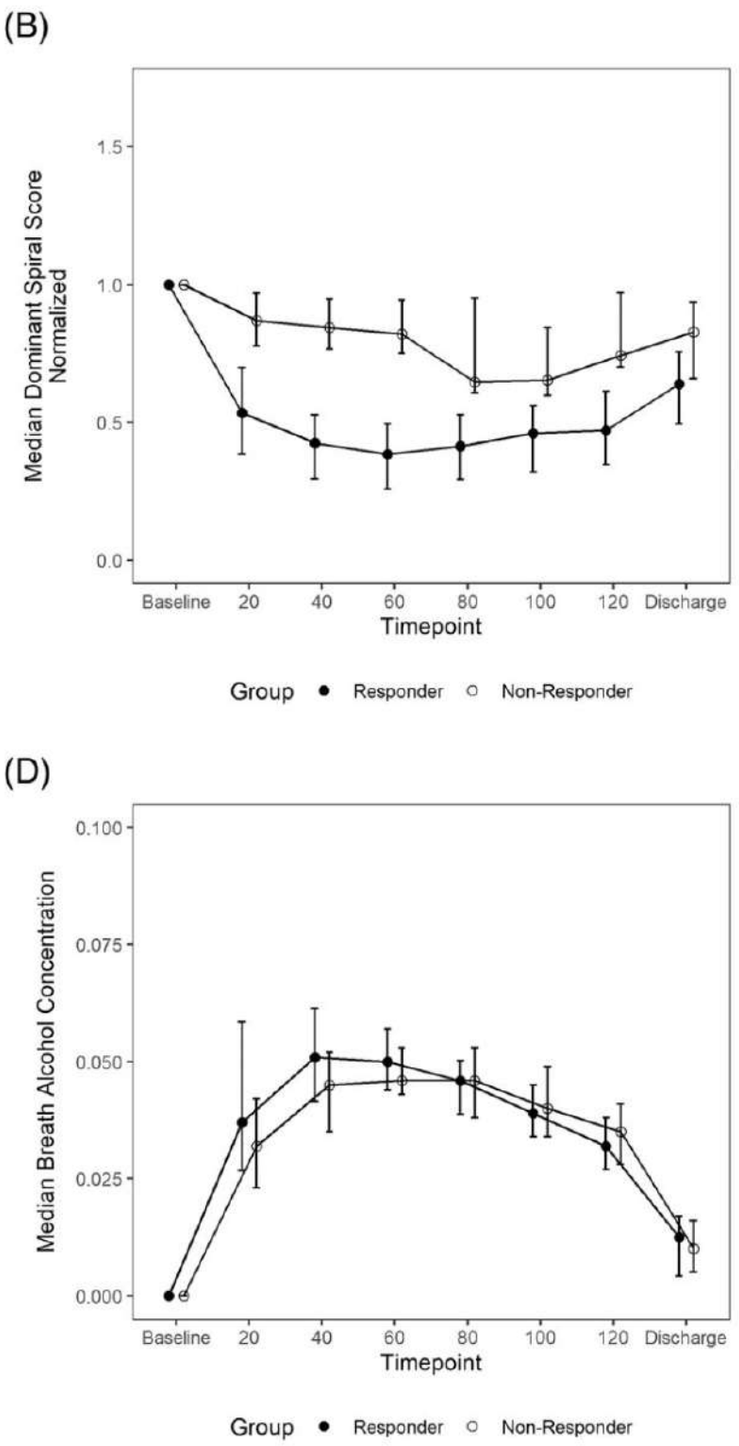
ANNALS of Clinical and Translational Neurology
Open Access
AMERICAN NEUROLOGICAL ASSOCIATION
INNOVATORS IN DISCOVERY, EDUCATION, AND CARE

RESEARCH ARTICLE

Objective response to ethanol in essential tremor: results from a standardized ethanol challenge study

Patrick McGurrin[1,2,†], Gina Norato[3,†], Johanna Thompson-Westra[2,4], Gayle McCrossin[2,5], Emily Lines[4], Codrin Lungu[6], Sanjay Pandey[7], Sule Tinaz[8], Bernhard Voller[9], Vijay Ramchandani[10], Mark Hallett[2] & Dietrich Haubenberger[2,3,11]

- Prospective, open-label, single-dose challenge
- Oral ethanol during
- Every 20 min for 120 min
- 80% were alcohol responsive (35% improvement)
- Change in objective tremor metrics correlated w/ breath alcohol concentration levels
- No change in ‘non-tremor’ metrics
- Self reported no correlation to objective change

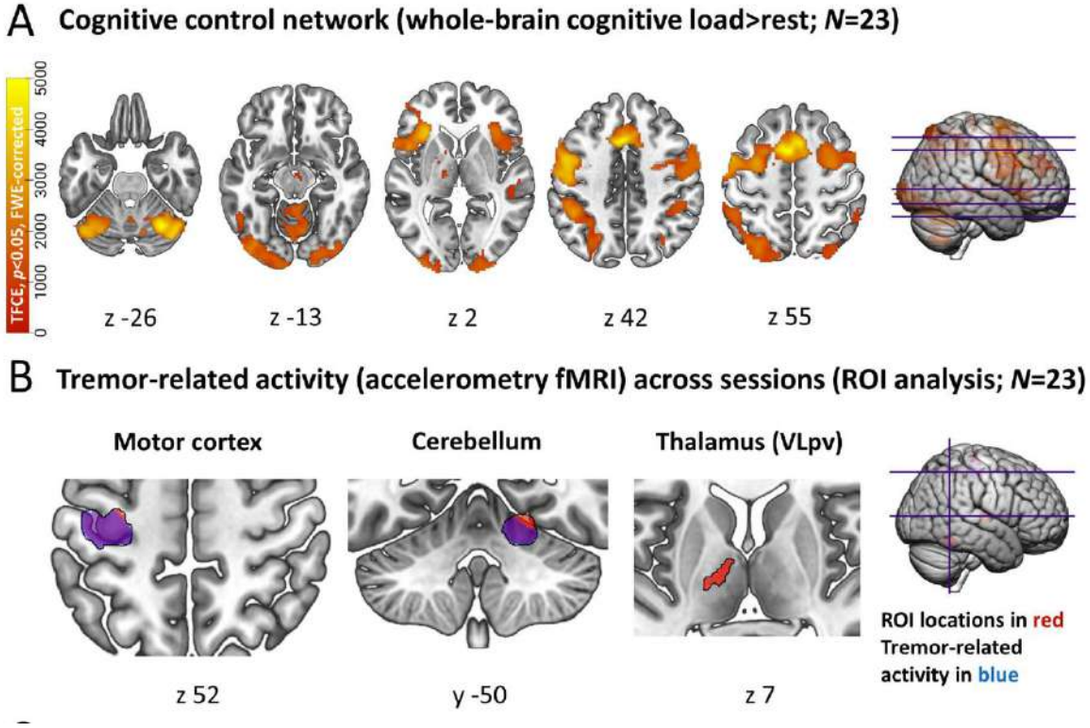


Annals of NEUROLOGY



Propranolol Reduces Parkinson's Tremor and Inhibits Tremor-Related Activity in the Motor Cortex: A Placebo-Controlled Crossover Trial

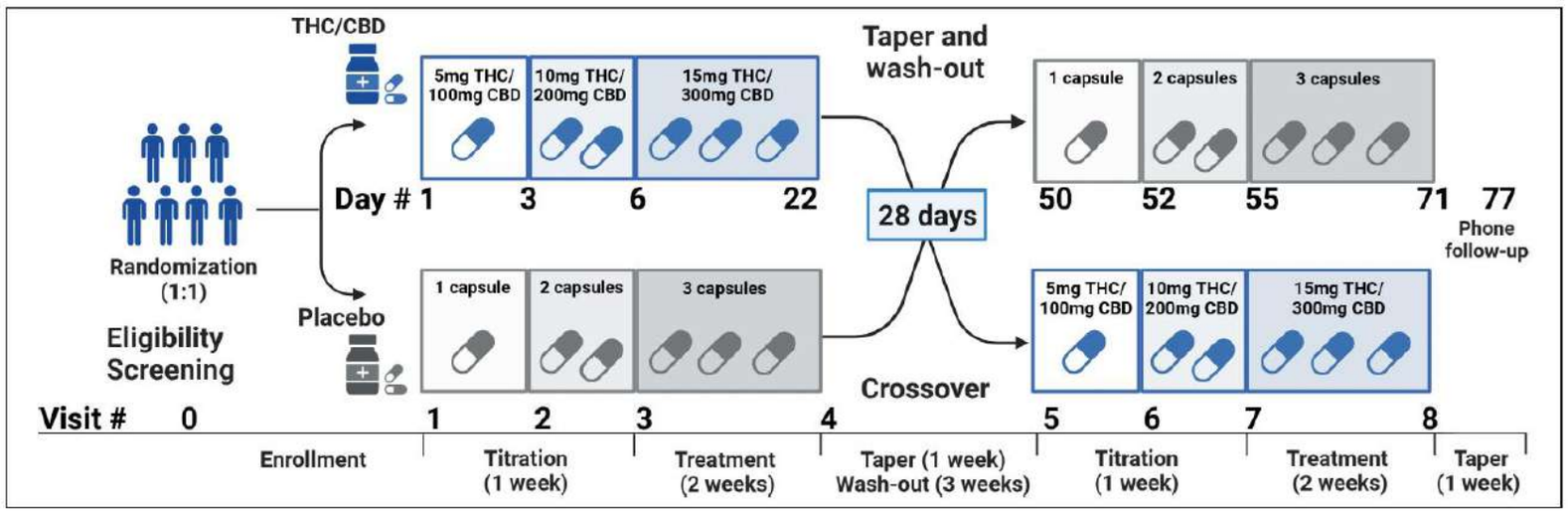
Anouk van der Heide, PhD [1,2] Maaike Wessel, MSc [2]



- Cross-over, double-blind intervention
- Propranolol 40mg vs. placebo
- 27 participants
- Tremor worsened during cognitive load
- Tremor improved w/ propranolol
- Found a stress-sensitive cognitive control network
- Reduced tremor-related activity in the motor cortex
- Propranolol effect was context-independent

Tremor
and Other Hyperkinetic Movements

Double-Blind, Randomized, Placebo-Controlled, Crossover Study of Oral Cannabidiol and Tetrahydrocannabinol for Essential Tremor





No effect in this double-blind, randomized, placebo-controlled efficacy and tolerability pilot trial

JAMA Neurology



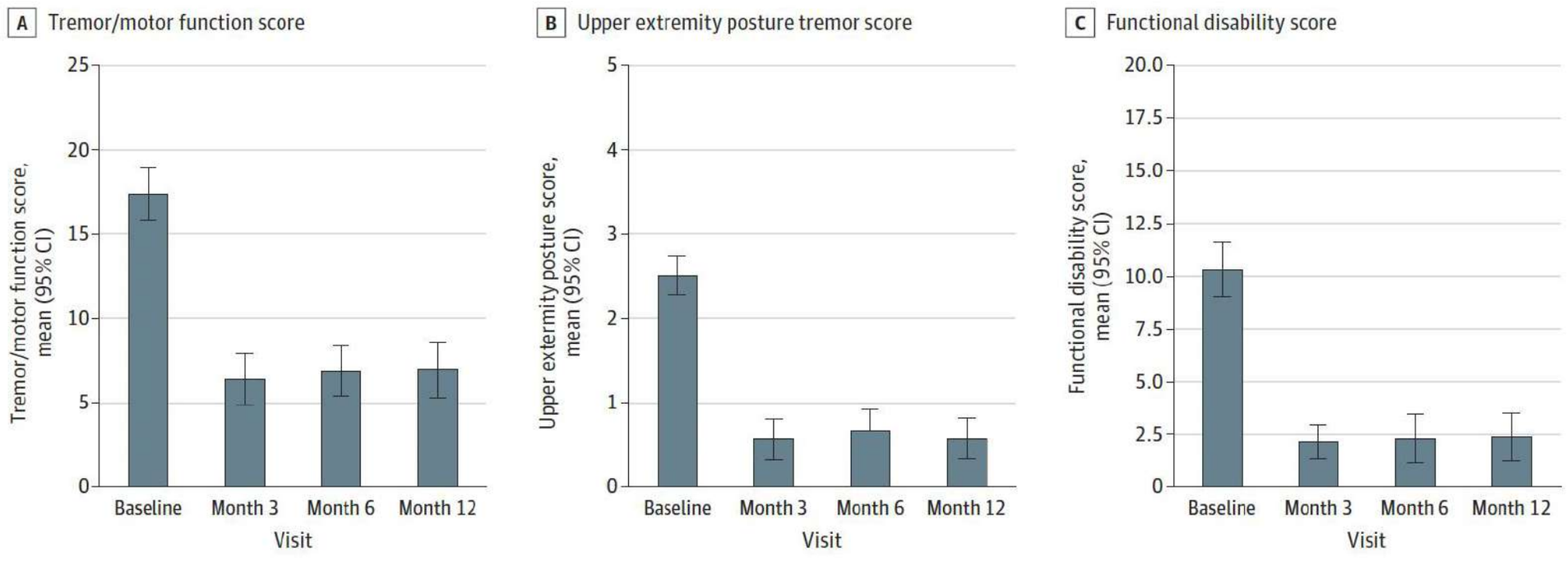
JAMA Neurology | Original Investigation

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

An Open-Label Clinical Trial

Michael G. Kaplitt, MD, PhD; Vibhor Krishna, MD; Howard M. Eisenberg, MD; W. Jeffrey Elias, MD; Pejman Ghanouni, MD, PhD; Gordon H. Baltuch, MD; Ali Rezai, MD; Casey H. Halpern, MD; Brian Dalm, MD; Paul S. Fishman, MD, PhD; Vivek P. Buch, MD; Shayan Moosa, MD; Harini Sarva, MD; Ann Marie Murray, MD

Figure 2. Tremor/Motor Scores, Postural Tremor Scores, and Tremor Disability Scores at Baseline and Follow-up After Staged Bilateral Focused Ultrasound Ablation



The number of participants assessed at baseline, month 3, month 6, and month 12 visits are 51, 50, 50, and 45, respectively.

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

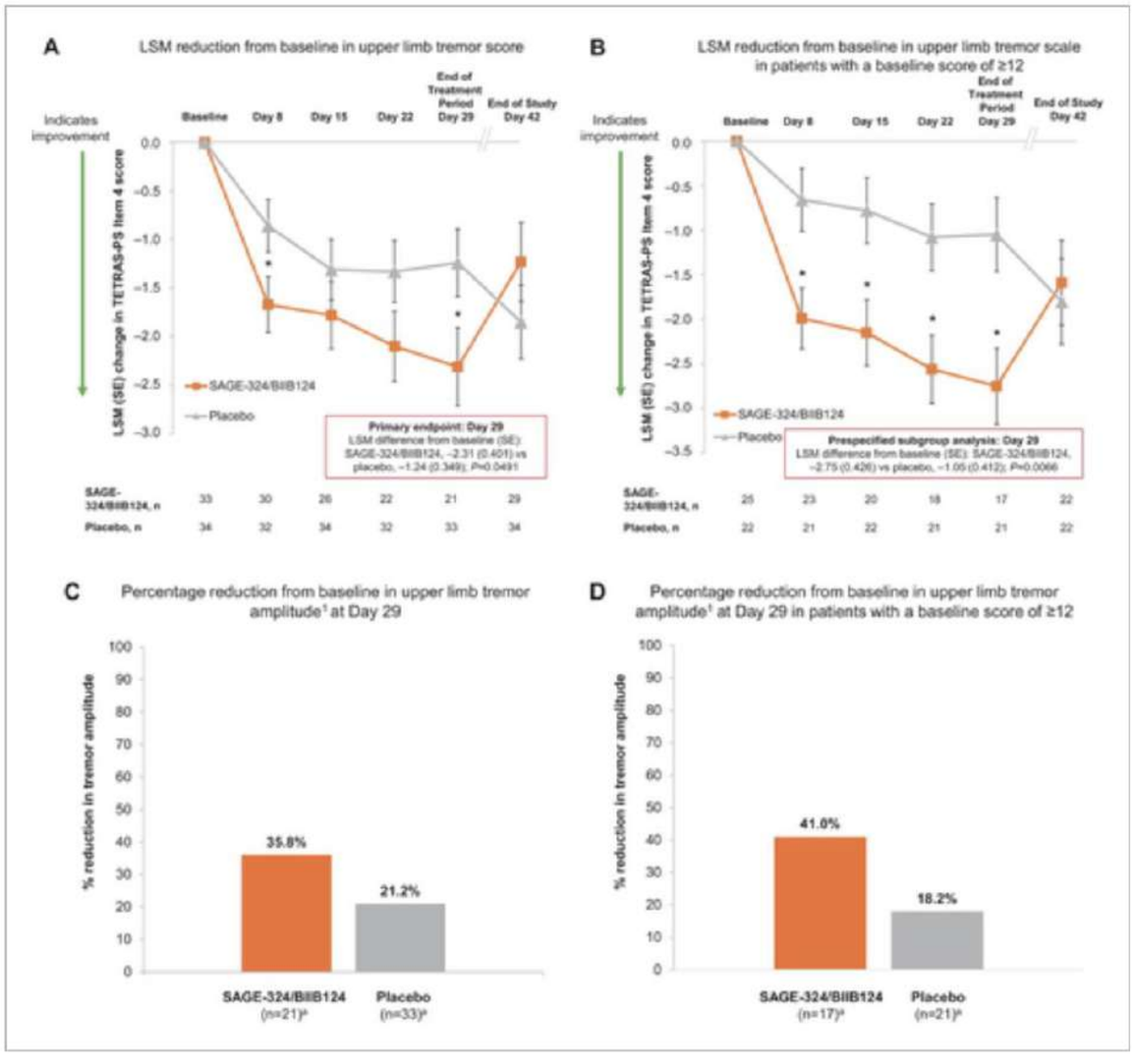
BRIEF REPORTS | Open Access

A Randomized Phase 2 KINETIC Trial Evaluating SAGE-324/BIIB124 in Individuals with Essential Tremor

Rodger J. Elble MD, PhD, William G. Ondo MD, Kelly E. Lyons PhD, Min Qin PhD, Svetlana Garafola MD, Bonnie Hersh MD, TinaMarie Lieu PhD, Dimitrios Arkilo MD, Rosalind Chuang MD ... See all authors

First published: 15 February 2024 | https://doi.org/10.1002/mds.29731

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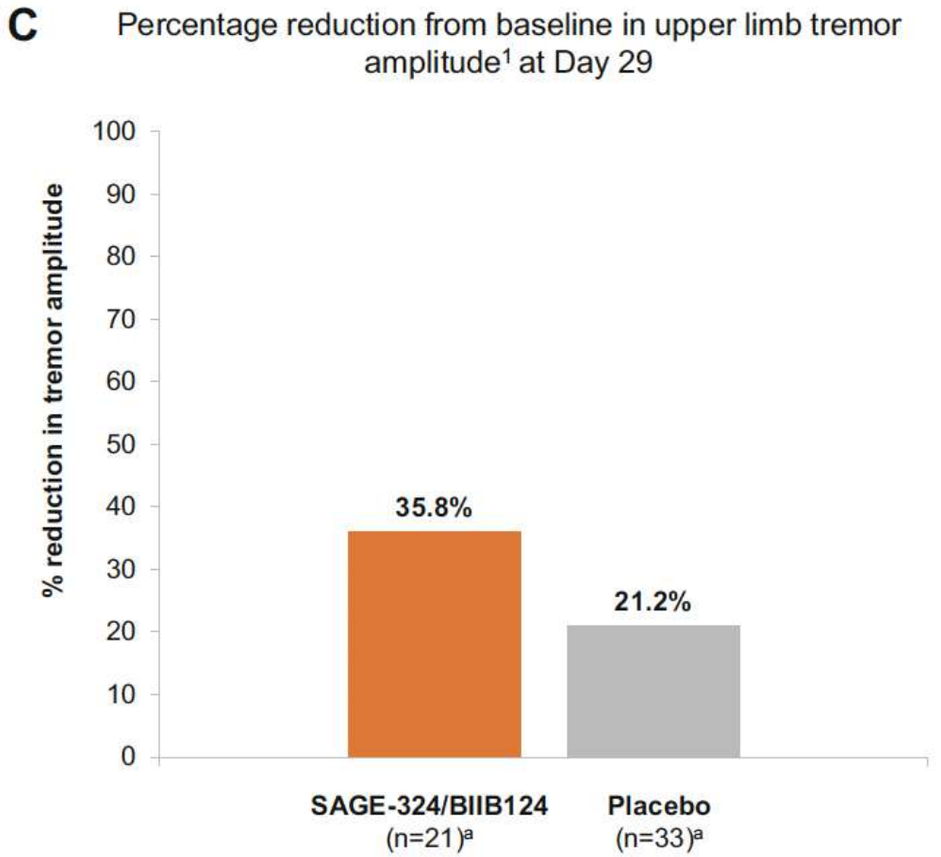
A Randomized Phase 2 KINETIC Trial Evaluating SAGE-324/ BIIB124 in Individuals with Essential Tremor

Rodger J. Elble, MD, PhD,[1] William G. Ondo, MD,[2]
Kelly E. Lyons, PhD,[3] Min Qin, PhD,[4]
Svetlana Garafola, MD,[4] Bonnie Hersh, MD,[5]
TinaMarie Lieu, PhD,[4] Dimitrios Arkilo, MD,[4]
Rosalind Chuang, MD,[5] Kemi Bankole, MBBCh,[4*] and
Rajesh Pahwa, MD[3]

69 individuals

Amplified inhibitory neurotransmission using a positive allosteric modulator

-Target: GABA-A receptor



RESEARCH ARTICLE

Essential Tremor Suppression with a Novel Anti-Tremor Orthosis: A Randomized Crossover Trial

Winfred Mugge, PhD,[1*] Liset E.M. Elstgeest, PhD,[2] Milan van Ginkel, MSc,[3] Lucas Pol, BSc,[3] IJsbrand de Lange, MSc,[4*] Nicola Pambakian, MSc,[4] Alvaro Assis de Souza, MSc,[4] Rick C. Helmich, MD, PhD,[5] and Daan J. Kamphuis, MD[3]



FIG. 1. The anti-tremor orthosis on the left, "sham" device on the right. The sham device has similar weight, usability, and feeling, but has no joint damping or a limit on wrist radial/ulnar deviation. The novel anti-tremor orthosis consists of an elbow piece and a hand piece, connected by a rigid extension element, via a total of three joints. The orthosis is completely passive, and therefore, does not require software or electronics for its operation.

The NEW ENGLAND JOURNAL of MEDICINE

RESEARCH SUMMARY

Trial of Botulinum Toxin for Isolated or Essential Head Tremor

Marques A et al. DOI: 10.1056/NEJMoa2304192

CLINICAL PROBLEM

Local injection of botulinum toxin is widely used to treat head tremor, but randomized trials assessing its effects are limited. In 2019, an evidence-based review commissioned by the Movement Disorder Society concluded that there is insufficient evidence for the use of any agent in the treatment of head tremor.

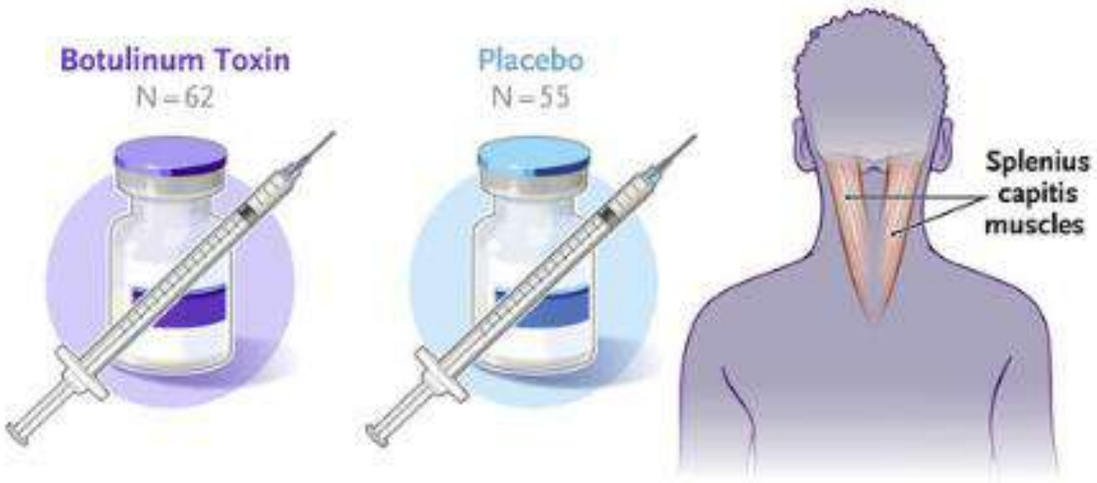
CLINICAL TRIAL

Design: A multicenter, double-blind, randomized, placebo-controlled trial conducted in France assessed the efficacy and safety of botulinum toxin injection in adults with isolated or essential head tremor.

Intervention: 117 patients were assigned to receive injections of botulinum toxin type A or placebo into each splenius capitis muscle under electromyographic guidance on day 0 and during week 12. The primary outcome was improvement by ≥2 points on the 7-point Clinical Global Impression of Change (CGI) scale at week 18.

RESULTS

Efficacy: The percentage of patients with improvement by ≥2 points on the CGI scale at week 18 was significantly greater in the botulinum toxin group than in the placebo





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

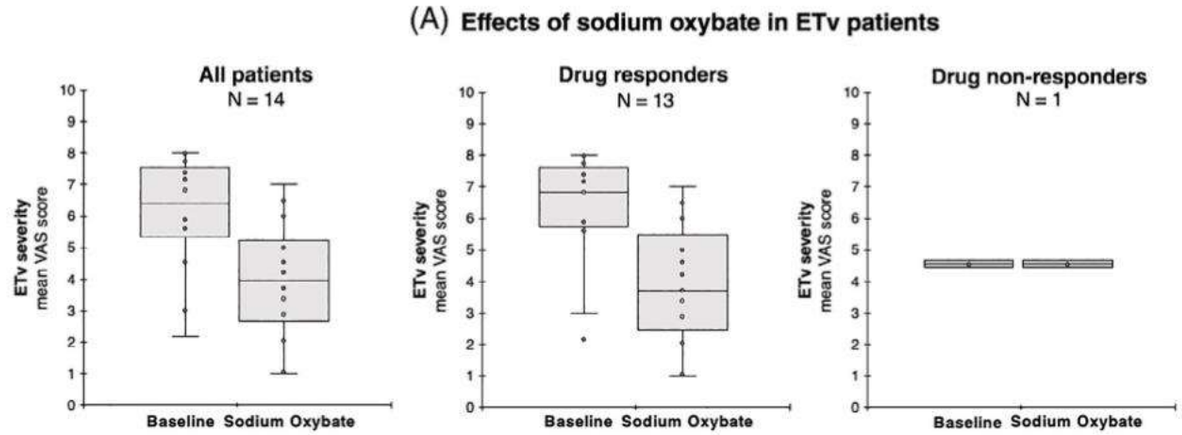


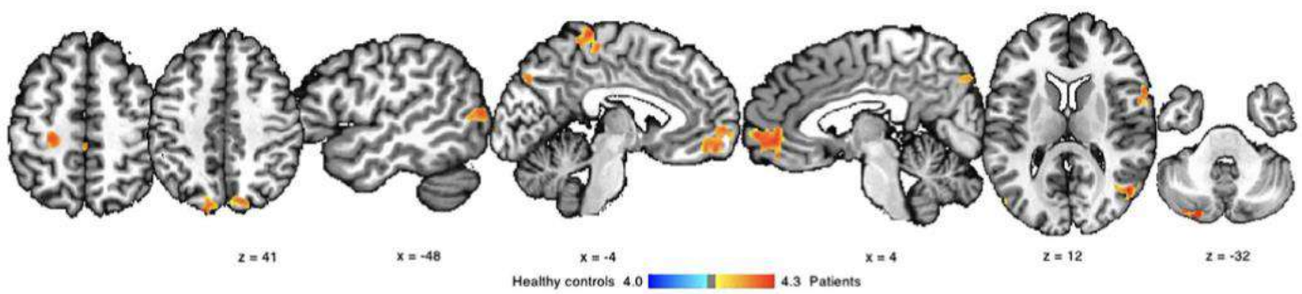
RESEARCH ARTICLE | Open Access

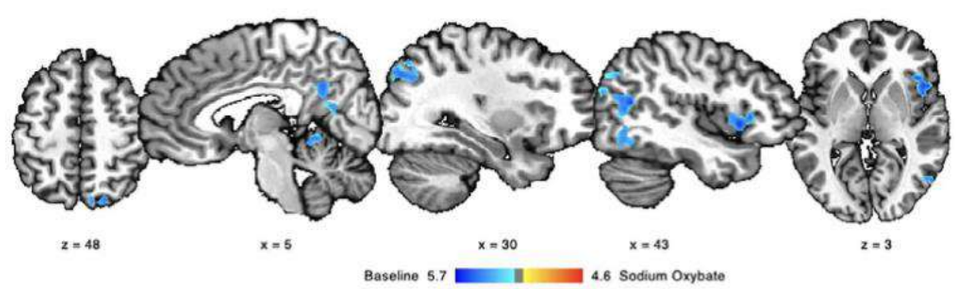
Sodium Oxybate in Alcohol-Responsive Essential Tremor of Voice: An Open-Label Phase II Study

Lena C. O'Flynn BA, Steven J. Frucht MD, Kristina Simonyan MD, PhD, Dr med

First published: 14 July 2023 | https://doi.org/10.1002/mds.29529 | Citations: 1

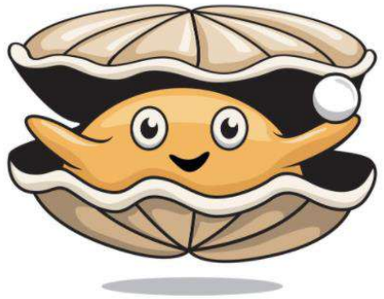








Michael Okun @MichaelOkun · Jan 12



Can **abdominal tremor** be part of Parkinson's disease? You bet you can. What about **invisible tremor**? Yep. Check out this case of continuous, rhythmic contractions of the rectus abdominis muscles by Neuville and Morenkova in @tremorjournal

Key points:

- Tremor is common in

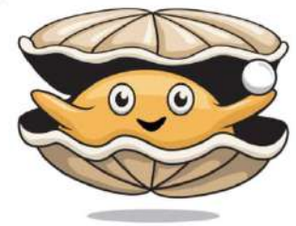
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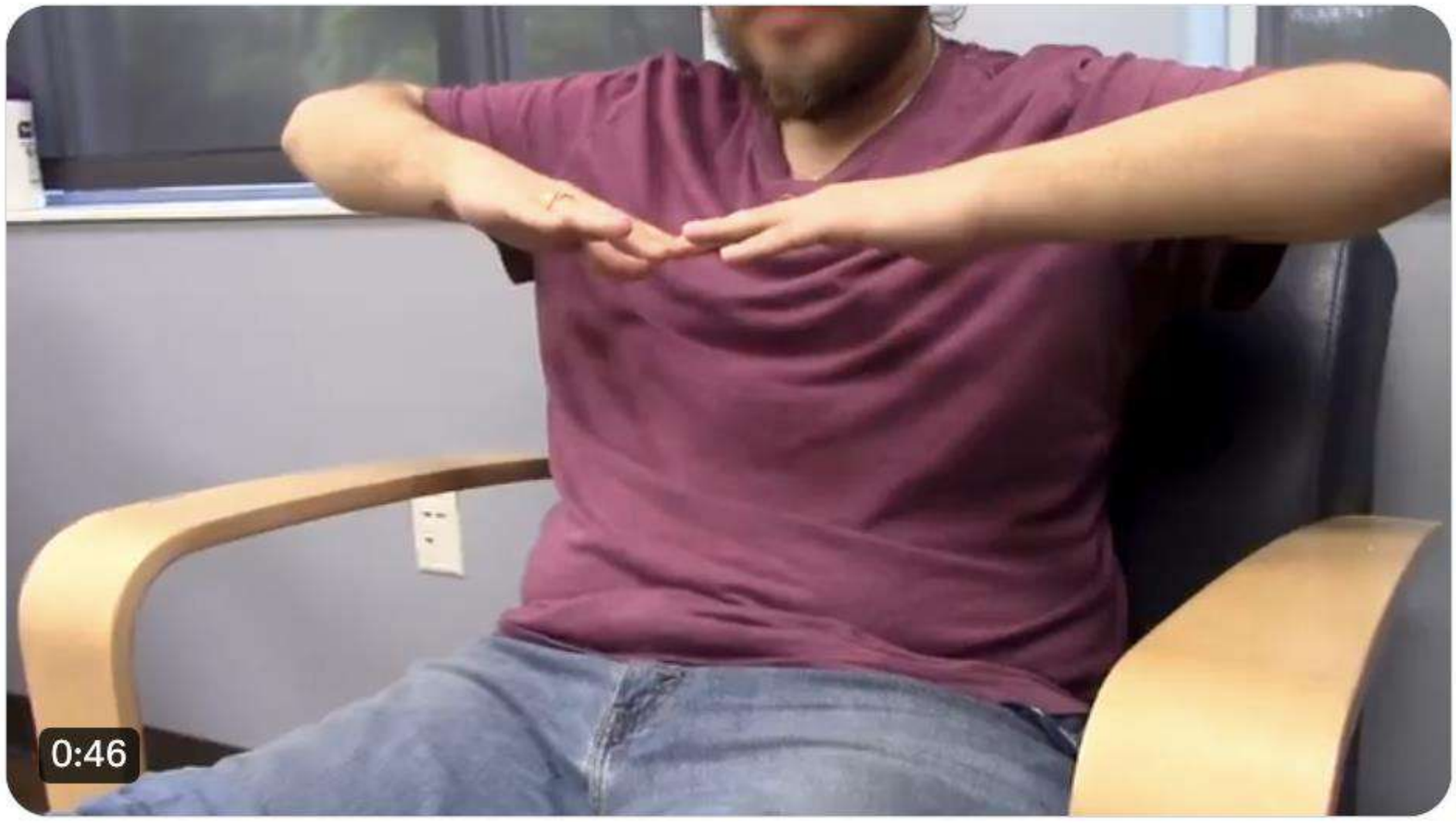


Michael Okun @MichaelOkun · Feb 10



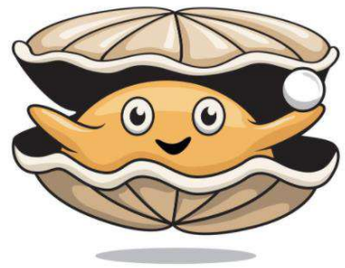
Can **tremor** occur in **Charcot-Marie-Tooth** neuropathy cases? You bet it can. For those of us old enough to remember the eponym **Roussy-Lévy syndrome**, you will enjoy this video and genetic case by Kumar, Subramanian and Shukla @FixelInstitute which appeared in a recent paper in

Show **more**

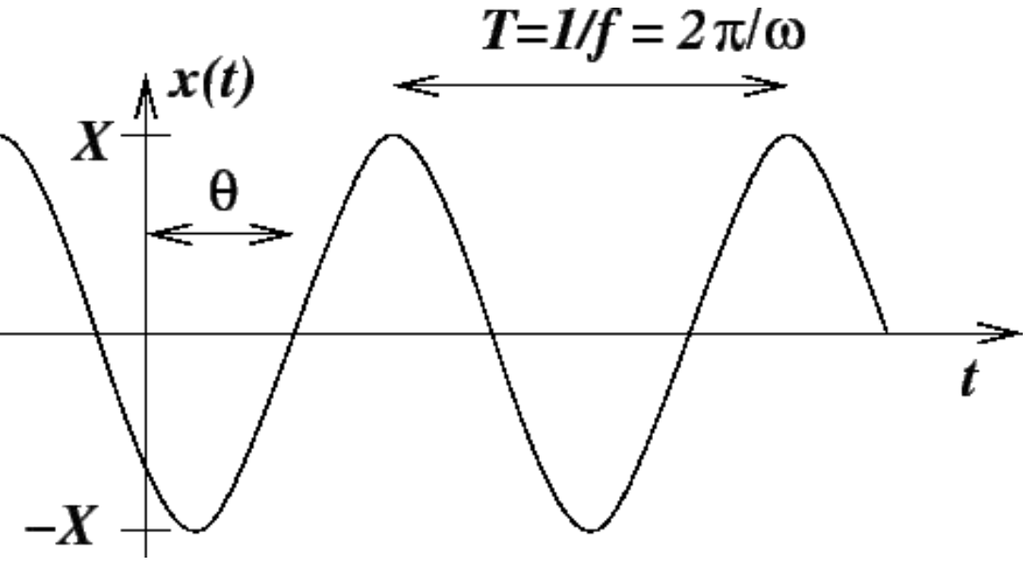


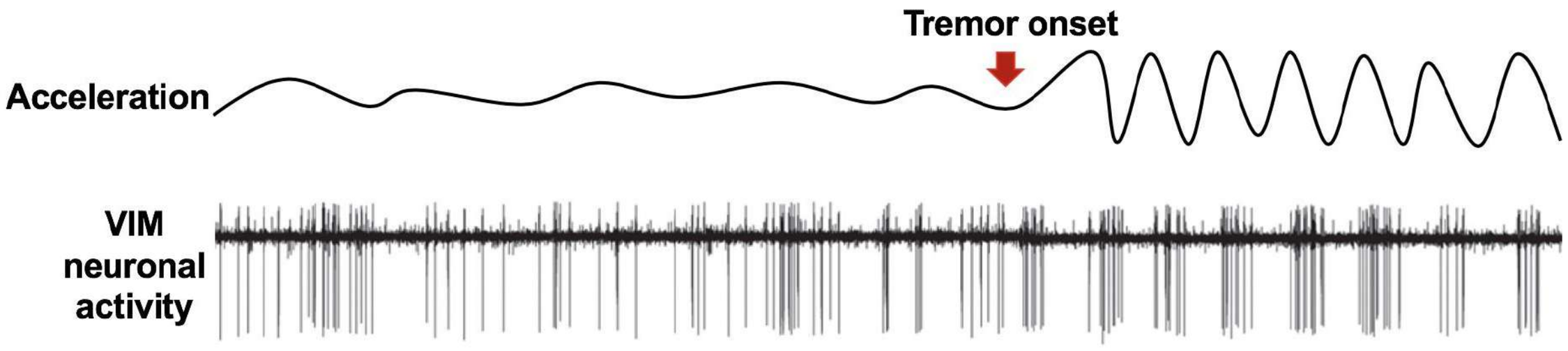
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Tremor: Definition



An involuntary, rhythmic oscillatory movement of a of body part(s)



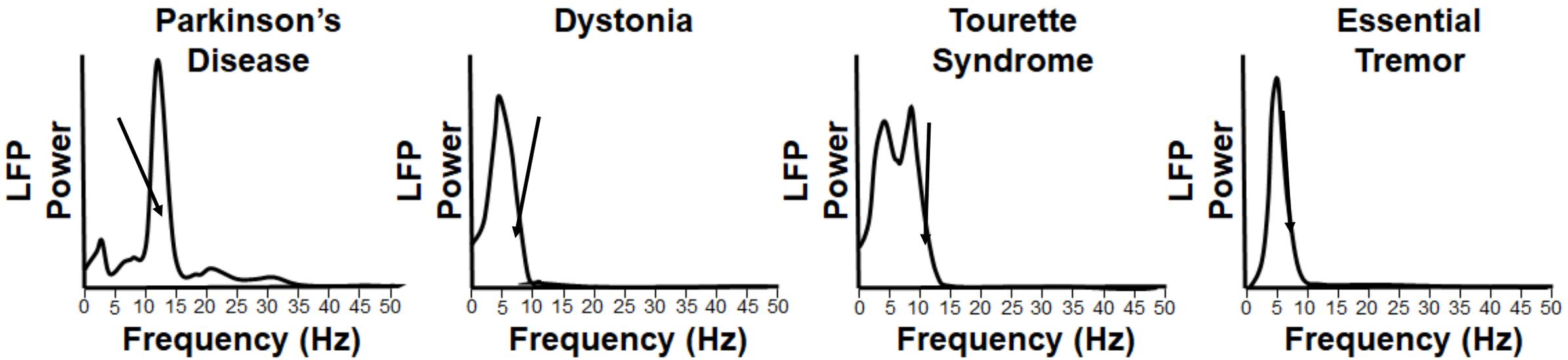


Milosevic et al., 2018. *Brain*

Oscillations

Disease specific and possibly symptom specific

Pathological oscillations: Overview



Parkinsonism and Related Disorders 59 (2019) 9–20

Contents lists available at ScienceDirect

Parkinsonism and Related Disorders

journal homepage: www.elsevier.com/locate/parkreldis

A review of basal ganglia circuits and physiology: Application to deep brain stimulation

Robert S. Eisinger[a,1], Stephanie Cernera[b,*,1], Aryn Gittis[c], Aysegul Gunduz[a,b,d,2], Michael S. Okun[a,d,2]

[a] Department of Neuroscience, University of Florida, Gainesville, FL, USA
[b] Department of Biomedical Engineering, University of Florida, Gainesville, FL, USA
[c] Biological Sciences and Center for Neural Basis of Cognition, Carnegie Mellon University, Pittsburgh, PA, USA
[d] Department of Neurology, Fixel Center for Neurological Diseases, University of Florida, Gainesville, FL, USA

HISTORICAL NEUROLOGY

Did General Douglas MacArthur have Parkinson disease?

A video and archival analysis

Lauren N. Bowen, BS
Irene A. Malaty, MD
Ramon L. Rodriguez, MD
Michael S. Okun, MD

Address correspondence and reprint requests to Lauren N. Bowen c/o Dr. Michael S. Okun, Department of Neurology, 100 S. Newell Drive, Bldg. 59, Box 100236, L3-100 Gainesville, FL 32611
lauren.bowen@ufl.edu

ABSTRACT

Background: Historians have suggested that MacArthur had Parkinson disease (PD), and that this may have influenced his military judgment. There is little evidence to support or to refute this suggestion.

Objective: We aimed in this article to review multiple cinematic images, as well as the personal writings of Douglas MacArthur to determine the likelihood that he had PD.

Methods: A complete review of the Western literature on Douglas MacArthur, including YouTube, Google Scholar/Google Images/Google Video, PubMed, and HighWirePress was undertaken. Over 200 minutes of film footage was analyzed, including such factors as MacArthur's facial profiles, facial expression, gait, posture, and movement. Handwriting samples from over 6 decades were compared for evidence of micrographia. Videos and handwriting samples were independently reviewed by 3 fellowship-trained movement disorders neurologists.

Results: Examination of video footage showed evidence of progression of head tremors, postural action tremors, and voice tremors. There were no clear indications of a masked face, rigidity, bradykinesia, or a resting tremor on film footage recorded from 1906 to 1964. There was no evidence of micrographia in handwriting samples. Oral testimony and letters written by an attending gastroenterologist present at MacArthur's death in 1964 revealed no evidence of parkinsonian features.

Conclusions: We conclude that MacArthur had mild essential tremor that was more evident in his postmilitary career. There was no evidence to suggest that he had a clinical diagnosis of progressive PD. **Neurology® 2011;76:1669–1672**

What did MacArthur have?



Movement Disorders
CLINICAL PRACTICE

Instagram for Measuring Tremor: Who Holds the Camera?



*Roberto Erro, MD, PhD,** *Cristiano Sorrentino, MD, and Paolo Barone, MD, PhD*

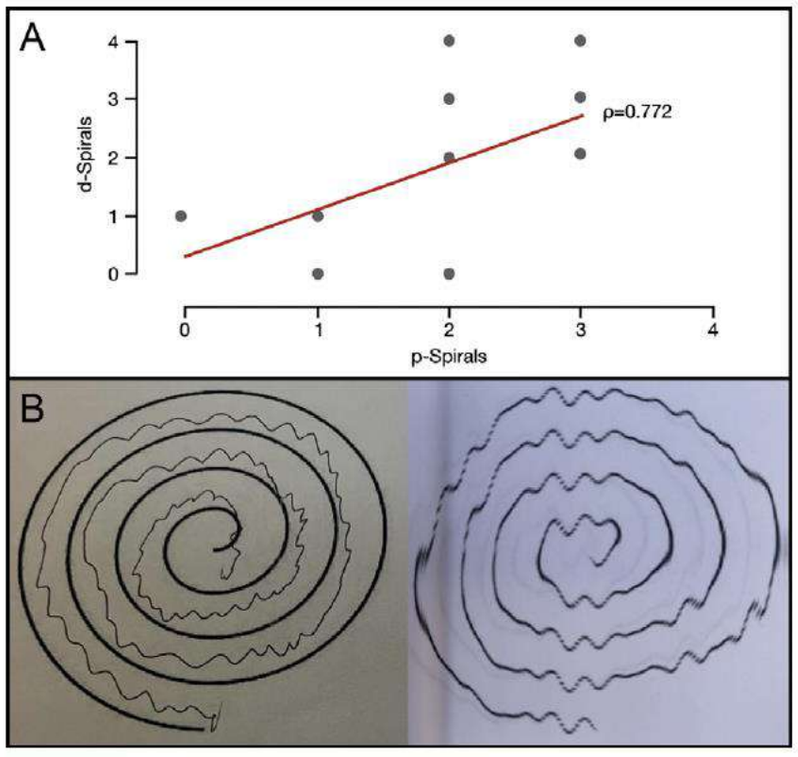
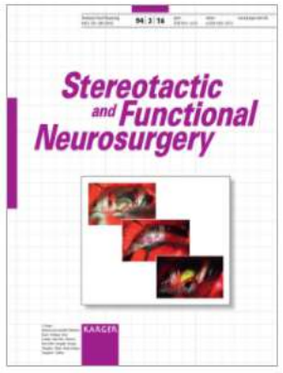


FIG. 1. (A) Best-fit Spearman rank correlation curve between drawn spirals (d-spirals) and photographed spirals (p-spirals). (B) Examples of drawn (left) and photographed (right) spirals in a patient with essential tremor.

Volume 94, Issue 3
August 2016



RESEARCH ARTICLES | JULY 09 2016

TREMOR12: An Open-Source Mobile App for Tremor Quantification

Subject Area: Neurology and Neuroscience , Surgery

Pieter L. Kubben; Mark L. Kuijf; Linda P.C.M. Ackermans; Albert F.G. Leentjes; Yasin Temel

Stereotact Funct Neurosurg (2016) 94 (3): 182–186.
https://doi.org/10.1159/000446610 Article history

Split-Screen Views Download Share Tools

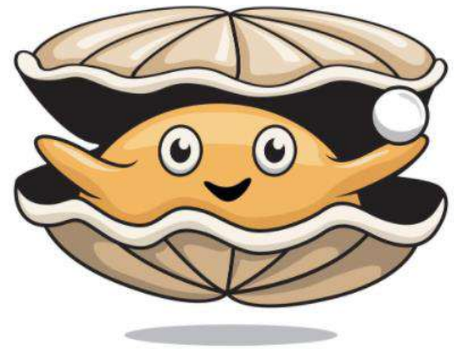


Tremor Analysis 4+
Christopher Lee
★★★★★ 5.0 • 4 Ratings
Free

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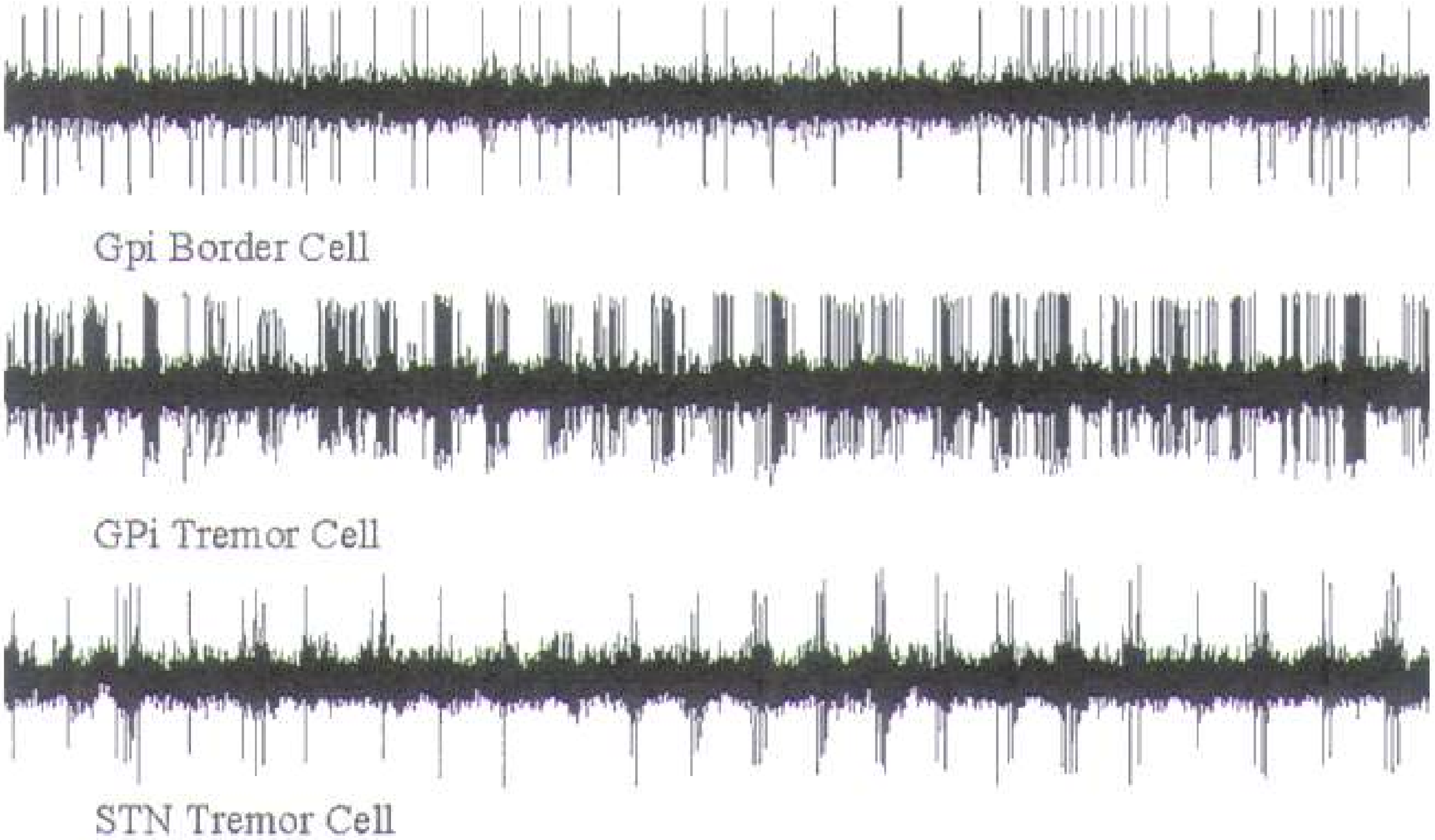
Tremor Measurement
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Tremor

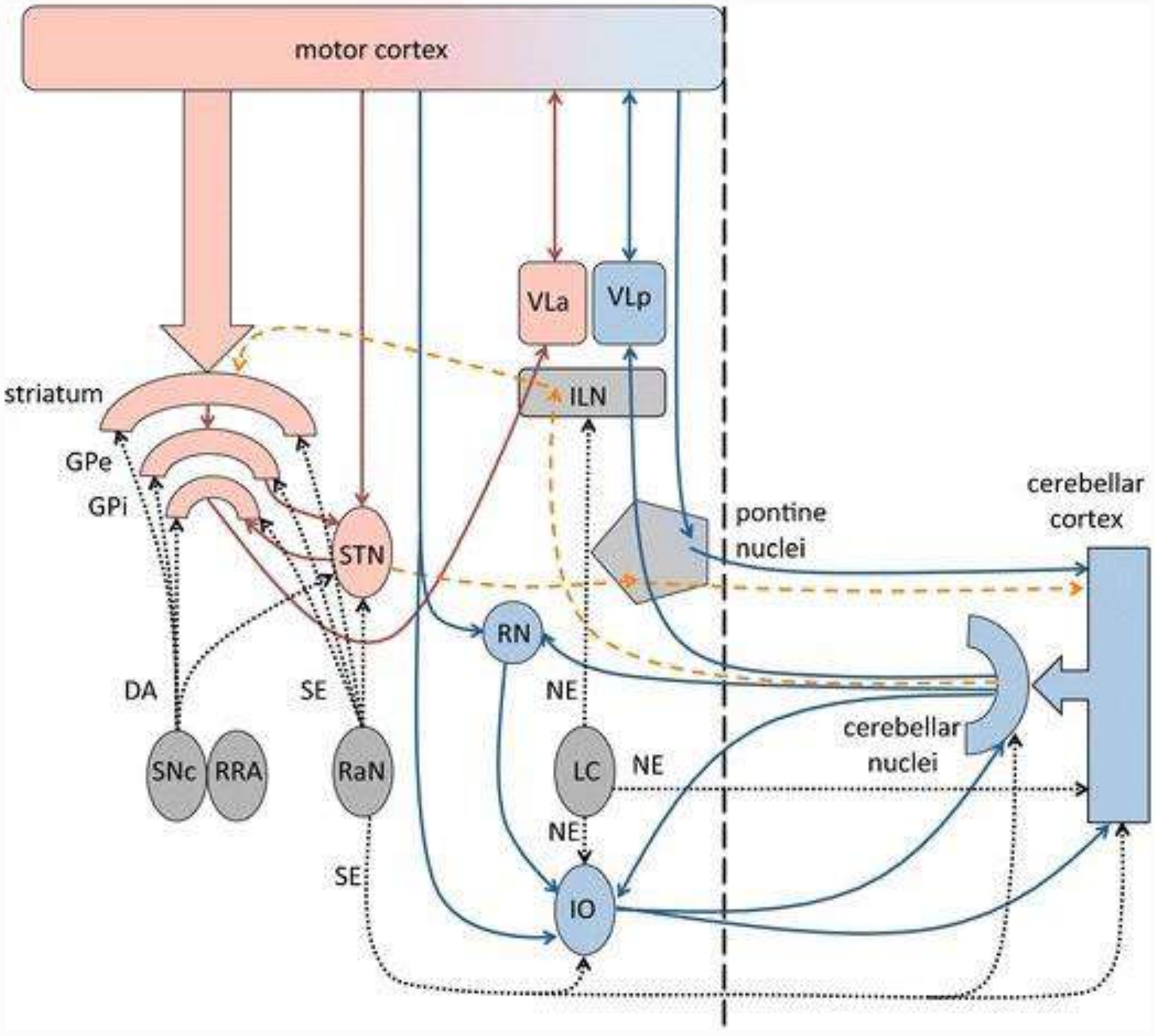


- Involuntary, rhythmic oscillation of muscle groups causing movement of a body part
- Frequency varies from ~4-12 Hz
- Amplitude varies from fine to coarse
- May occur at rest, with posture, or with action
- May be unifocal, multi-focal, or generalized
- May affect head, face, jaw, voice, tongue, trunk, or extremities

Rhythmic Tremor Cells



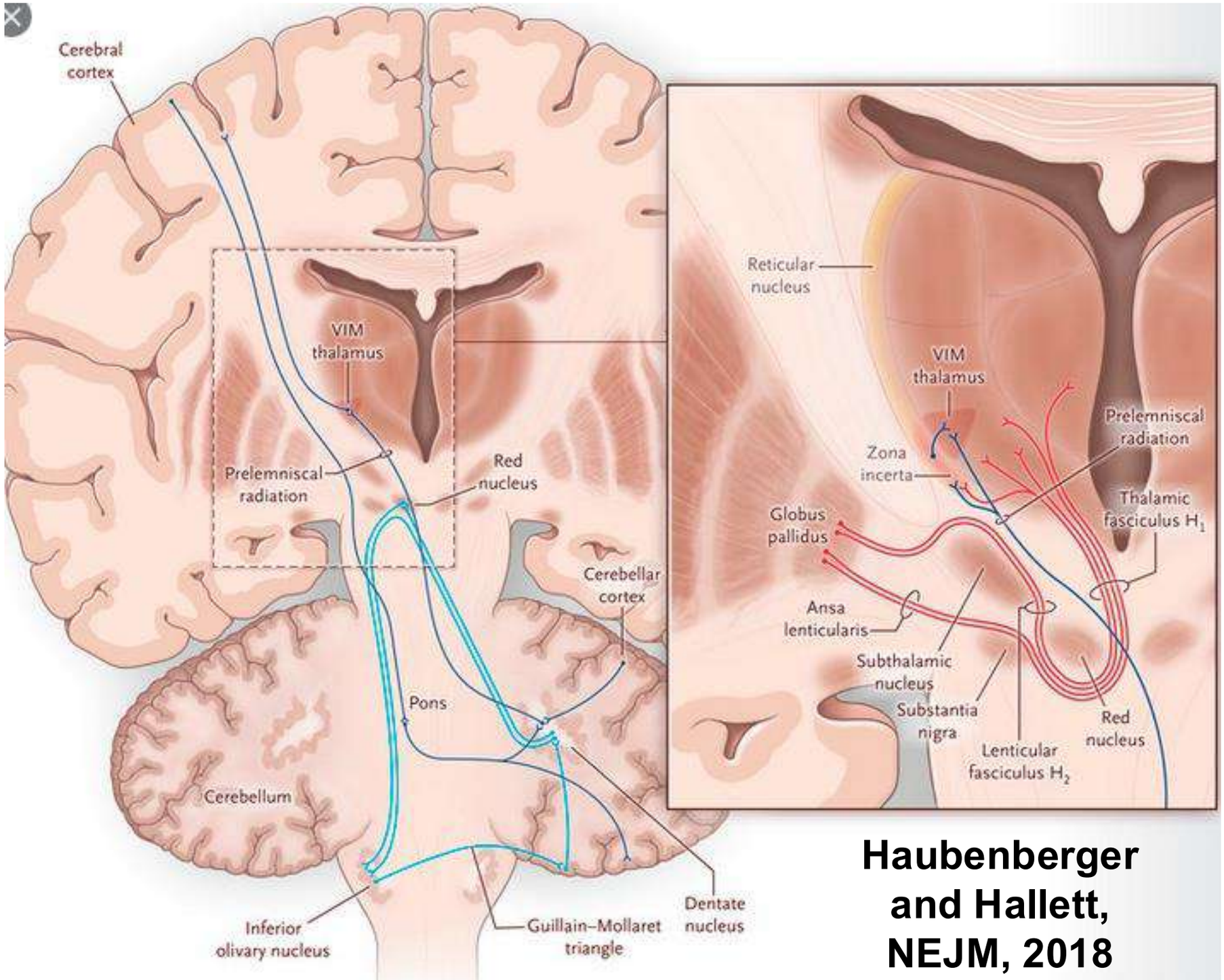
Functionalneurosurgery.net



Helmich, et. al. 2013

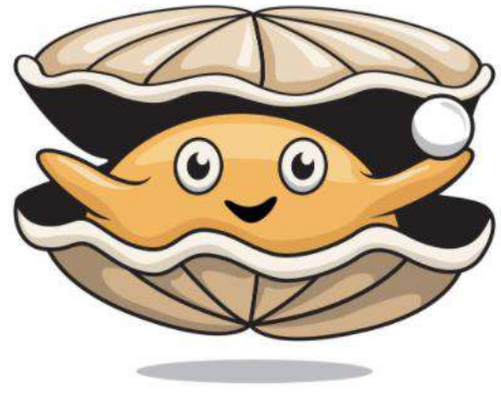
Current Neurology and Neuroscience Reports

Mechanism of Action



Haubenberger and Hallett, NEJM, 2018

Commonly mistaken as tremor



- Cortical tremor-myoclonus
- Asterixis (negative myoclonus)
- Rhythmic Dyskinesias (as in Biphasic Dyskinesias)
- Epilepsia Partialis Continua
- Stereotypies
- Clonus
- Hereditary geniospasm (chin quivering)

MDS Task Force on Tremor Proposed Classification Scheme

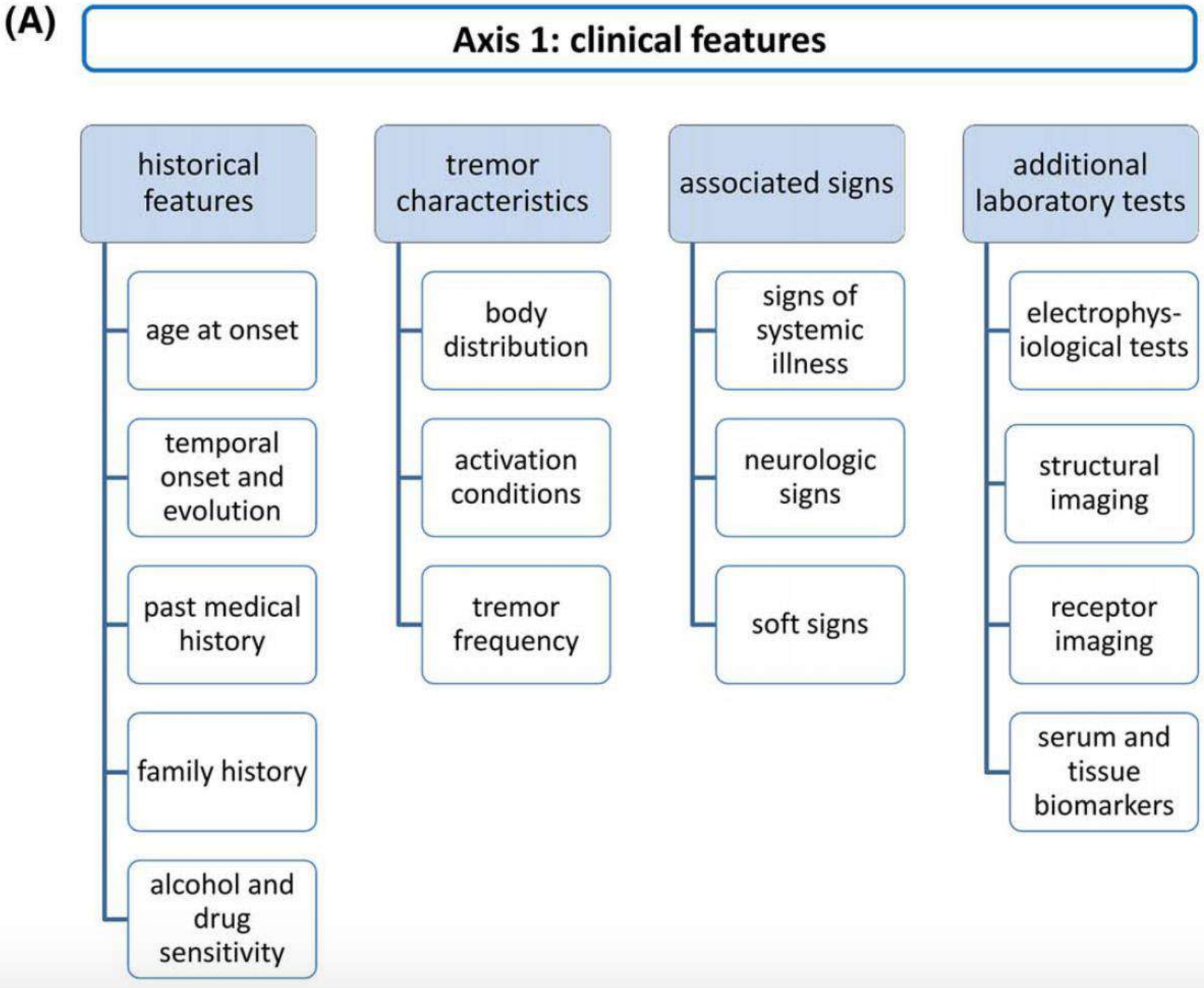
RESEARCH ARTICLE

Consensus Statement on the Classification of Tremors. From the Task Force on Tremor of the International Parkinson and Movement Disorder Society

Kailash P. Bhatia, MD, FRCP,[1] Peter Bain, MD, PhD,[2] Nin Bajaj, MD, PhD, FRCP,[3] Rodger J. Elble, MD, PhD,[4] Mark Hallett, MD, PhD,[5] Elan D. Louis, MD,[6] Jan Raethjen, MD, PhD,[7] Maria Stamelou, MD, PhD,[8] Claudia M. Testa, MD, PhD,[9] Guenther Deuschl, MD, PhD,[7*] and the Tremor Task Force of the International Parkinson and Movement Disorder Society[†]

- Axis 1 Clinical Characteristics
- Axis 2 Etiology

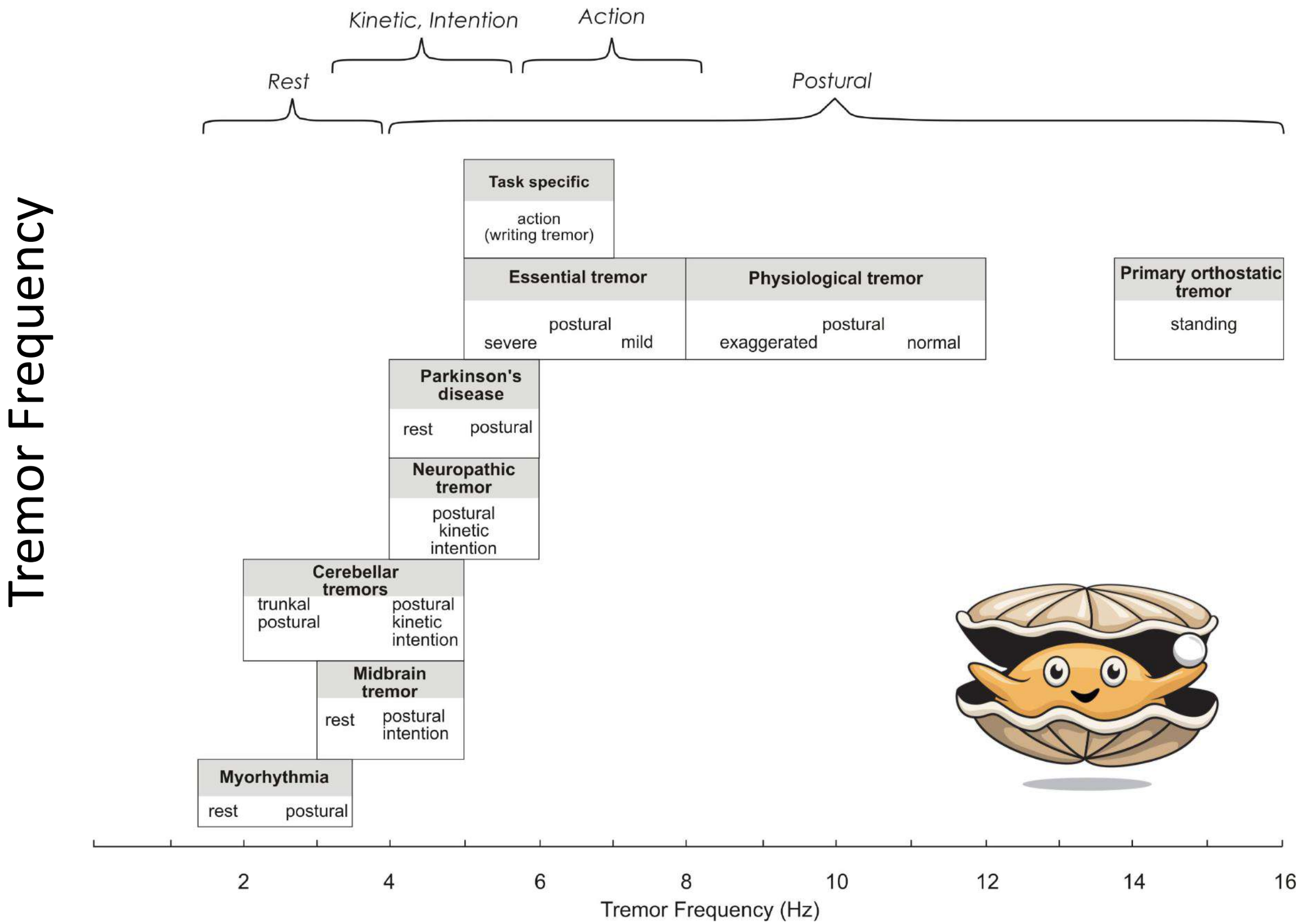
Axis I


(A)
Axis 1: clinical features
historical features
age at onset
temporal onset and evolution
past medical history
family history
alcohol and drug sensitivity
tremor characteristics
body distribution
activation conditions
tremor frequency
associated signs
signs of systemic illness
neurologic signs
soft signs
additional laboratory tests
electrophys-iological tests
structural imaging
receptor imaging
serum and tissue biomarkers

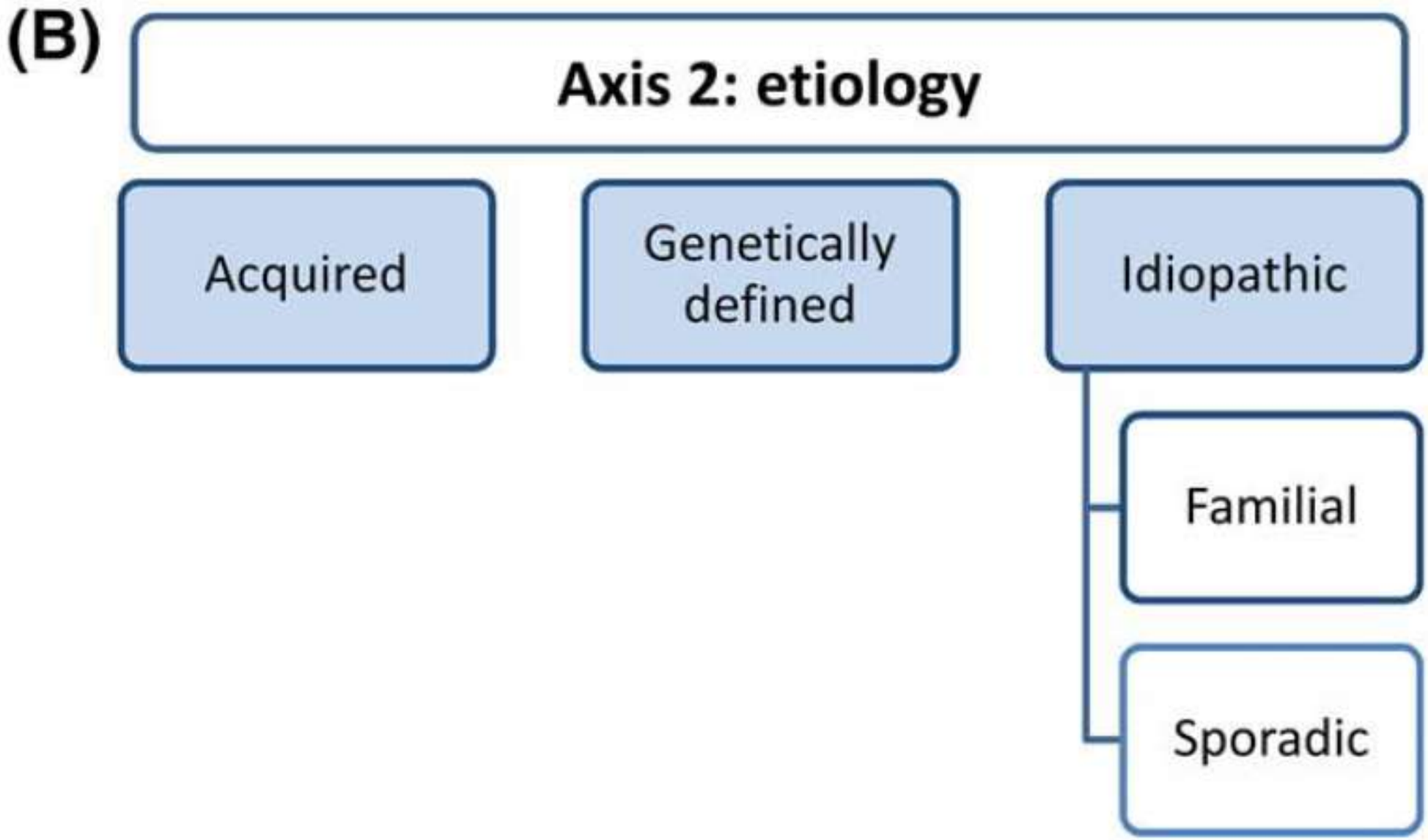
Tremor Characteristics

- Based on Activation
- Rest tremor
- Action tremor
- Postural tremor
  - Position specific
  - Intention(terminal kinetic)
    - simple kinetic
    - task specific

Don’t be fooled by frequency



Axis II


(B)
Axis 2: etiology
Acquired
Genetically defined
Idiopathic
Familial
Sporadic

Physiological Tremor

- 8-12Hz
- No other signs (normal finding)

Mechanisms

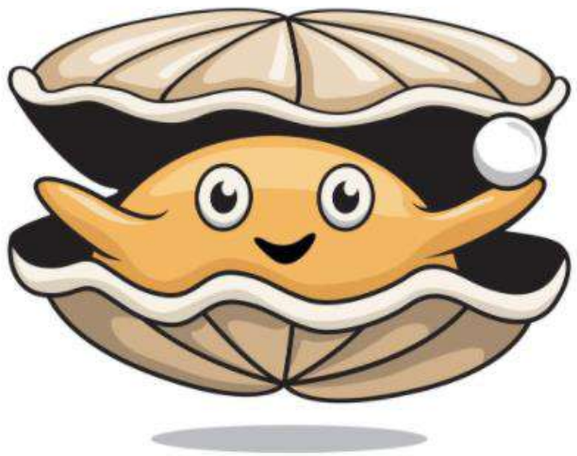
- Mechanical component
  - damped oscillations
    - muscle contraction
    - Cardio-ballistic impulse
    - Discontinuities of innervation
- Reflex enhancement
- Central component
    - Olivo-cerebellar system

Exaggerated Physiological Tremor

Similar mechanism to physiological tremor
…but of larger amplitude

Think these 5 potential causes:

- Drugs
- Fatigue
- Anxiety
- Hypoglycemia
- Thyrotoxocosis



Essential Tremor



Papers suggesting increase PD pathology in ET populations (Louis v. Shils)

Journal of Neuropathology & Experimental Neurology, 2023, 82, 454–455
https://doi.org/10.1093/jnen/nlad021
Advance access publication 21 March 2023
Letter to the Editor

OXFORD

Letter to the Editor

Prevalence of Lewy pathology in essential tremor is twice as high as expected: A plausible explanation for the enhanced risk for Parkinson disease seen in essential tremor cases

Elan D. Louis, MD[1]*, Phyllis L. Faust, MD, PhD[2]

[1]Department of Neurology, University of Texas Southwestern Medical Center, Dallas, Texas, USA
[2]Department of Pathology and Cell Biology, Columbia University Irving Medical Center and the New York Presbyterian Hospital, New York, New York, USA

*Send correspondence to: Elan D. Louis, MD, Department of Neurology, University of Texas Southwestern Medical Center, 5323 Harry Hines Blvd, Dallas, TX 75390-8813, USA;
E-mail: elan.louis@UTSouthwestern.edu

RESEARCH ARTICLE

Conversion Rate of Essential Tremor to Essential Tremor Parkinson Disease

Data From a Prospective Longitudinal Study

Elan D. Louis, MD, Diane Berry, PhD, Ali Ghanem, MD, and Stephanie A. Cosentino, PhD

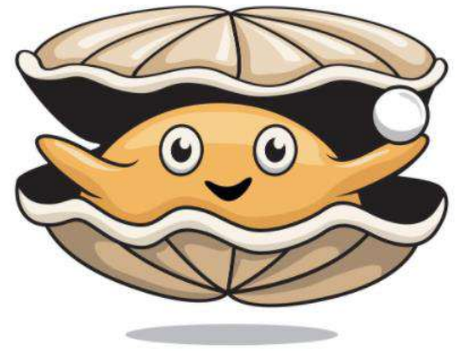
Neurology: Clinical Practice 2023;13:e200162. doi:10.1212/CPJ.0000000000200162

Correspondence
Dr. Louis
elan.louis@utsouthwestern.edu

Essential Tremor

- The most common movement disorder
- 10 million people in the U.S.
- 20 times more prevalent than Parkinson's disease
- Estimated 300-415 cases per 100,000 people

Essential Tremor



- **Postural-action** tremor disorder (may also occur at rest); most commonly affects hands but can also affect head, voice, tongue, and legs
- **Onset:** mean age 45, with bimodal incidence peaks in late 20s and early 60s; slowly progressive
- **Family history** common (17-70%); genetics not completely understood
- **Genetics:** Family History in around 50% (AD)
- ETM1-3 loci, LINGO1 variants, FUS gene variant

Essential Tremor

- Tremor is usually the most noticeable symptom
- Postural and/or action tremor of hands, head, voice, tongue, legs, trunk
- Tremor is biphasic and involves agonist and antagonist muscles
- May temporarily improve with alcohol
- Absence of other neurological signs (except mild parkinsonism, cerebellar signs, or dystonia in some series)

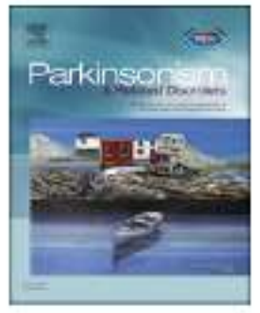
Essential Tremor

- Large effect on quality of life and ADLs
- 15-25% of patients seen in clinical practice retire prematurely
- No cure

Contents lists available at ScienceDirect

Parkinsonism and Related Disorders

journal homepage: www.elsevier.com/locate/parkreldis



Review

It is time to remove the 'benign' from the essential tremor label☆

Elan D. Louis [a,b,c,d,*], Michael S. Okun [e,f]

[a] Department of Neurology, College of Physicians and Surgeons, Columbia University, New York, NY, USA
[b] Taub Institute for Research on Alzheimer's Disease and the Aging Brain, College of Physicians and Surgeons, Columbia University, New York, NY, USA
[c] GH Sergievsky Center, College of Physicians and Surgeons, Columbia University, New York, NY, USA
[d] Department of Epidemiology, Mailman School of Public Health, Columbia University, New York, NY, USA
[e] Department of Neurology, University of Florida, Movement Disorders Center, Gainesville, FL, USA
[f] Department of Neurosurgery, University of Florida, Movement Disorders Center, Gainesville, FL, USA

- Cognitive abnormalities
- Mood disturbance
- Psychiatric co-morbidities
- Gait disorder
- Auditory deficits

Pharmacologic Treatment

- Beta-blockers (propranolol, metoprolol, nadolol)
- Primidone
- Benzodiazepines
- Other agents (clozapine, gabapentin, mirtazapine, nimodipine)
- Botulinum toxin injections (postural > action)
- Drug-induced adverse effects common

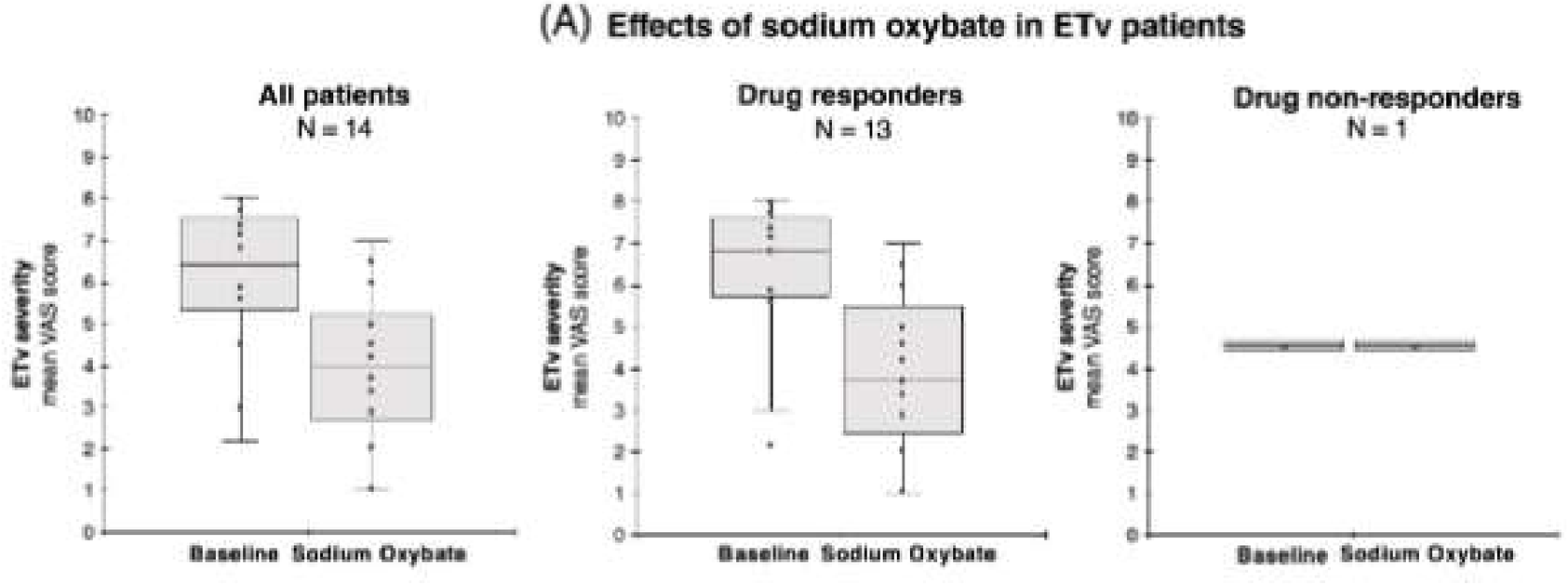
Movement Disorders
Official Journal of the International Parkinson and Movement Disorder Society

RESEARCH ARTICLE | Open Access

Sodium Oxybate in Alcohol-Responsive Essential Tremor of Voice: An Open-Label Phase II Study

Lena C. O'Flynn BA, Steven J. Frucht MD, Kristina Simonyan MD, PhD, Dr med

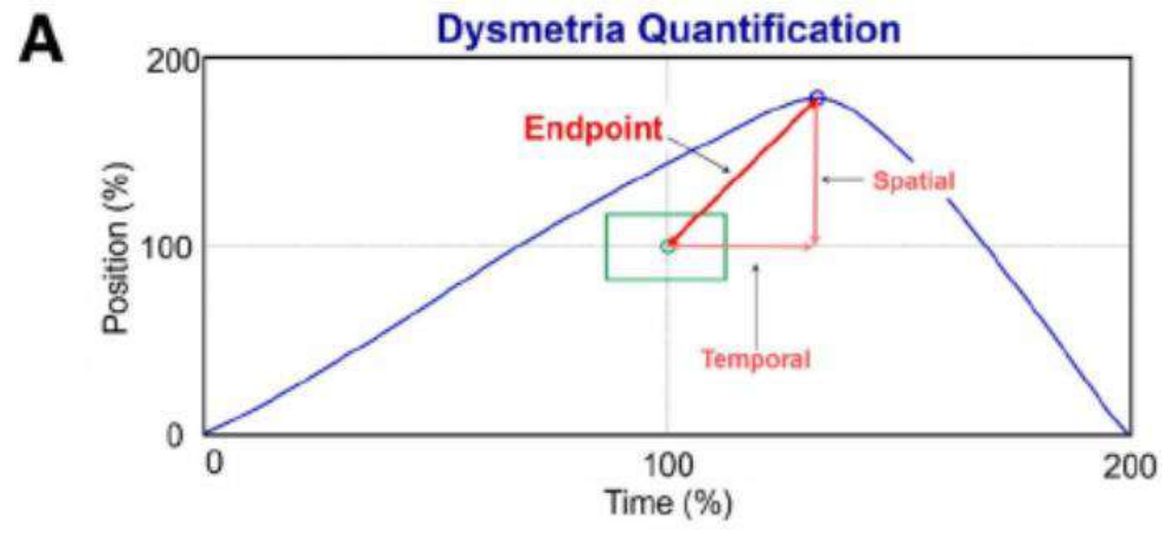
First published: 14 July 2023 | https://doi.org/10.1002/mds.29529



Separating Tremor and Ataxia

Quantitative Separation of Tremor and Ataxia in Essential Tremor

Agostina Casamento-Moran, PhD,[1] Basma Yacoubi, PhD,[1] Bradley J. Wilkes, PhD
Christopher W. Hess, MD,[2] Kelly D. Foote, MD,[2] Michael S. Okun, MD,[2]
Aparna Wagle Shukla, MD,[2] David E. Vaillancourt, PhD,[1,2] and Evangelos A. Christou, PhD



AAN Guideline 2011

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November 08, 2011; 77 (19) SPECIAL ARTICLE

Evidence-based guideline update: Treatment of essential tremor

Report of the Quality Standards Subcommittee of the American Academy of Neurology

T.A. Zesiewicz, R.J. Elble, E.D. Louis, G.S. Gronseth, W.G. Ondo, R.B. Dewey, M.S. Okun, K.L. Sullivan, W.J. Weiner

First published October 19, 2011, DOI: https://doi.org/10.1212/WNL.0b013e318236f0fd

At least half a dozen ongoing trials…

- Level A *established as effective*: propranolol, primidone alprazolam, atenolol, gabapentin (monotherapy), sotalol, topiramate
- Level B *probably effective*: nadolol, nimodipine, clonazepam, botulinum toxin A, deep brain stimulation, thalamotomy
- Level C *possibly effective*: and gamma knife thalamotomy (Level U, insufficient evidence)
- *FUS: randomized data
- *TRIO wearable device PROSPECT TRIAL open label
- *Not reviewed in a guideline

Typical Doses

MEDICATION	DOSAGE	POTENTIAL SIDE EFFECTS
Propranolol	60-320 mg divided 2-3 times daily	Contraindicated in cardiac arrhythmias, diabetes, and pulmonary disorders. Watch for hypotension & depression
Propranolol LA	60-320 mg, 1-2 times daily	Same as above
Primidone	50-500 mg (divided into TID or QHS)	Sedation, nausea dizziness, confusion.(Start low & go slow.)
Gabapentin	900-2400 mg (divide into TID)	Leukopenia, somnolence, dizziness, ataxia.
Topiramate	Up to 400 mg/day	Paresthesia, anorexia, difficulty with concentration, kidney stones.
Clonazepam	0.5-6 mg/day	Drowsiness. Dependence

Fernandez, H. (2007). *A practical approach to movement disorders diagnosis and medical and surgical management*. New York: Demos Medical Pub.

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



BRIEF REPORT | Full Access

Non-Persistence of Tremorolytic Effect of Perampanel in Essential Tremor: Real-World Experience with 50 Patients

Alexandre Gironell MD, PhD ✉, Berta Pascual-Sedano MD, PhD, Juan Marín-Lahoz MD, PhD, Jesús Pérez MD, PhD, Javier Pagonabarraga MD, PhD

First published: 26 September 2022 | https://doi.org/10.1002/mdc3.13576

ORIGINAL ARTICLE

Perampanel: Medical Alternative for Essential Tremor?

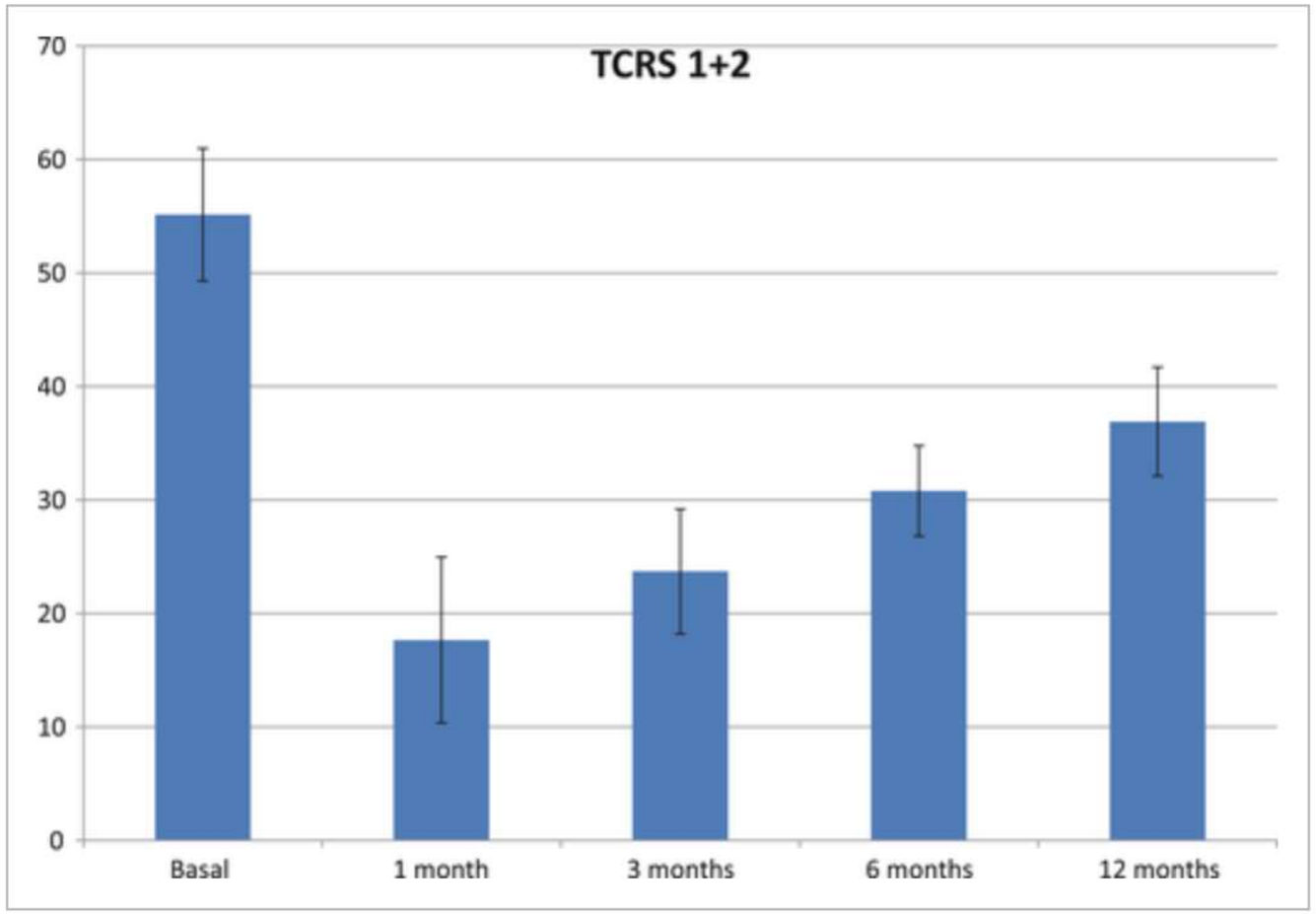
Lola Díaz-Feliz, MD, Cici Feliz-Feliz, MD,* Javier Del Val, MD,* Marta Ruiz-López, MD, PhD,† and Pedro J. García-Ruiz, MD, PhD**

First-in-class selective, noncompetitive AMPA α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor antagonist

Blocks glutamate activity in the postsynaptic

AMPA receptors

Used in epilepsy



Adverse effects: dizziness and instability, weight gain, and mood changes)
Dose reduction was necessary in 30-40%

‘Parkinson’s’ Resting Tremor

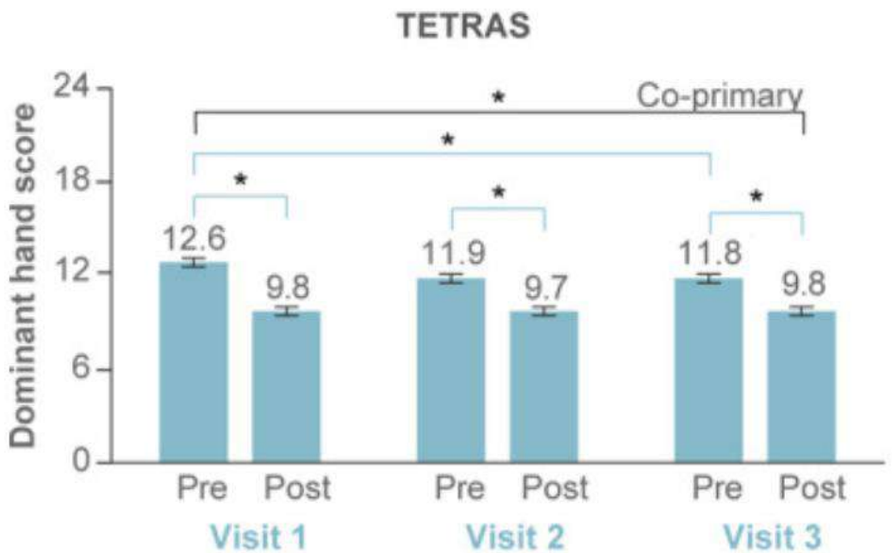
- Rest tremor
- Pill rolling upper limb
- Attenuated during movement
- Reappears with new posture “re-emergent”
- Evident during walking “dependent”
- May appear ‘faster or myoclonic’ in younger cases

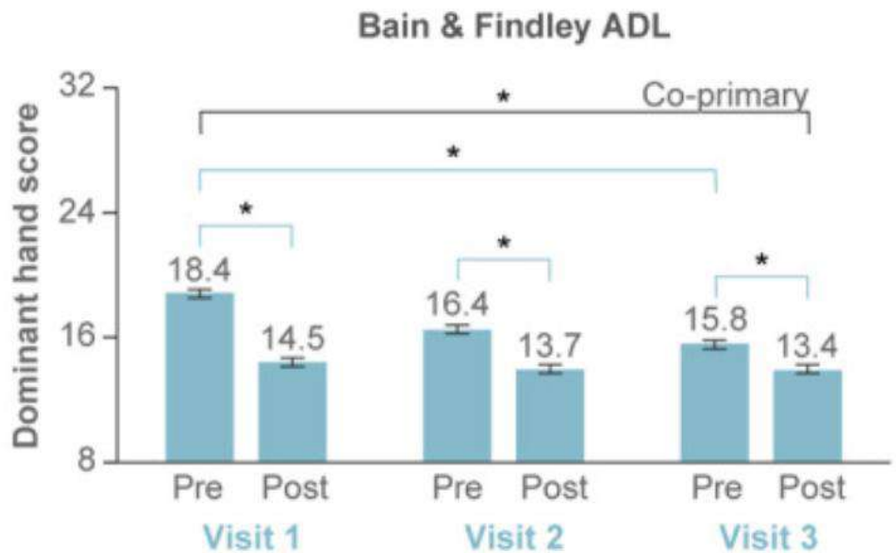


Open label data for a wearable…

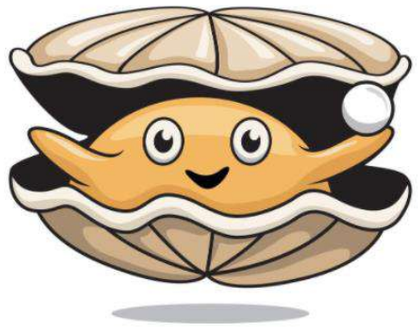
FDA Supports Cala Trio as Potential Therapy for Action Tremors in Hands







ET Plus



Tremor Classification Criteria

Essential Tremor (ET)

- Bilateral tremor of the upper limbs with or without head tremor or tremor of other locations
- Duration of at least 3 years
- Absence of dystonia, ataxia, or parkinsonism

Essential Tremor Plus

- Same clinical features of ET
- Additional "soft" neurological signs (e.g. mild memory impairment, impaired tandem gait, subtle body posturing similar to dystonia)

Parkinsonism

- Bradykinesia and rigidity
- Unilateral or asymmetric resting tremor (hands may exhibit pill rolling tremor)
- Rest tremor diminishes with initiation of muscle contraction

Dystonic

- Tremor in a body part affected by dystonia
- Symptoms reduced by *geste antagoniste* (sensory tricks)
- Task specificity
- Idiopathic, familial, or sporadic
- Dystonia + tremor in different body parts = tremor associated with dystonia

Investigative Otolaryngology, 2021



ET, ET Plus or dystonic tremor?

Soft signs not enough…

Bayesian Interpretation of Essential Tremor Plus

Rodger J. Elble

Department of Neurology,
Southern Illinois University
School of Medicine,
Springfield, IL, USA

Essential tremor (ET) plus is a new tremor classification that was introduced in 2018 by a task force of the International Parkinson and Movement Disorder Society. Patients with ET plus meet the criteria for ET but have one or more additional systemic or neurologic signs of uncertain significance or relevance to tremor ("soft signs"). Soft signs are not sufficient to diagnose another tremor syndrome or movement disorder, and soft signs in ET plus are known

Table 2. Sensitivity and specificity of signs that suggest a dystonia syndrome

Sign*	Sensitivity	Specificity	Reference
Lower limb action tremor	0.5	0.7	Rajalingam et al.[74]
Irregular rhythm and jerkiness	?	?	See text
Highly asymmetric upper limb tremor	?	?	See text
Unusual postures (e.g., finger pointing)	0.20	0.90	Vives-Rodriguez and Louis[75]
Mirror dystonia	0.67	0.67	Sitburana et al.[76]
Muscular overflow contractions	0.28	0.96	Sitburana et al.[76]

*Cohort is assumed to consist of patients with essential tremor and dystonic tremor syndromes

Journal of Clinical Neurology, 2022

Asymmetric resting or postural tremor without clear bradykinesia?

Long standing asymmetric tremor

Rest/postural tremor

± FH

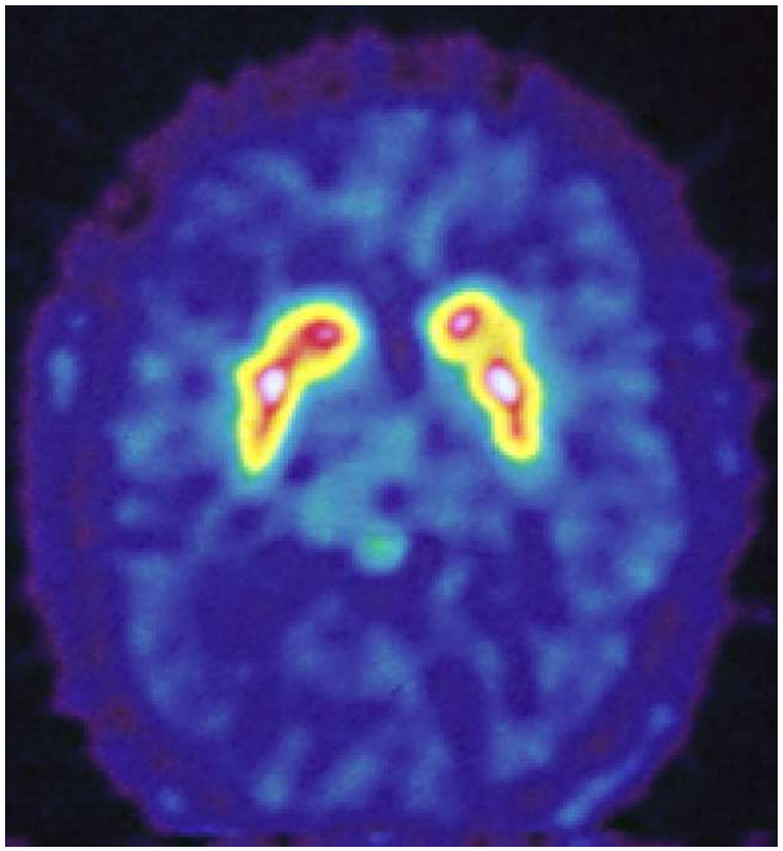
± alcohol responsive

Cases shown to be Parkinson's disease

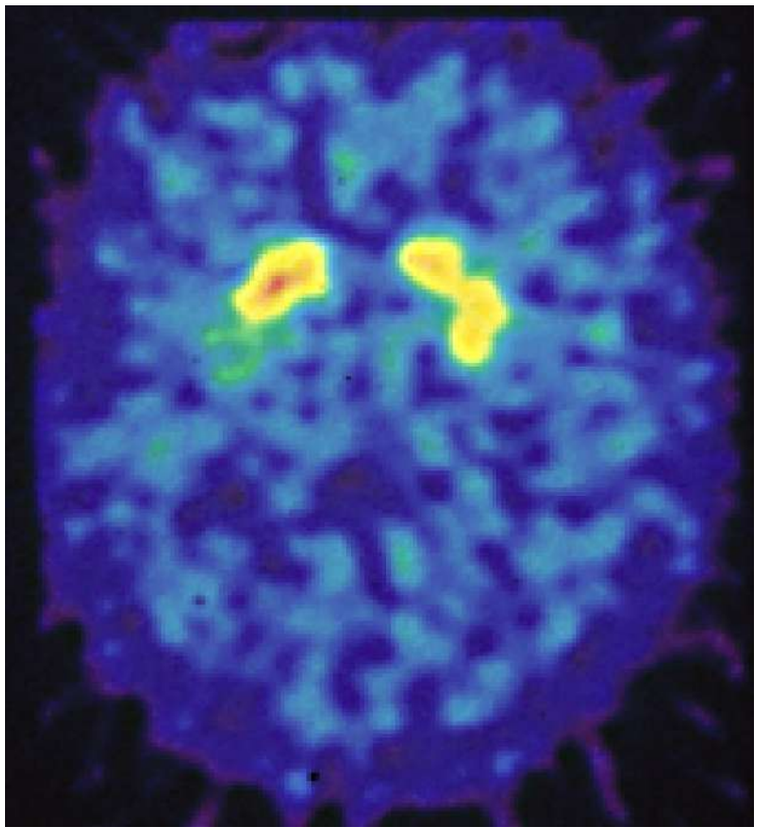
Brooks et al Neurology 2002

Chaudhuri et al JNNP 2005

^{18}F-dopa PET in asymmetric rest tremor



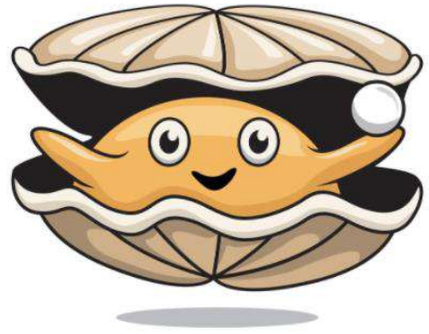
Normal



Isolated rest tremor

Courtesy Professor D Brooks, Imperial College, London

Different types of tremor in Parkinson's disease and Response to treatment



	Rest tremor	Postural-Action
Levodopa	+++	0
Anticholinergics	++	0
Dopamine agonists	++	0
Amantadine	+	0
β-blockers	+	++
Benzodiazepines	+	+
Primidone	0	0

Dystonic Tremor

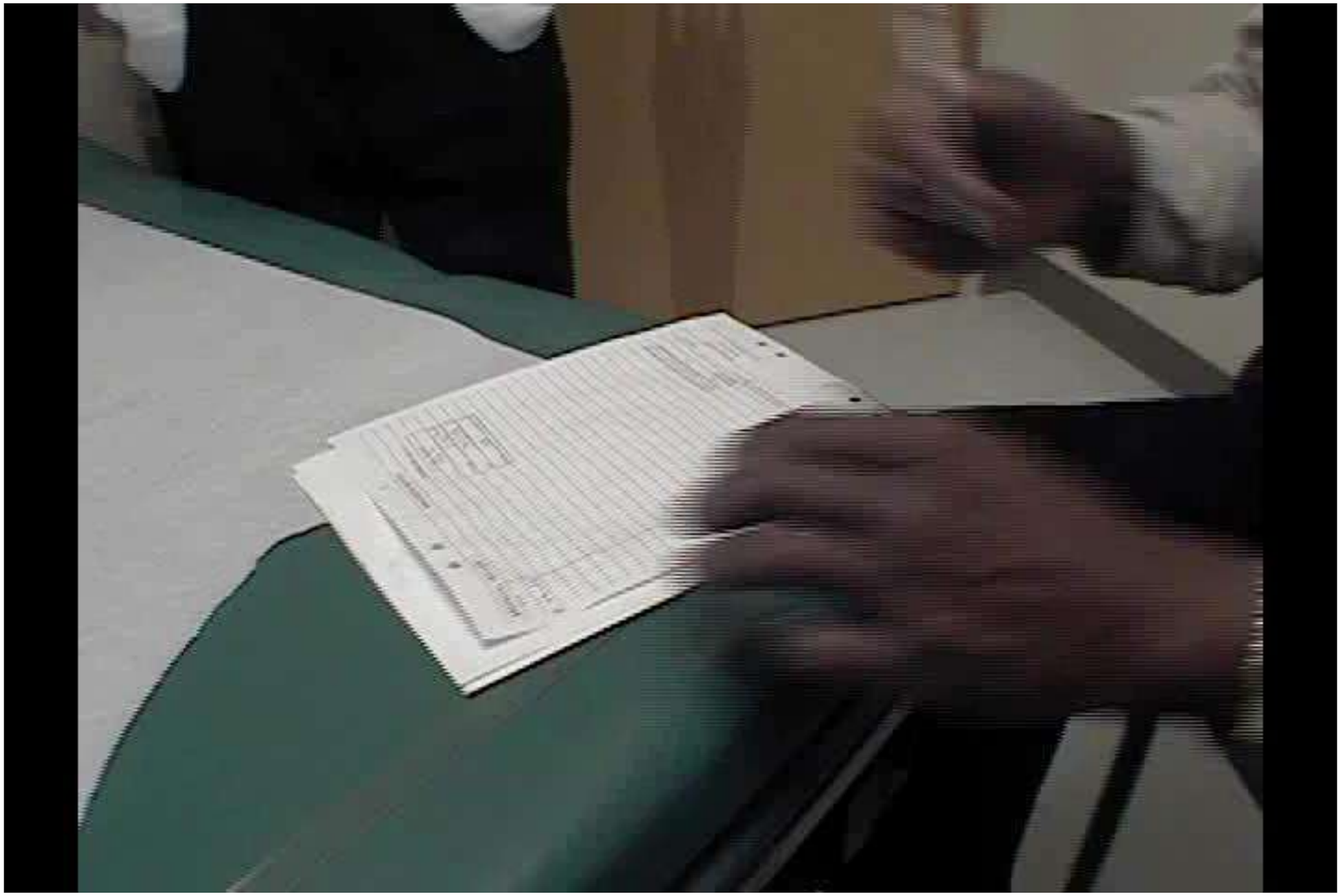


When you observe a head tremor…

- “Postural”
- 4-8Hz
- Differential:
  - Essential tremor
  - Cerebellar disease (titubation)
  - Cervical Dystonia
  - Isolated (focal) – usually tremulous cervical dystonia

Dystonic Tremor

- Postural, kinetic, action tremor (2-6Hz)
- Dystonic posturing
- Action dystonia (writing)
- Task specific action tremor
- Arms > Head > Legs



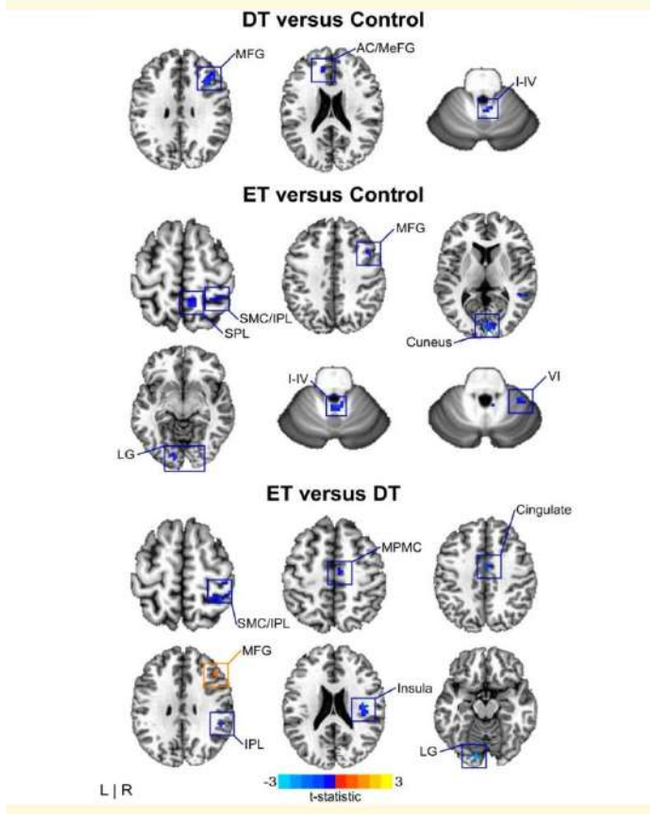
Network Level Connectivity

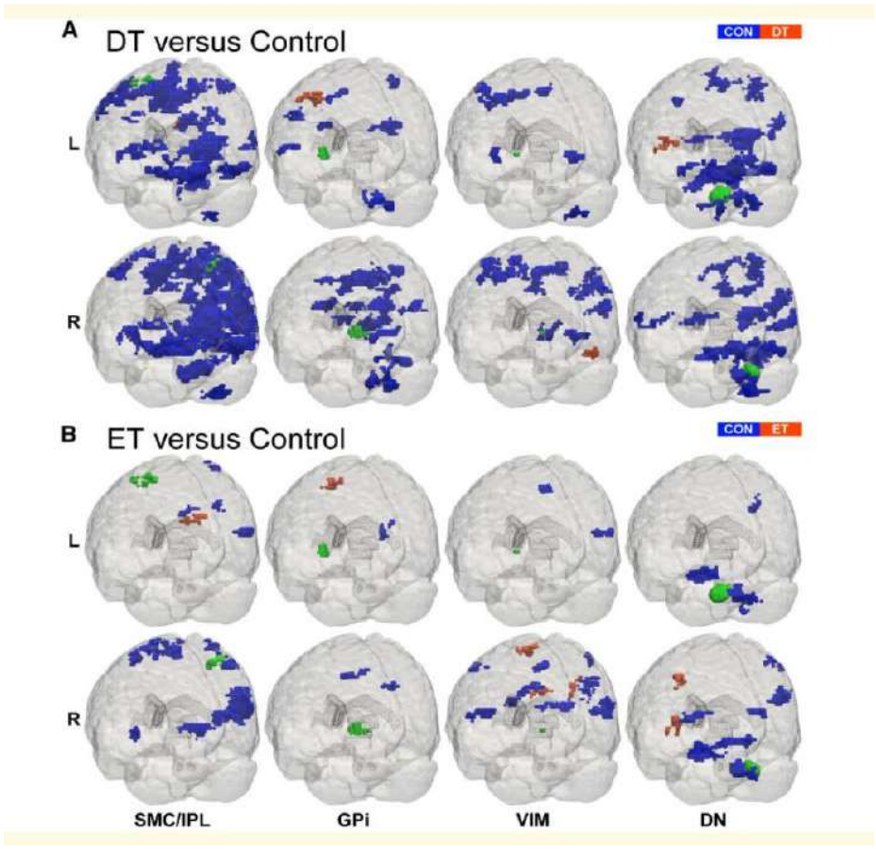
doi:10.1093/brain/awz085 BRAIN 2019: 142; 1644–1659 | 1644

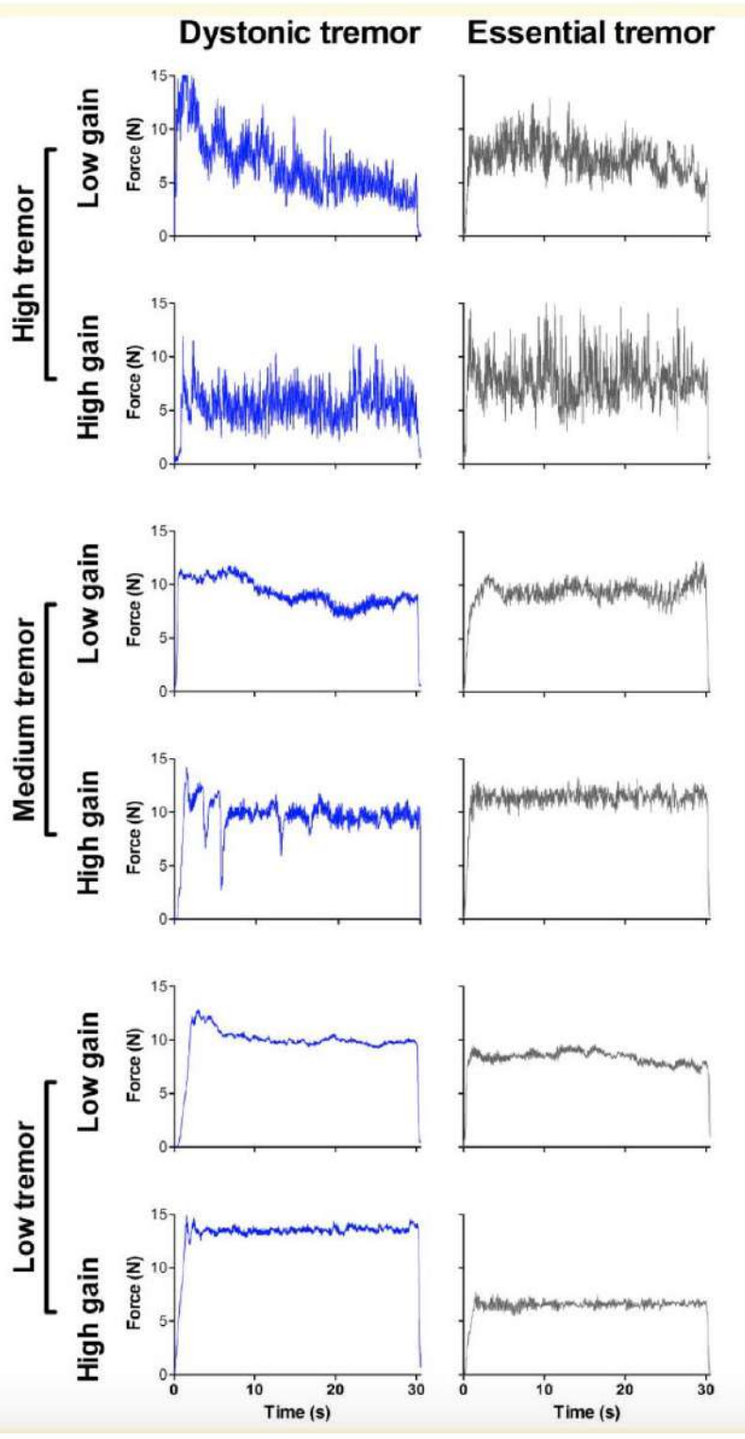
BRAIN
A JOURNAL OF NEUROLOGY

Network-level connectivity is a critical feature distinguishing dystonic tremor and essential tremor

Jesse C. DeSimone,[1] Derek B. Archer,[1] David E. Vaillancourt[1,2,3] and Aparna Wagle Shukla[3,4]



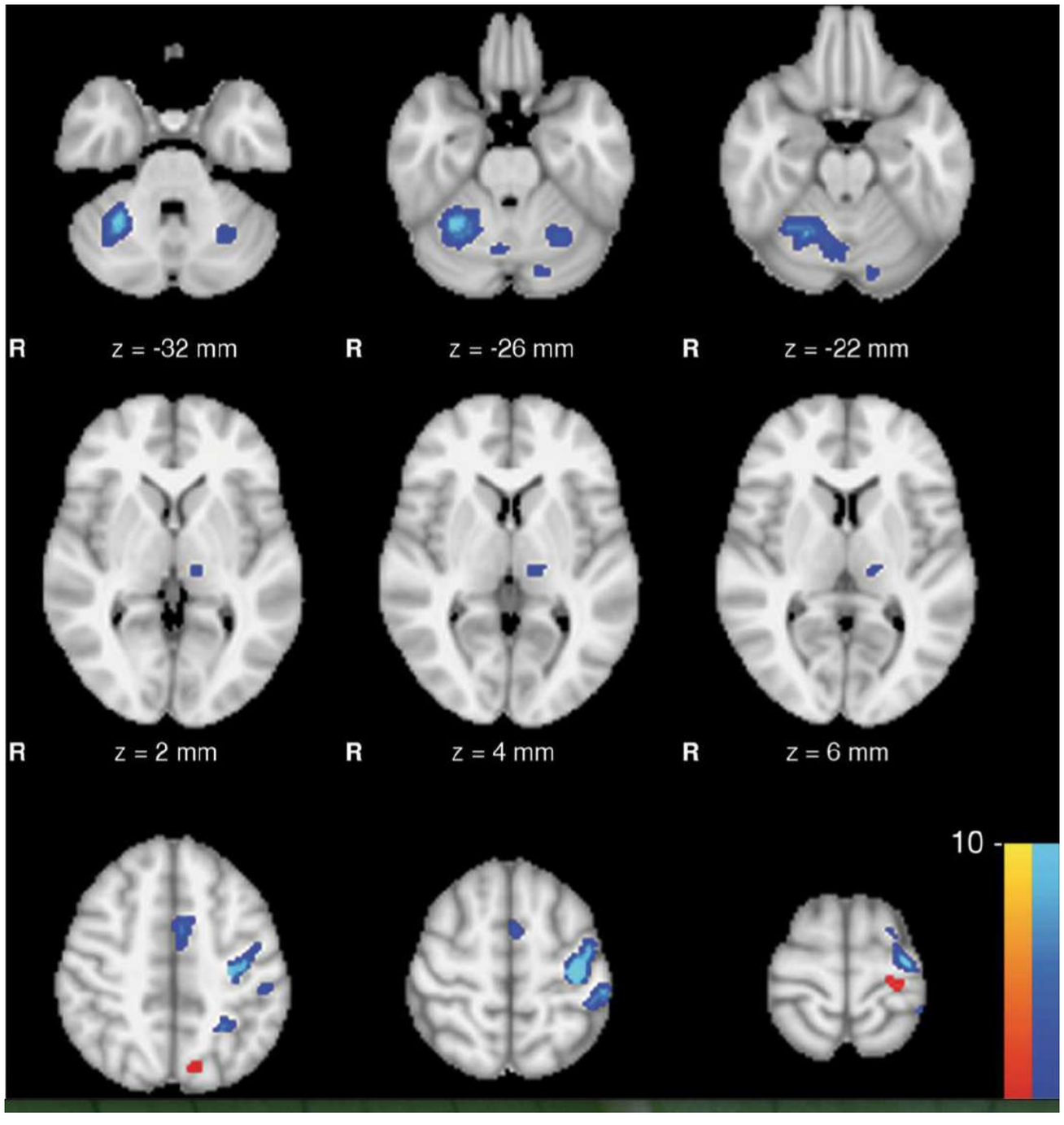




Cerebellar activation

Fig. 1 Results of the between-group (healthy controls and ET patients) comparison activation map. Maps of higher activated clusters in healthy controls compared to ET patients (*blue*) and in ET patients compared to healthy controls (*red*) superimposed on standard MNI template (Z threshold >5; cluster p threshold <0.001)

J Neurol (2015) 262:719–728




Pre-OP

Multiple Sclerosis Tremor



May Accompany the Diagnosis

- Some Studies More than Half of Patients
- Severe and Can be at Rest, Posture, Action
- Resemble Outflow or Midbrain Tremors

Multiple Sclerosis Tremor



Palatal ‘Tremor’



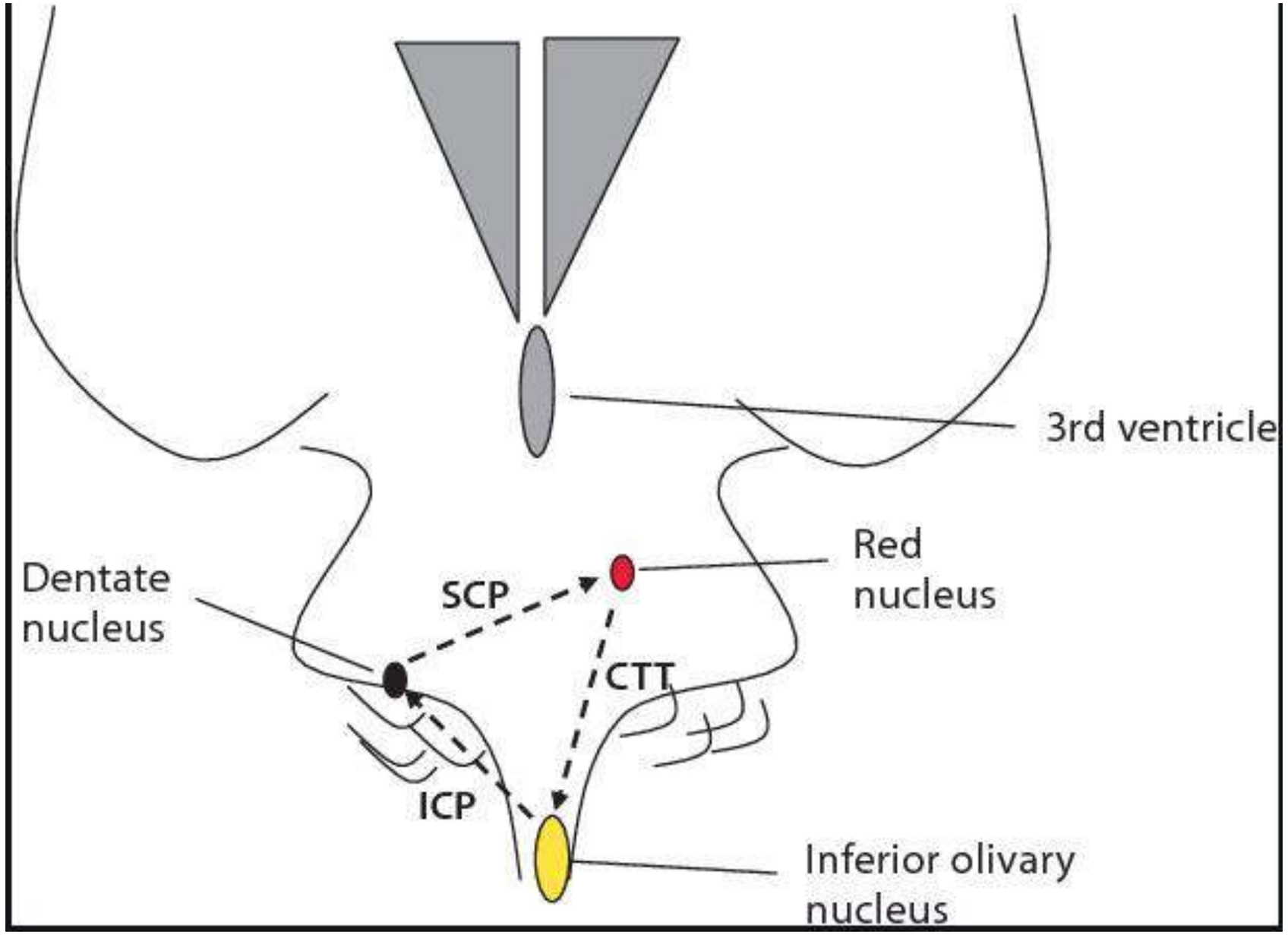
Symptomatic Palatal Tremor



Palatal Tremor

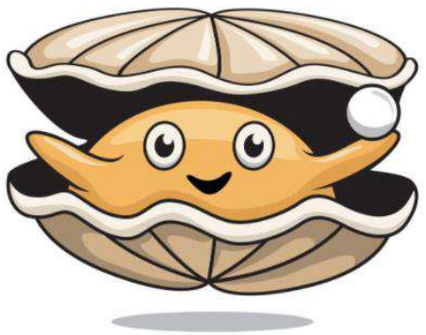
Essential Palatal Myoclonus	**Symptomatic Palatal Myoclonus**
25% of cases	***Most cases***
No lesions	Lesion in Mollaret triangle Presence of ocular abnormalities, facial asymmetry, hemiparesis, etc Abnormality on neuroimaging (e.g. olivary nucleus hypertrophy)
Audible click: **tensor** veli palatini inserts in Eustachian tube (entire soft palate)	**No audible click**: **levator** veli palatini (edges only)
Myoclonus and click **disappears** in sleep	Myoclonus **persist** during sleep
Can be transiently ***aborted*** by patient, certain *neck postures, mouth opening*	**Cannot be aborted**

Mechanism Symptomatic Palatal Tremor



Imaging





Is it palatal tremor or myoclonus?

- Ask Rabbi of תְּנוּעָה ‘movement and medicine’



Maimonides (Moshe Ben Maimon) (1138–1204)
12th-century Spanish-North African Talmudist, philosopher, and law codifier

Palatal Tremor
Is it more tremor-ish or myoclon-ish?

Rabbi of תְּנוּעָה ‘movement and medicine’

Treatment of mental illness ‘on equal footing as that of physical illness.’



Maimonides

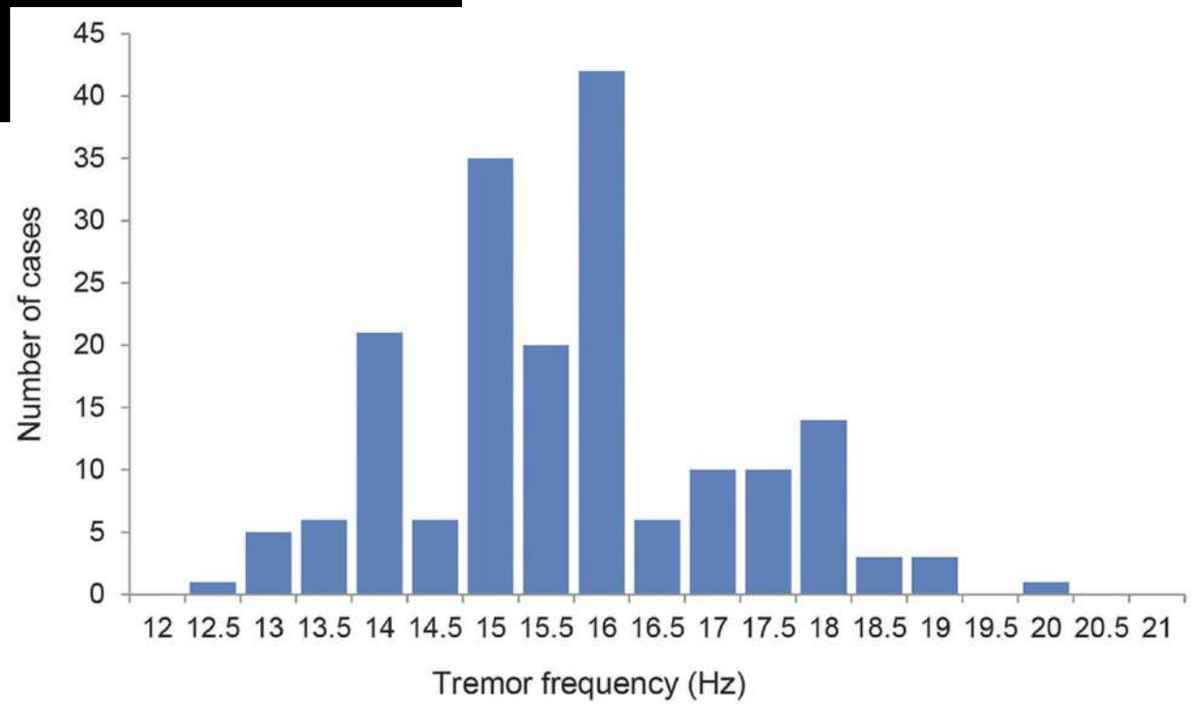
‘Yiddish’ reveals the answer

Slow, rhythmic, no antagonist muscle (tremor-ish)

Orthostatic Tremor

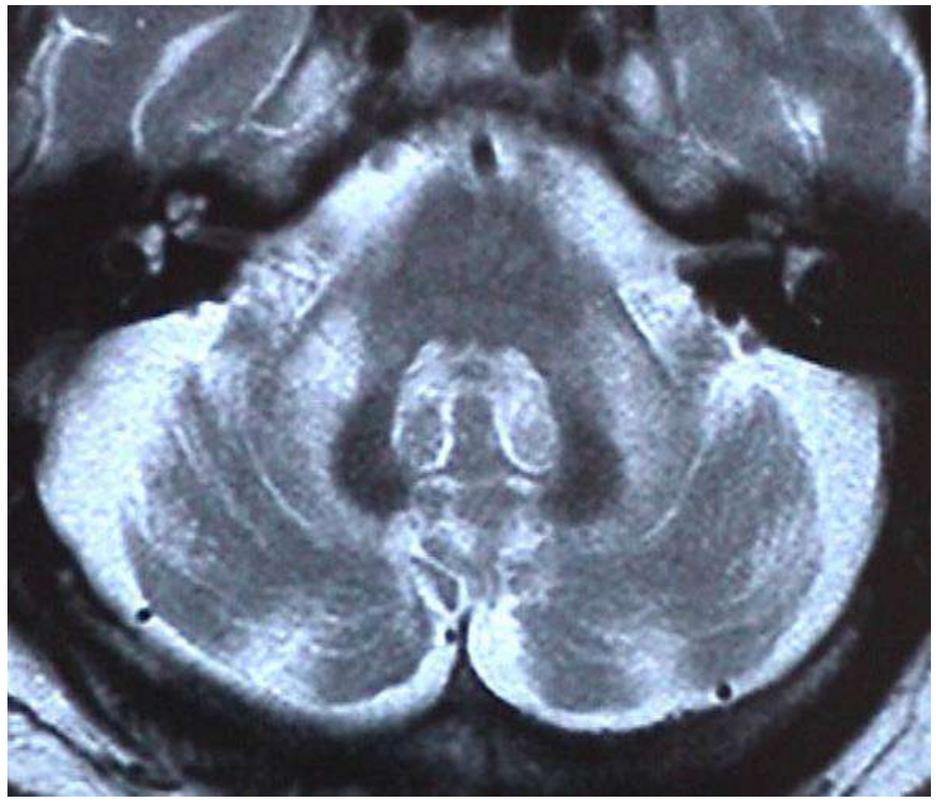
- Legs, trunk
- Standing
- Fast- 16-18 Hz

- Sensation of unsteadiness while standing
- Tremor easier to feel or auscultate than see
- Measure frequency muscle contraction


45
40
35
30
25
20
15
10
5
0
Number of cases
12 12.5 13 13.5 14 14.5 15 15.5 16 16.5 17 17.5 18 18.5 19 19.5 20 20.5 21
Tremor frequency (Hz)

Fragile X tremor ataxia syndrome

- Tremor
  - action, postural, resting
- Parkinsonism
  - hypokinetic gait
- Ataxia
- Frontal-cognitive dysfunction



- FMR 1 gene premutation expansion
- 14% have FH PD

- MRI characteristics
- Pathology intranuclear neuronal and astrocytic inclusions
- cf MSA cytoplasm, oligodendrocytes

Secondary Tremor

- Cerebellar disease
- Midbrain disease
- Thalamic infarction
- Neuropathic tremor
- Drug induced

Holmes Tremor

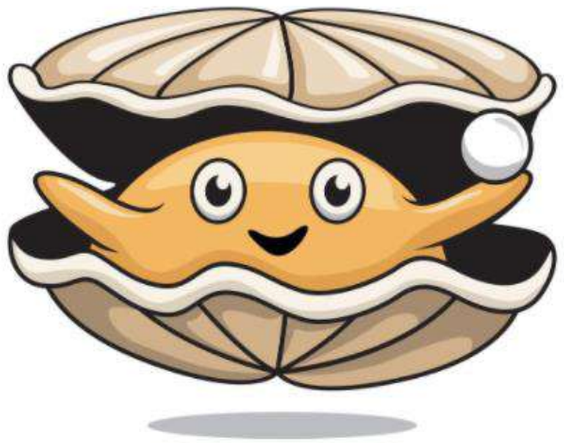
- Midbrain Tremor, Thalamic Tremor, Rubral tremor

- Rest, postural, intention
- 2-4Hz
- Particularly affects arms
- Worse in some postures “wing beating”
- Marked intention exacerbation

- Other signs reflecting structural midbrain lesion
    - Trauma
    - MS
    - Vascular lesions
    - Wilson’s disease

Drug-induced tremors

John C Morgan, Kapil D Sethi



	Action or postural tremor	Intention tremor	Resting tremor
Antiarrhythmics	Amiodarone, mexiletine, procainamide	..	..
Antibiotics, antivirals, and antimycotics	..	Vidarabine	Co-trimoxazole, amphotericin B
Antidepressants and mood stabilisers	Amitriptyline, lithium, SSRIs	Lithium	SSRIs, lithium
Antiepileptics	Valproic acid	..	Valproic acid
Bronchodilators	Salbutamol, salmeterol	Salbutamol, salmeterol	..
Chemotherapeutics	Tamoxifen, cytarabine, ifosfamide	Cytarabine, ifosfamide	Thalidomide
Drugs of misuse	Cocaine, ethanol, MDMA, nicotine	Ethanol	Cocaine, ethanol, MDMA, MPTP
Gastrointestinal drugs	Metoclopramide, cimetidine	..	Metoclopramide
Hormones	Thyroxine, calcitonin, medroxyprogesterone	Epinephrine	Medroxyprogesterone
Immunosuppressants	Tacrolimus, ciclosporin, interferon-alfa	Tacrolimus, ciclosporin	..
Methylxanthines	Theophylline, caffeine	..	..
Neuroleptics and dopamine depleters	Haloperidol, thioridazine, cinnarizine, reserpine, tetrabenazine	..	Haloperidol, thioridazine, cinnarizine, reserpine, tetrabenazine

Additional data from Deuschl et al.[2] MDMA=3,4-methylenedioxymethamphetamine (ecstasy); MPTP=1-methyl-4-phenyl-1,2,5,6-tetrahydropyridine; SSRIs=selective serotonin reuptake inhibitors.

Table: **Main drugs known to cause postural, intention, and resting tremors**

Wilson's Disease

Wilson's disease

2012 – centenary of the first publication on Wilson's disease



BRAIN [MARCH, 1912.]

PART IV., VOL. 34.

Original Articles and Clinical Cases.

PROGRESSIVE LENTICULAR DEGENERATION: A FAMILIAL NERVOUS DISEASE ASSOCIATED WITH CIRRHOSIS OF THE LIVER.[1]

BY S. A. KINNIER WILSON, M.D., B.Sc.EDIN., M.R.C.P.LOND.
Registrar to the National Hospital, Queen Square, London.
(*From the Laboratory of the National Hospital, Queen Square.*)

215 pages, the longest paper ever published in Brain

Wilson's disease

Clinical presentation (Gowers patient, 1887)

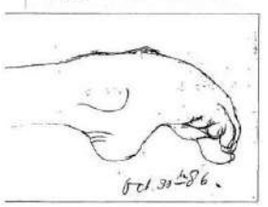
=> ***contractures, spasms***, ... dystonia appears today as the main feature but this term was not available at that time











Wilson's disease

Clinical presentation (Wilson's patient W1)







Wilson's disease

Wilson's patients W2, W3 & W4











severe orofacial dystonia with large mouth opening

Wilson's Disease

- Chromosome 13 (ATP7B Genetic Test)
- K-F Rings if cerebral disease
- Blood, Liver, Neuropsychiatric manifestations
- Smile- risus sardonicus
- Need urine copper excretion, blood copper levels are not enough, nor is cerruloplasmim
- Liver biopsy is the gold standard; now genetics
- Wing-beating tremor is not only manifestation
- Workup for any movement disorder in a young person

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



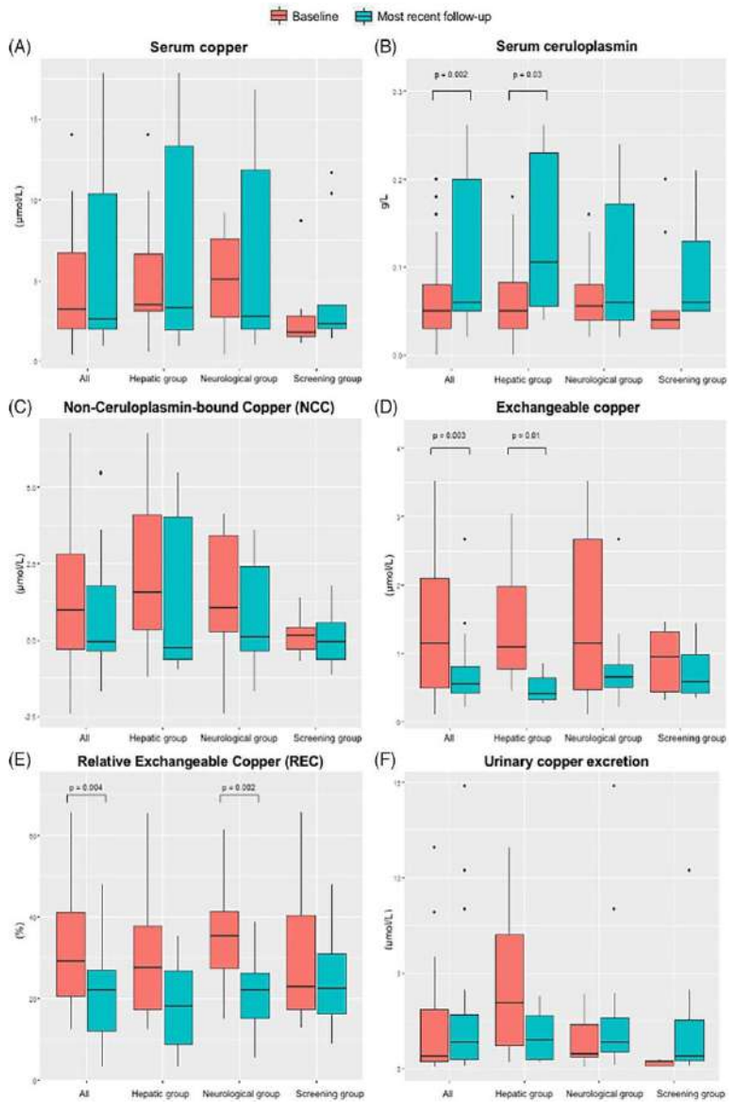
Research Article | Open Access

Diagnosis and Outcomes of Late-Onset Wilson's Disease: A National Registry-Based Study

Christelle Nilles MD, Mickael Alexandre Obadia MD, Rodolphe Sobesky MD, PhD, Jérôme Dumortier MD, PhD, Olivier Guillaud MD, Chloé Laurencin MD ... See all authors

TABLE 2. First- and second-line treatments and tolerance

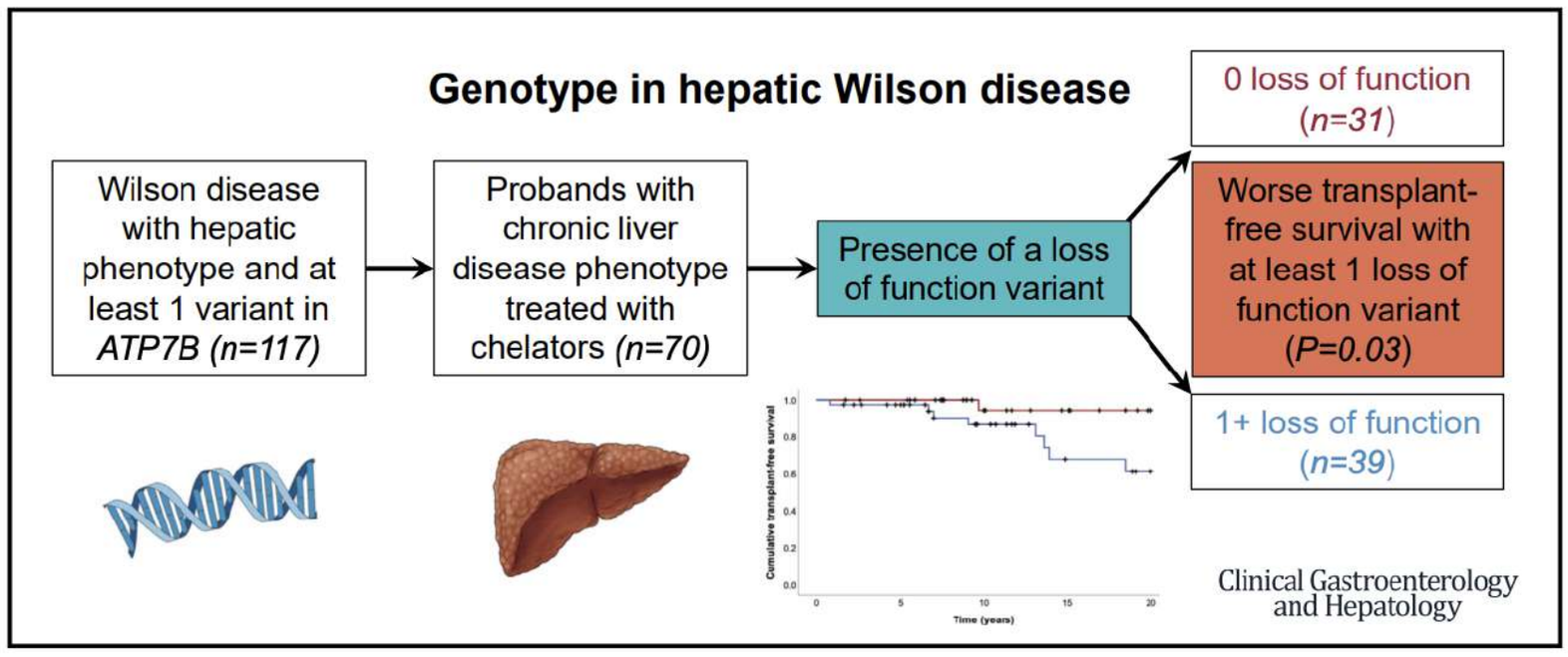
Variable	Neurological group	Hepatic group	Screened group	All
First-line treatment				
n	19	13	12	44
D-Penicillamine	12 (63)	8 (62)	5 (42)	25 (57)
Zinc acetate	5 (26)	1 (8)	2 (17)	8 (18)
Trientine salt	2 (11)	0	2 (17)	4 (9)
Liver transplantation	0	4 (31)	0	4 (9)
No treatment	0	0	3 (25)	3 (7)
Clinical worsening under treatment	7/18 (39)	2/12 (17) [a]	1/8 (13)	10/38 (26)
Presence of D-penicillamine side effects leading to discontinuation of treatment [b]	3/18 (17)	2/12 (17)	0/8	5/38 (13)



ATP7B Genotype and Chronic Liver Disease Treatment Outcomes in Wilson Disease: Worse Survival With Loss-of-Function Variants

Jeremy S. Nayagam,[1,2] Rebecca Jeyaraj,[1] Pierre Foskett,[1] Anil Dhawan,[1,3] Aftab Ala,[1,4,5] Deepak Joshi,[1] Adrian Bomford,[1] and Richard J. Thompson[1,2,3]

[1]Institute of Liver Studies, King's College Hospital, London, United Kingdom; [2]Institute of Liver Studies, King's College London, London, United Kingdom; [3]Paediatric Liver, GI and Nutrition Centre, King's College Hospital, London, United Kingdom; [4]Department of Gastroenterology and Hepatology, Royal Surrey NHS Foundation Trust, Guildford, Surrey, United Kingdom; and [5]Department of Clinical and Experimental Medicine, University of Surrey, Guildford, Surrey, United Kingdom



- Loss of function variants worse outcome.

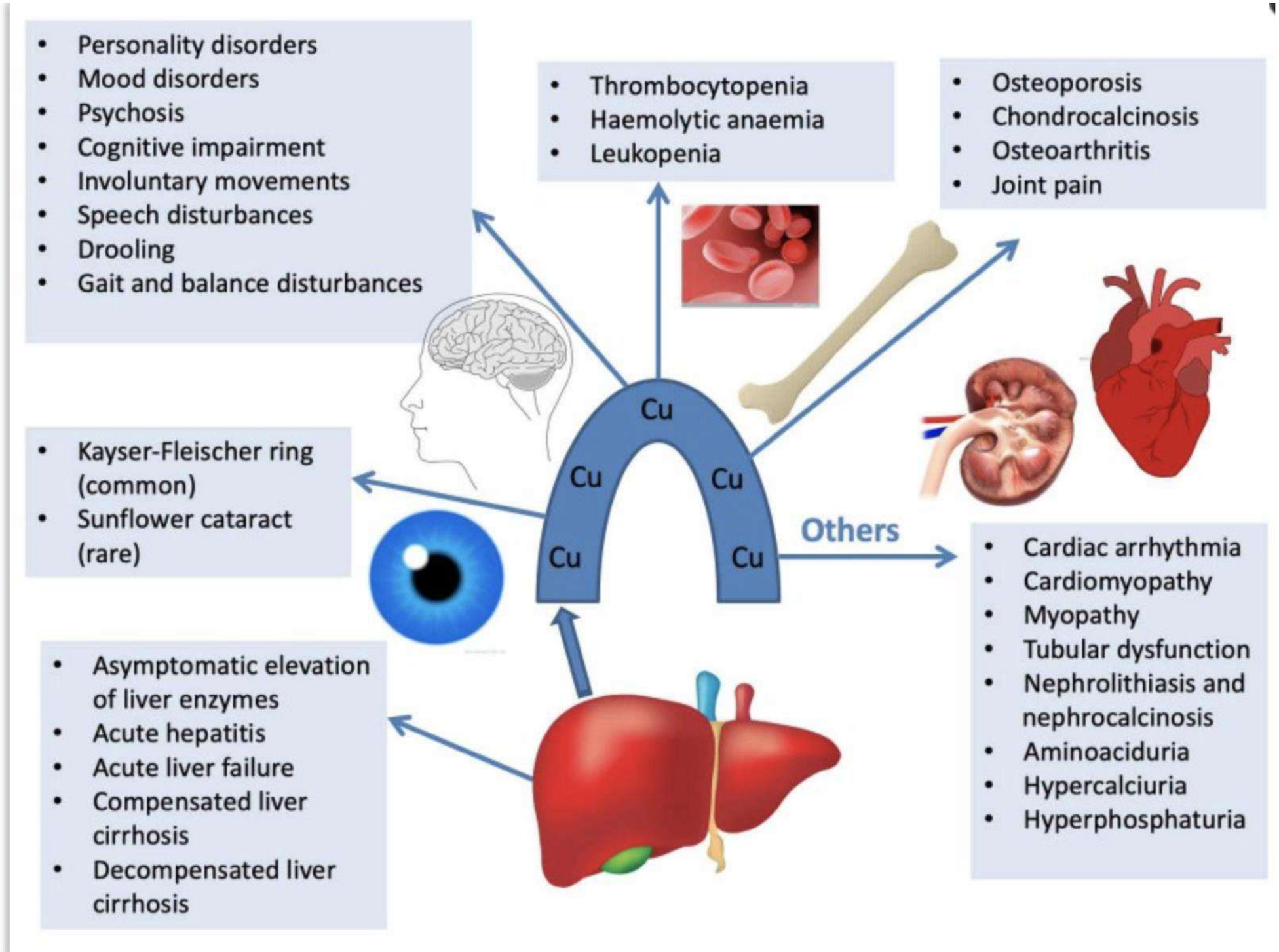
91 variants.

- At least 1 LOF variant was present in ½ cohort.
- Worse transplant-free survival for patients prescribed chelation therapy in patients with at least 1 LOF variant.

Wilson’s Disease



When You Think Wilson's Think 'Multi-system'



Clinical Presentation

- Younger patients often develop hepatic manifestations
- Older patients with WD -neurological issues
- 20-30% of the patients have prominent psychiatric and behavioral issues
- Movement Disorders –often in combination
  - -dystonia
  - -parkinsonism
  - -tremor
  - -ataxia
  - -dysarthria
  - -rarely chorea

Dysphagia and drooling may occur

Neurological Manifestations

- Vacuous smile (risus)
- Wing beating tremor (uncommon)
- Corticospinal tract signs rare
- Seizures may occur
- Some patients have eye movement abnormalities
- In dark eyed patients Kayser Fleischer rings may or MAY NOT be observed with naked eye examination-
- Neurological Wilson without KF rings-rare

Wilson’s Disease



Listen to the Speech





Wilson's original description

There is a most unusual thing
Known as the Kayser Fleischer ring.
In fact, it is so very rare
Few doctors know when it is there.
So, whether brown or whether green
It's very, very seldom seen.
Had it been red, or even pink,
Why then I really dare to think
That most physicians would perchance
See it with a perfunctory glance.
So, let us deem it right and proper
To seek this little ring of copper.

The Lancet, 1969, II, 740

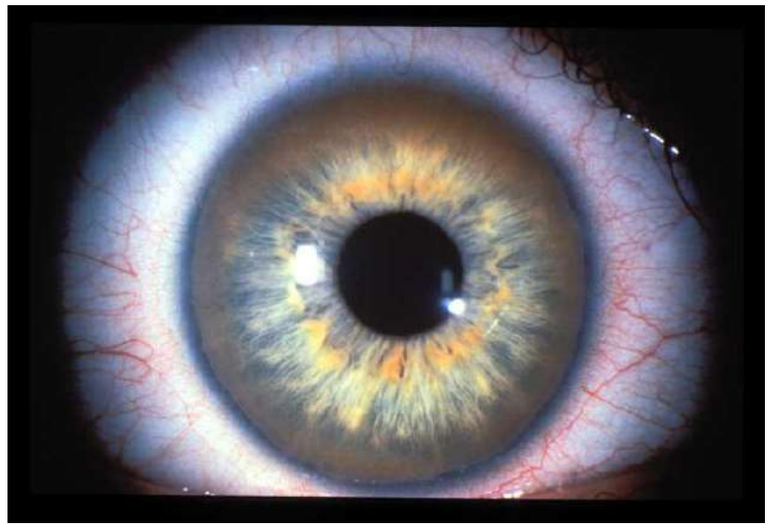
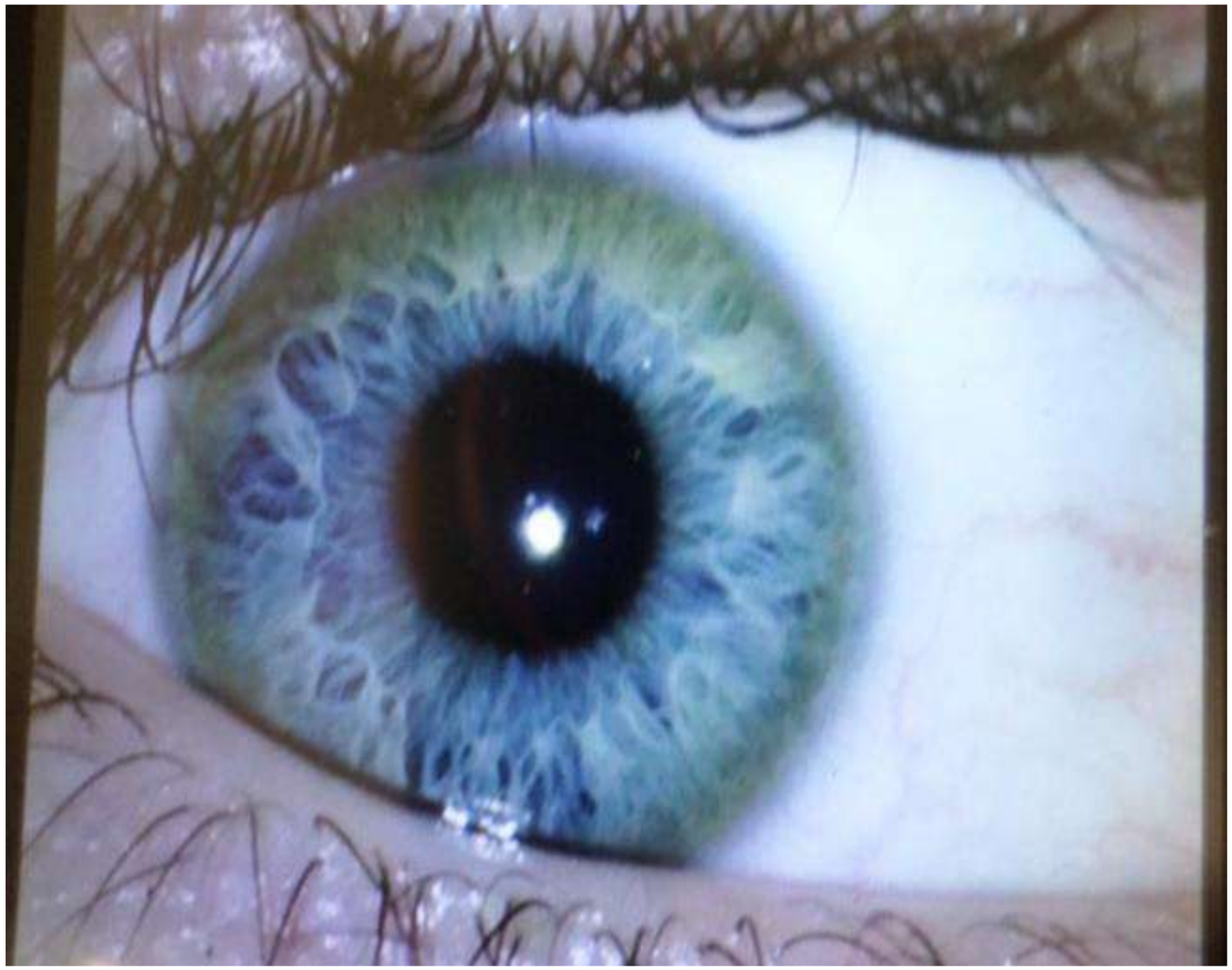




FIG. 1. Patient with hepatolenticular degeneration described by S. A. K. Wilson in 1912[47] (from *Brain*, vol. 34, page 327, with the courtesy of the Editor).

CNS = KF Ring

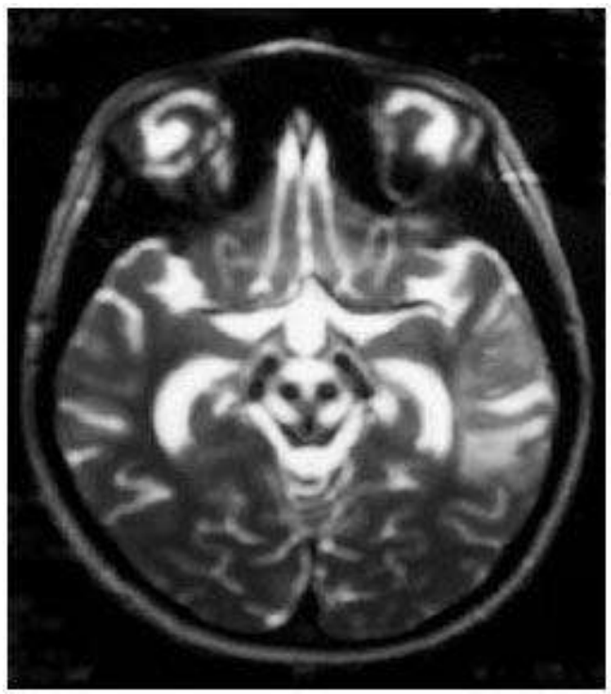


PANDA SIGN

The "double panda sign" in Wilson's disease

Dina A. Jacobs, Clyde E. Markowitz, David S. Liebeskind, Steven L. Galetta

First published October 13, 2003, DOI: https://doi.org/10.1212/01.WNL.0000085871.98174.4E





Liver-Brain Diseases

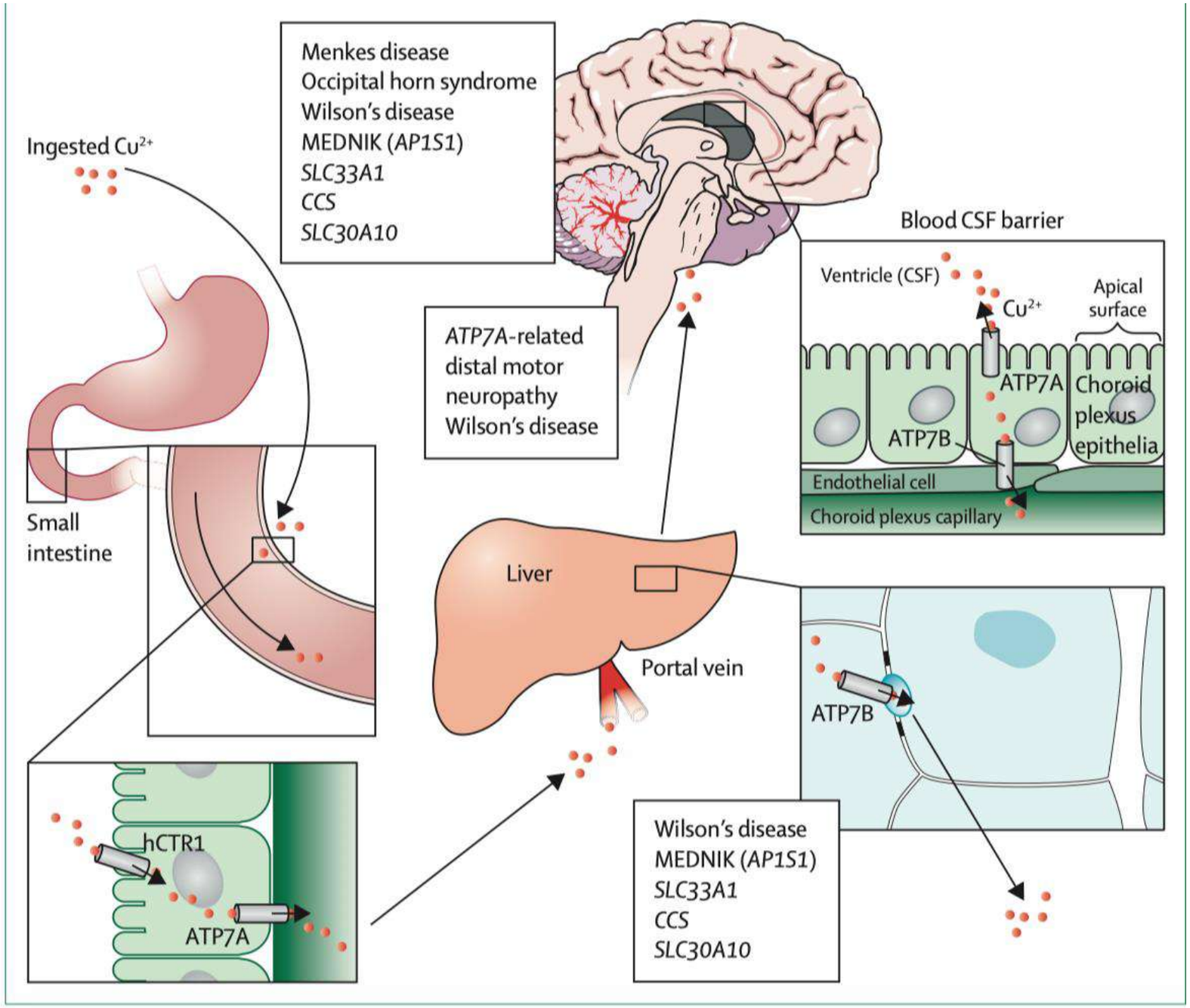


Figure 1: **Healthy copper metabolism and the molecular mechanisms of copper disease**

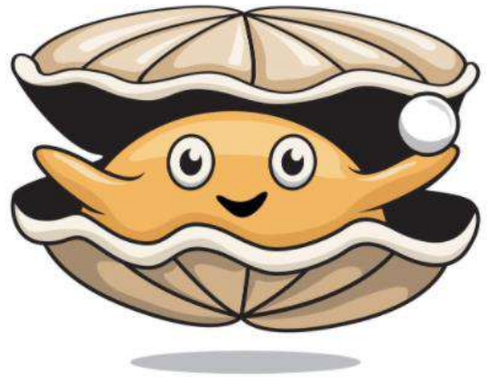
Clues to diagnosis

- Underlying liver disease
- Unexplained episode of hemolysis
- Renal tubular acidosis
- Secondary amenorrhea
- Low platelet count

Diagnostic tests

- Low ceruloplasmin usually <10mg/dL
- Increased 24 hours urinary copper
- Slit Lamp examination
- Neuroimaging
- Liver biopsy (increased copper >200microgram/gm tissue)
- Genetic testing-preferred to invasive liver biopsy

Treatment



- Start early
- Chelation therapy with penicillamine or trientine-initial worsening in 20%
- Tetrathiomolybdate is effective-experimental(bis-choline form promising)
- Zinc alone insufficient for initial therapy but very useful for maintenance.
- Overaggressive de-coppering can lead to copper deficiency and its consequences

Cuprior®
European version of Cuvrior® (trientine tetrahydrochloride)



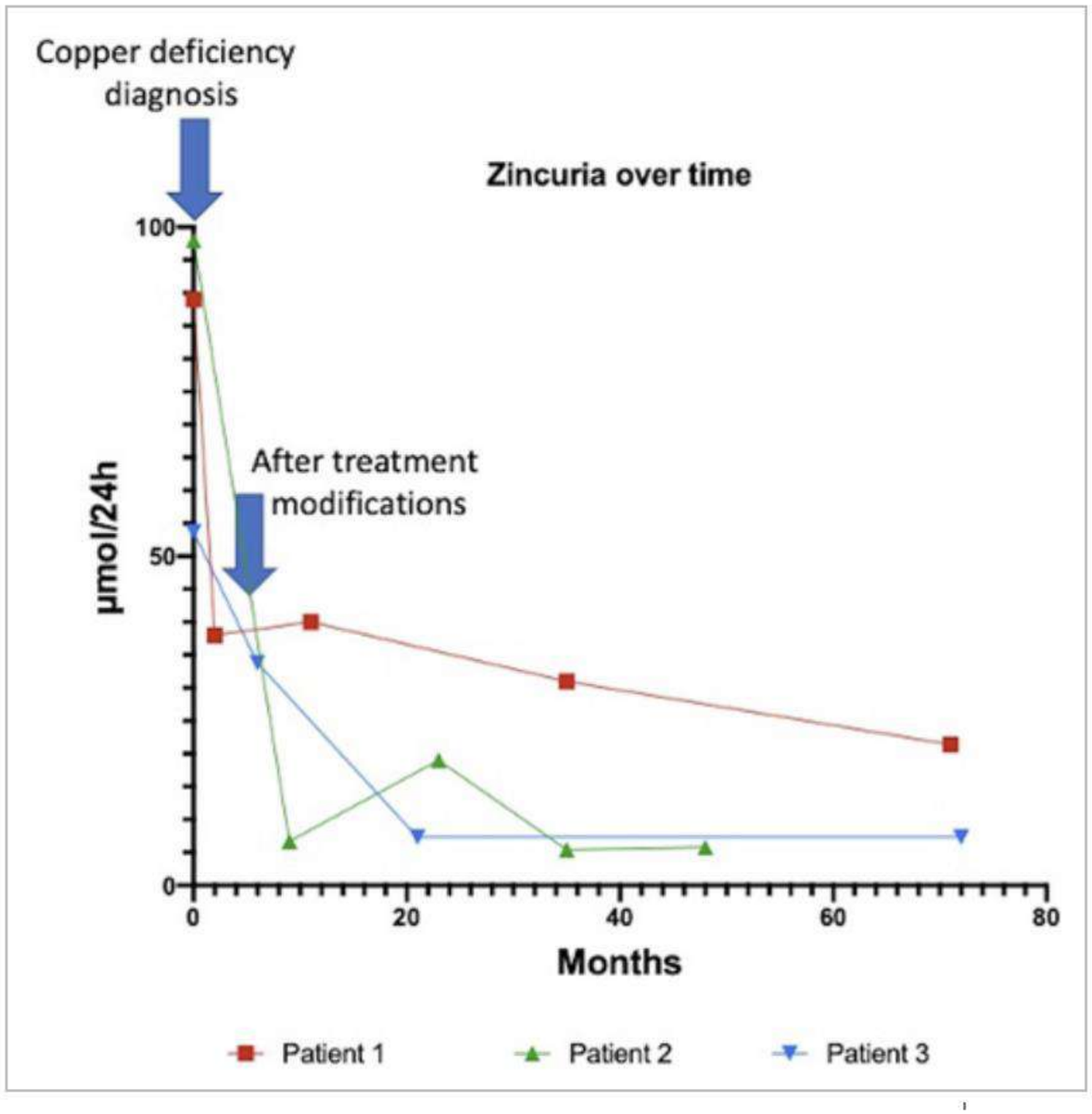
Permission from Aurelia Poujois Neurologist in France to show this case

RESEARCH ARTICLE | Full Access

Can Patients with Wilson's Disease Develop Copper Deficiency?

Kevin Chevalier MD, Mickaël Alexandre Obadia MD, Nouzha Djebrani-Oussedik PharmD, PhD, Aurélia Poujois MD, PhD

First published: 12 June 2023 | https://doi.org/10.1002/mdc3.13813 | Citations: 1



Extremely low levels of serum copper.

Serum and urinary zinc values were high.

All patients showed an iron deficiency.

THE LANCET
Gastroenterology & Hepatology
Volume 7, Issue 6, June 2022, Pages 560-575



Review

Investigation and management of Wilson's disease: a practical guide from the British Association for the Study of the Liver

Samuel Shribman MRCP [a*], Thomas Marjot MRCP [b*], Abubakar Sharif MRCPCH [c*], Sunitha Vimalesvaran MRCPCH [d*], Prof Aftab Ala FRCP [e, f], Prof Graeme Alexander FRCP [g], Prof Anil Dhawan MD [d], James Dooley FRCP [g], Godfrey T Gillett PhD [h], Prof Deirdre Kelly MD [c], Alisdair McNeill PhD [i], Prof Thomas T Warner PhD [a], Valerie Wheater [j], William Griffiths PhD [k, †], Prof Oliver Bandmann PhD [l, †] ✉, British Association for the Study of the Liver Rare Diseases Special Interest Group

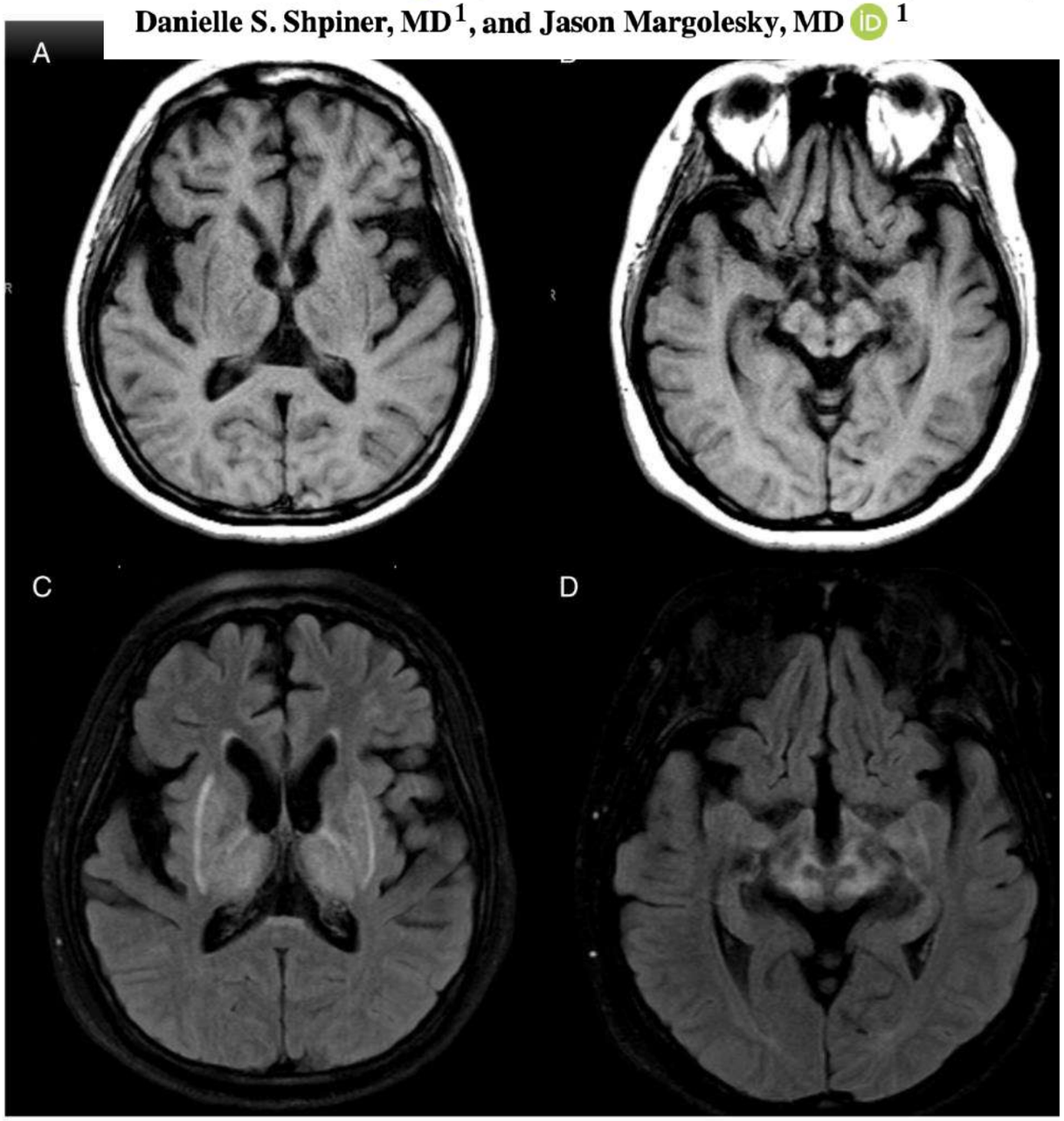
The Neurohospitalist
Volume 14, Issue 1, January 2024, Pages 99-103
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https://doi.org/10.1177/19418744231203277

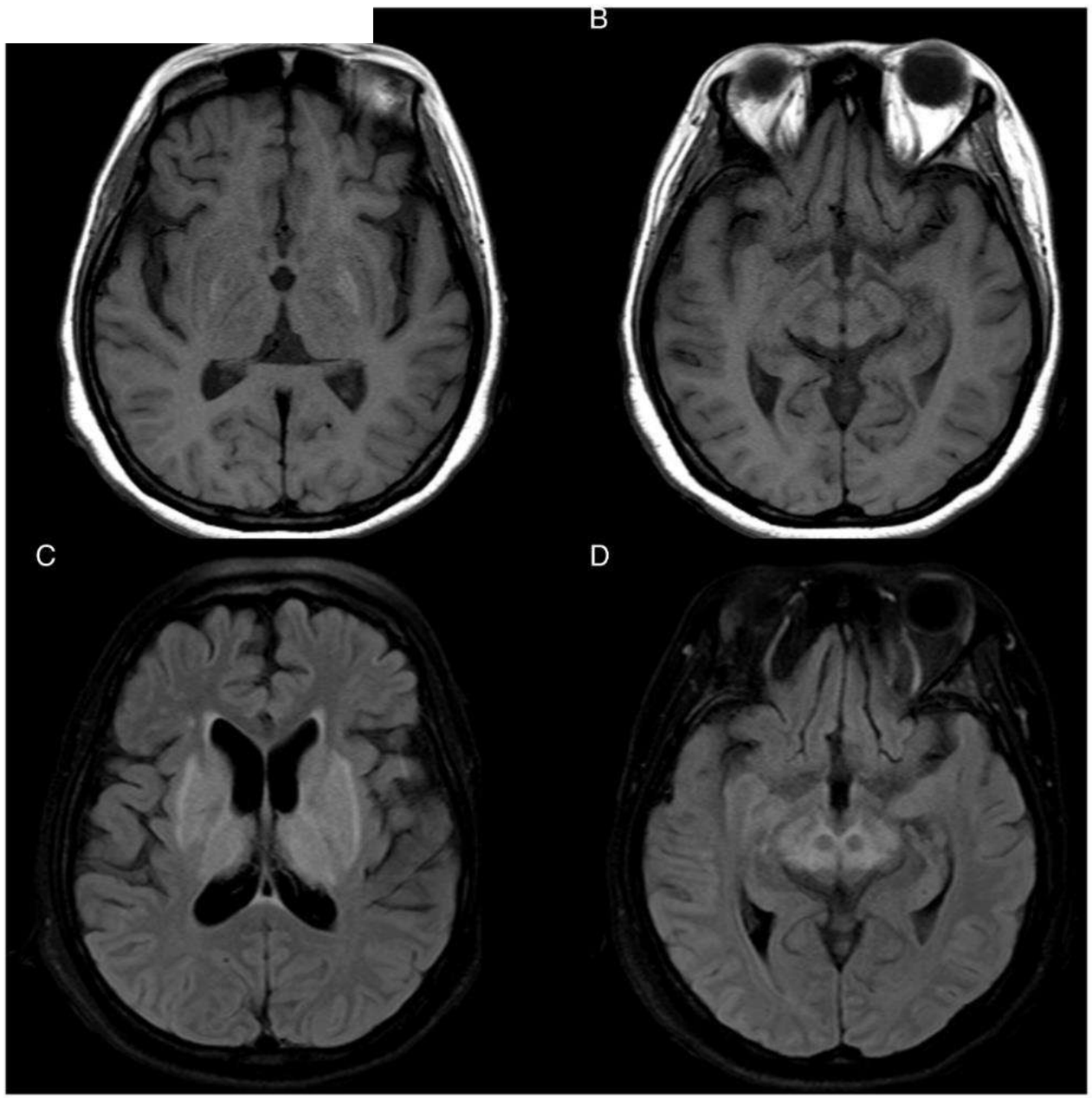
Sage Journals

Case Reports

Treating the Neurologic Manifestations of Wilson's Disease With Liver Transplantation

Sarah Marmol, MD [1,*], Paul Walker Maeder-York, MS, MPH [1,*], Jennifer Hislop, MD [2], Danielle S. Shpiner, MD [1], and Jason Margolesky, MD [1]





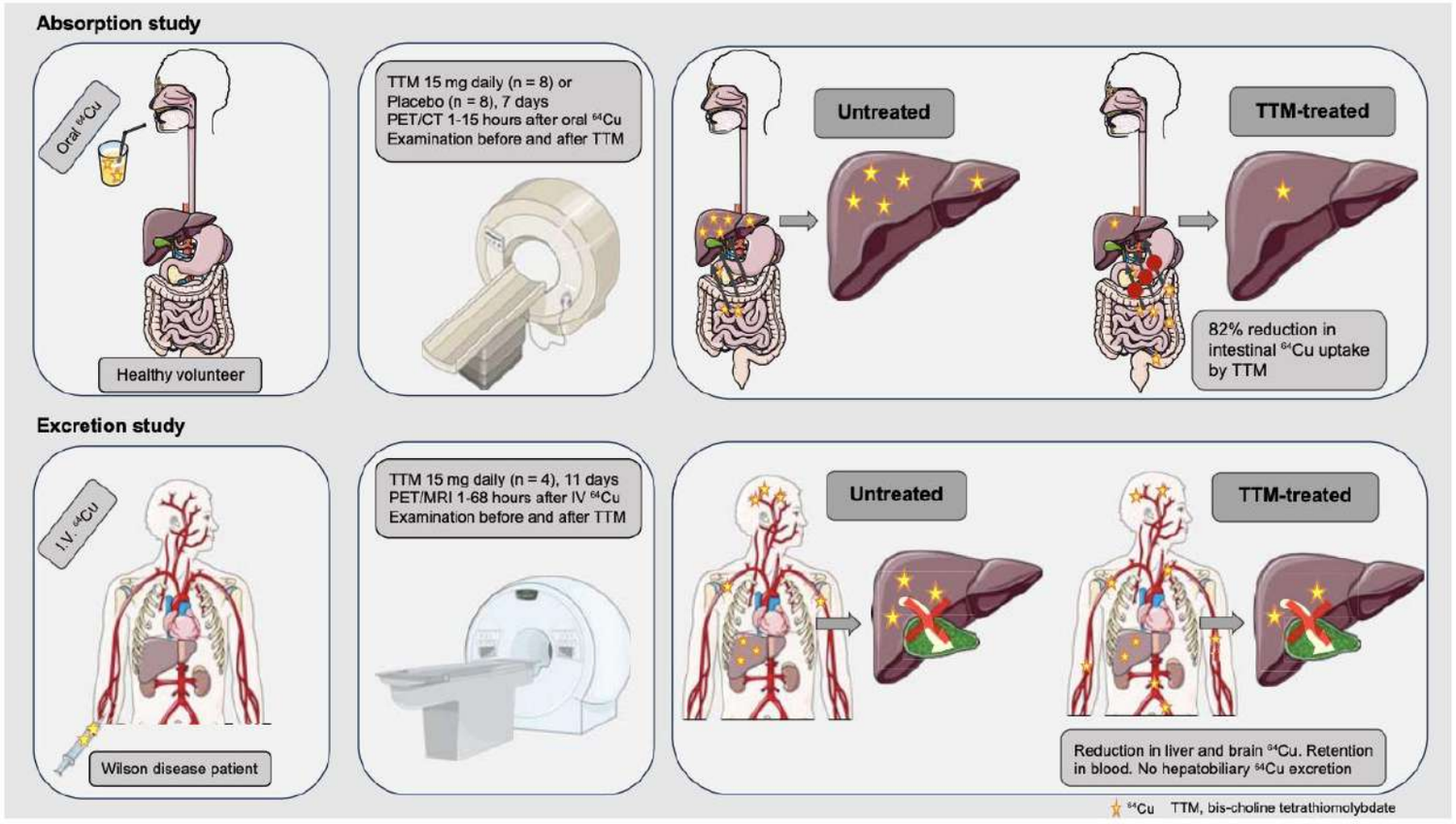
Research Article
DILI, Autoimmune, Cholestatic and Genetic Diseases

JOURNAL
OF HEPATOLOGY

Effects of tetrathiomolybdate on copper metabolism in healthy volunteers and in patients with Wilson disease

Authors

Frederik Teicher Kirk, Ditte Emilie Munk, Eugene Scott Swenson, …, Michael L. Schilsky, Peter Ott, Thomas Damgaard Sandahl



Highlights

- ^{64}Cu PET/CT/MRI can detect the uptake and distribution of ^{64}Cu in the body.
- TTM is a highly effective copper-binding agent.
- The mode of action depends on the compartment it is active in.
- TTM very efficiently reduces intestinal ^{64}Cu uptake.
- TTM rapidly binds ^{64}Cu in blood and reduces copper availability to the liver and brain.

Hindawi
Case Reports in Hepatology
Volume 2023, Article ID 3985823, 3 pages
https://doi.org/10.1155/2023/3985823

Case Report

Plasmapheresis for Fulminant Wilson's Disease Improves Mental Status and Coagulopathy

Quarshie Glover [1] **and William Nicholas Rose** [2]

[1]*Department of Medicine, University of Wisconsin Hospital, 600 Highland Ave, Madison, WI 53792, USA*
[2]*Department of Pathology, University of Wisconsin Hospital, 600 Highland Ave, Madison, WI 53792, USA*

Table 1: Table showing improvement in INR and serum creatinine after starting plasmapheresis.

	INR	Creatinine (mg/dl)
Day 1 (11/08)	2.4	1.7
Day 2 (11/09) *	2.6	2.96
Day 3 (11/10)	1.5	2.72
Day 4 (11/11)	1.6	2.09
Day 5 (11/12)	1.5	1.68

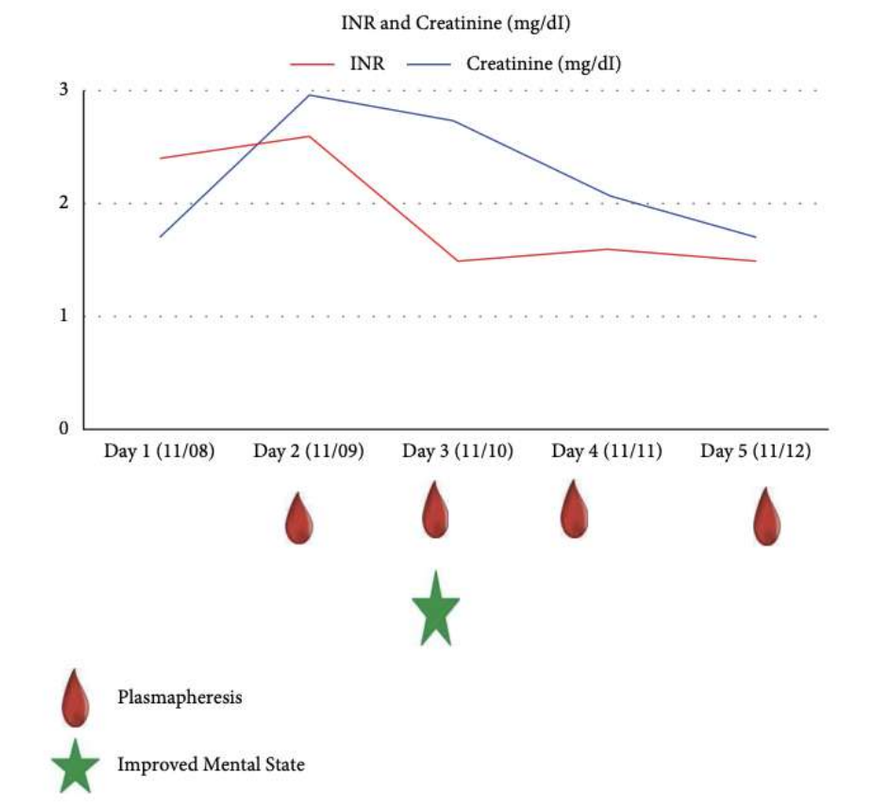


Figure 1: Improved INR, creatinine, and mental state after starting plasmapheresis.

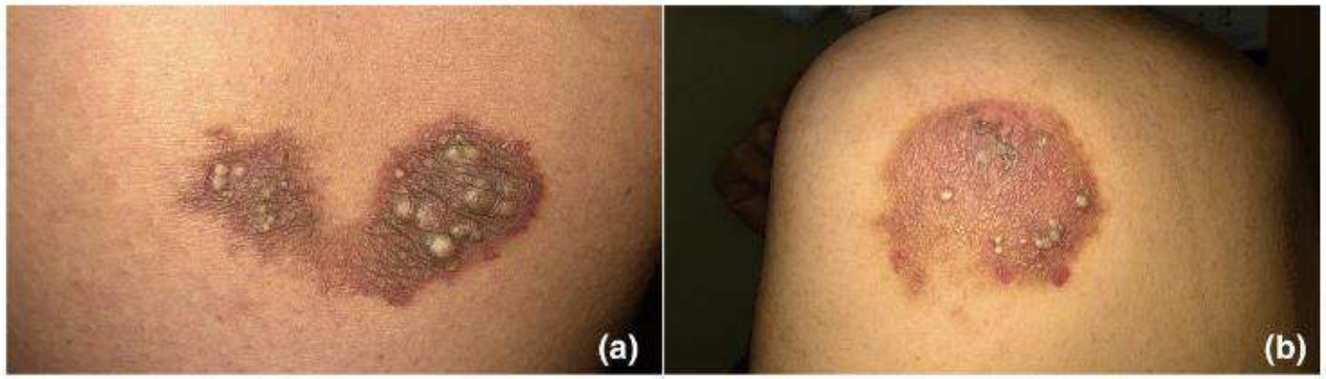
Australasian Journal of Dermatology

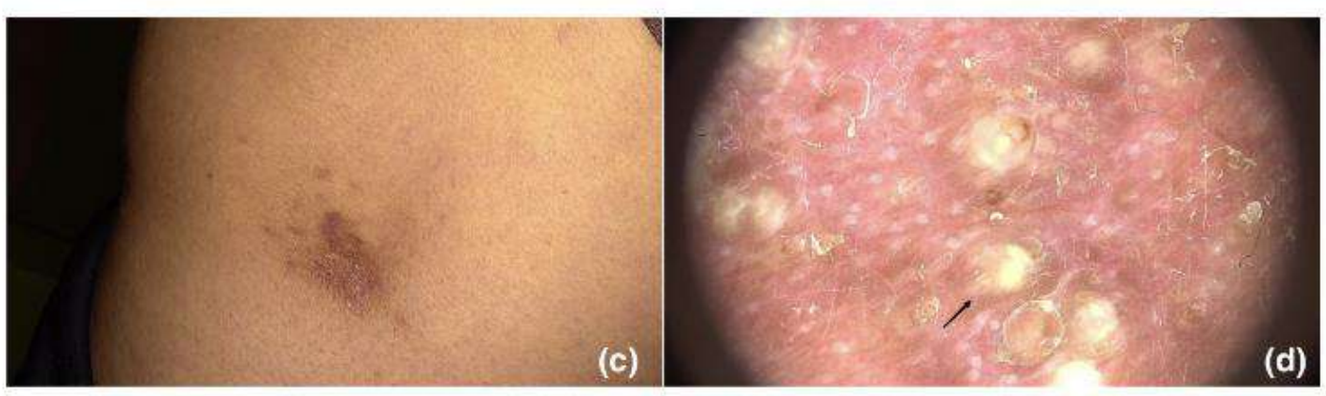
BRIEF REPORT | Full Access

Penicillamine-induced degenerative dermopathy in a patient with Wilson's disease

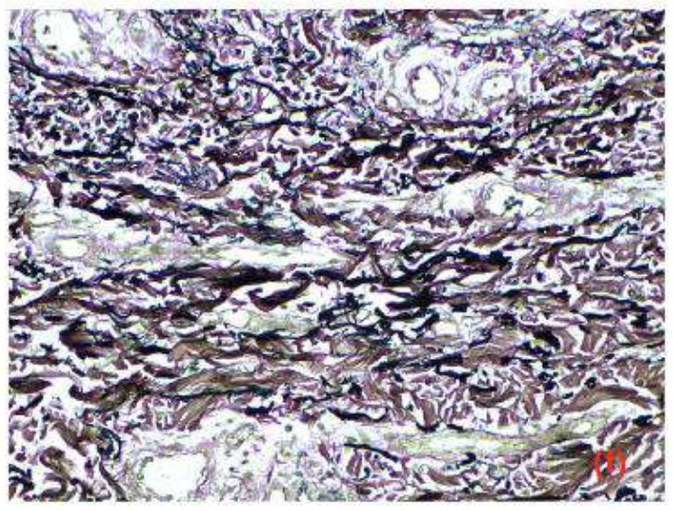
Yuting Chen MD, Yangyang Qiu MD, Meiqing Chen MD, Ying Jiang MD, Xiaoyan Qiu M.B., Lujuan Gao MD

First published: 24 December 2022 | https://doi.org/10.1111/ajd.13963

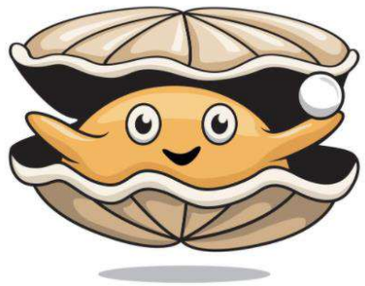








Take home points



- Wilson Disease is a great mimic
- Always think of Wilson's Disease in a 'younger' patient with a movement disorder
- Clinical presentation is variable, and so is the MRI
- KF rings may be absent even with slit lamp examination
- You can 'over-chelate'

Thank You

Twitter, Instagram, Threads:
@MichaelOkun
Blog: www.planplan.org



Contact Information:
okun@neurology.ufl.edu

UFHealth
NORMAN FIXEL INSTITUTE FOR NEUROLOGICAL DISEASES

Parkinson's Foundation

Tourette Association of America
Awareness. Research. Support.

Tyler's Hope for a Dystonia Cure

NIH
National Institutes of Health

If you want to learn more check out these slides:

Tremor and Wilson's Disease What's New



Movement Disorders
CLINICAL PRACTICE

RESEARCH ARTICLE

Can Patients with Wilson's Disease Develop Copper Deficiency?

Kevin Chevalier, MD,[1,2] Mickaël Alexandre Obadia, MD,[1,2] Nouzha Djebrani-Oussedik, PharmD, PhD,[2,3] and Aurélia Poujois, MD, PhD[1,2,*]

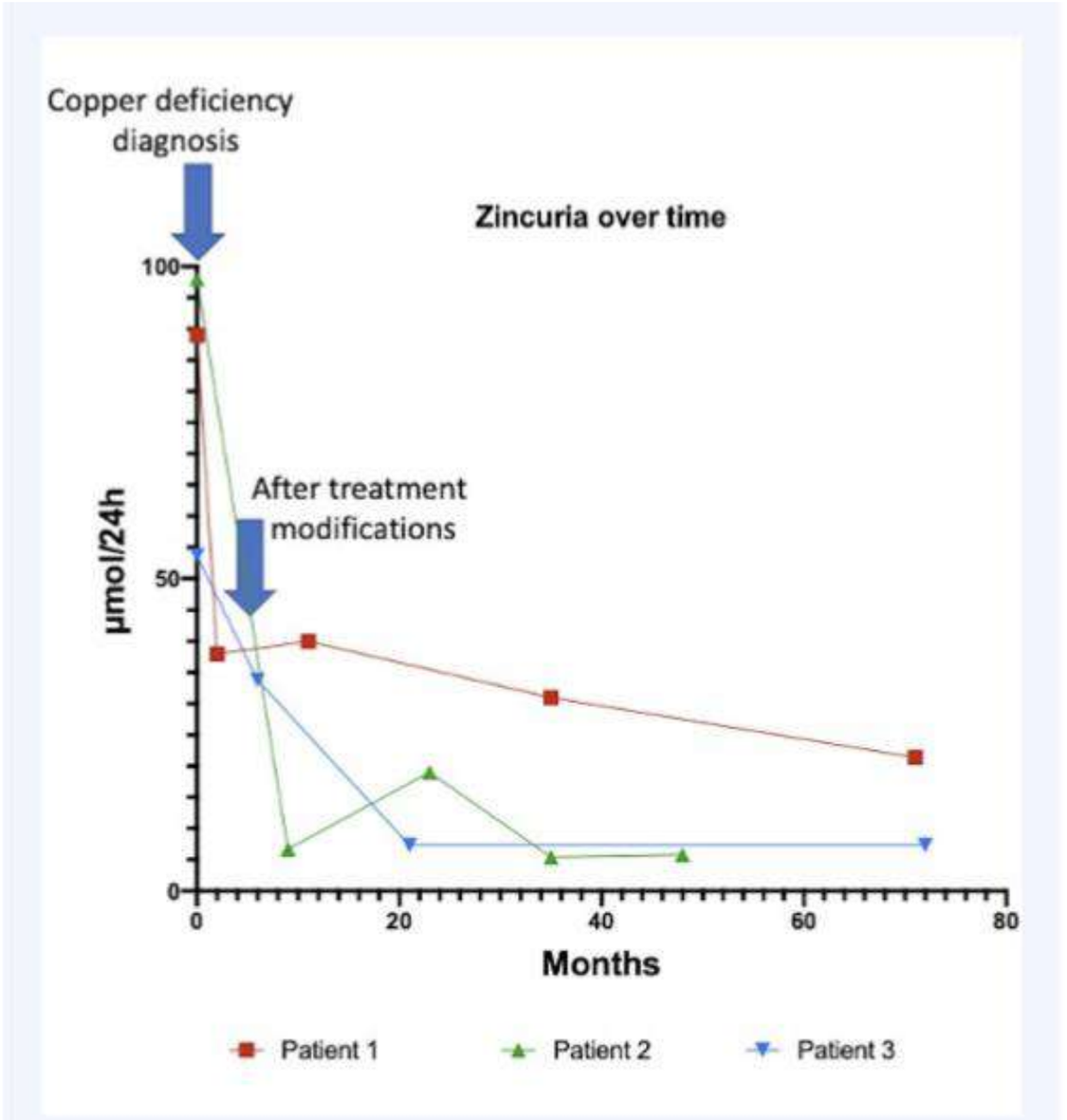


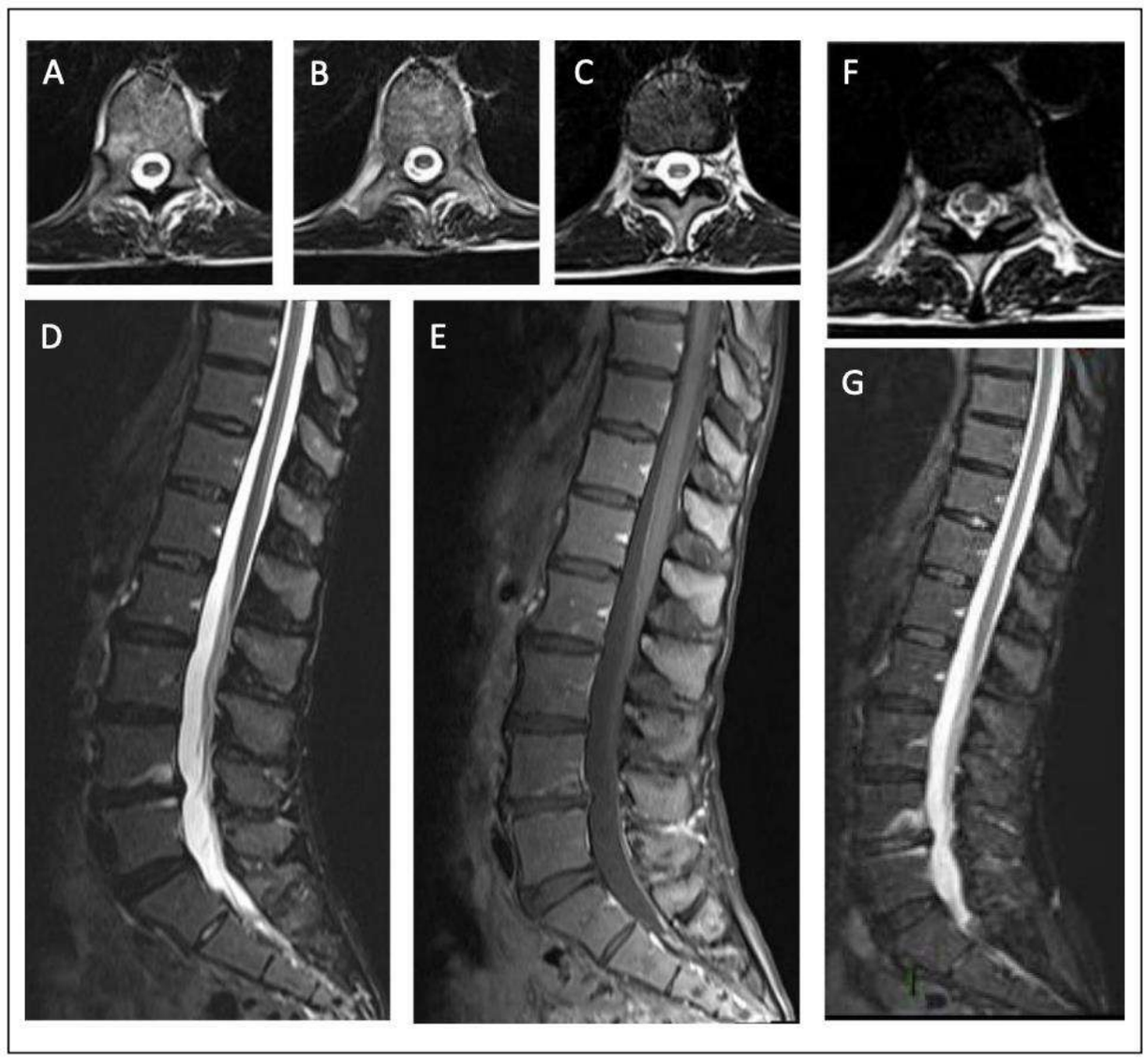
FIG. 1. Zincuria values over time.

Neurological Sciences (2024) 45:987–996
https://doi.org/10.1007/s10072-023-07126-8

REVIEW ARTICLE

Neurological complications due to copper deficiency in the context of Wilson disease treatment: a case report with long-term follow-up and review of the literature

Danilo Tornabene[1,2] · Paola Bini[2] · Matteo Gastaldi[2] · Elisa Vegezzi[2] · Carlo Asteggiano[1,2] · Enrico Marchioni[2] · Luca Diamanti[2]



Brain and Behavior

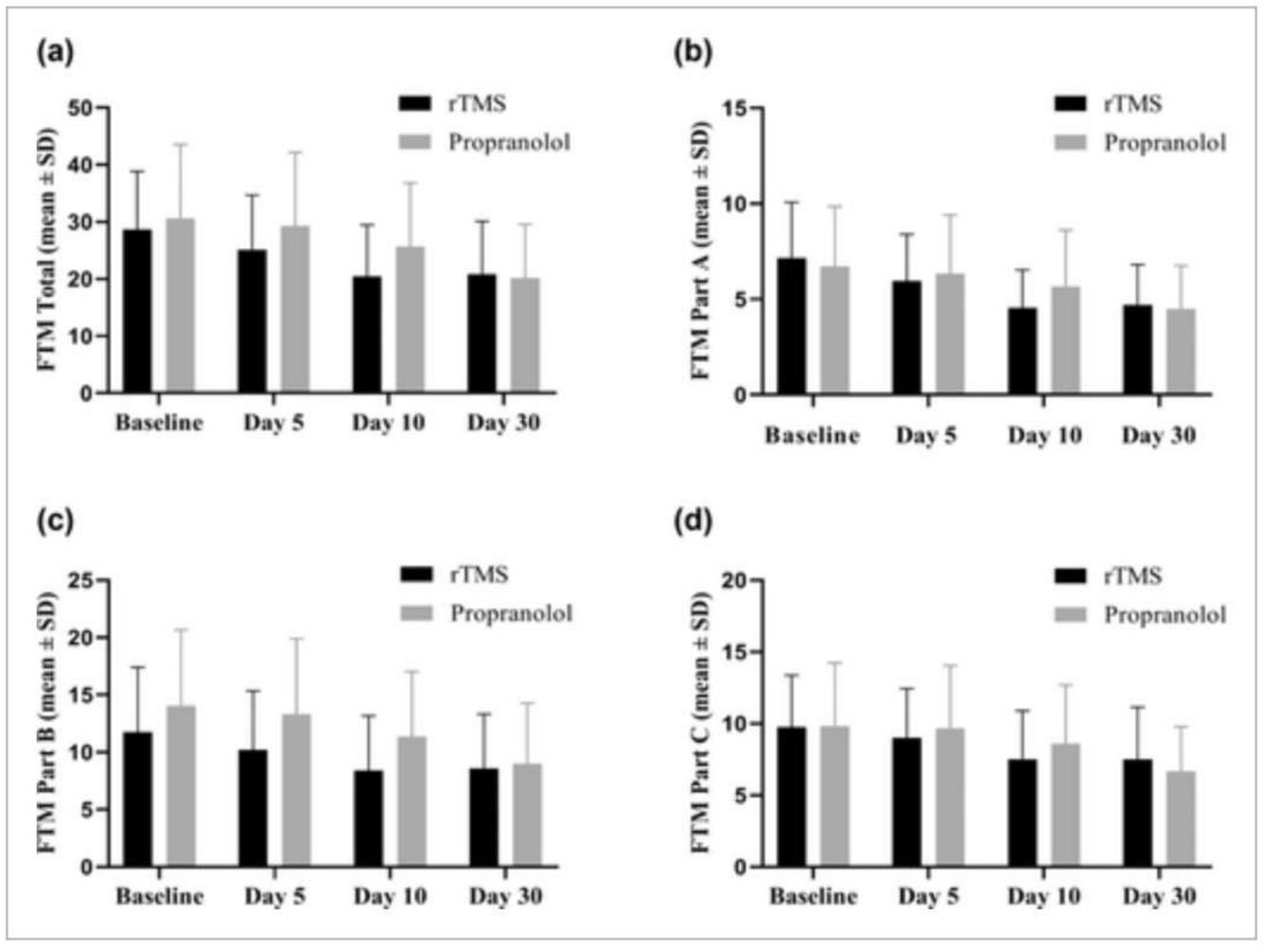
Forward Series

ORIGINAL ARTICLE | Open Access

Cerebellar repetitive transcranial magnetic stimulation versus propranolol for essential tremor

Yue Lv, Mengran Wang, Juan Yang, Jin Shi, Tingting Xuan, Junmei Zhang, Dandan Du, Jiang Cheng ✉, Haining Li ✉

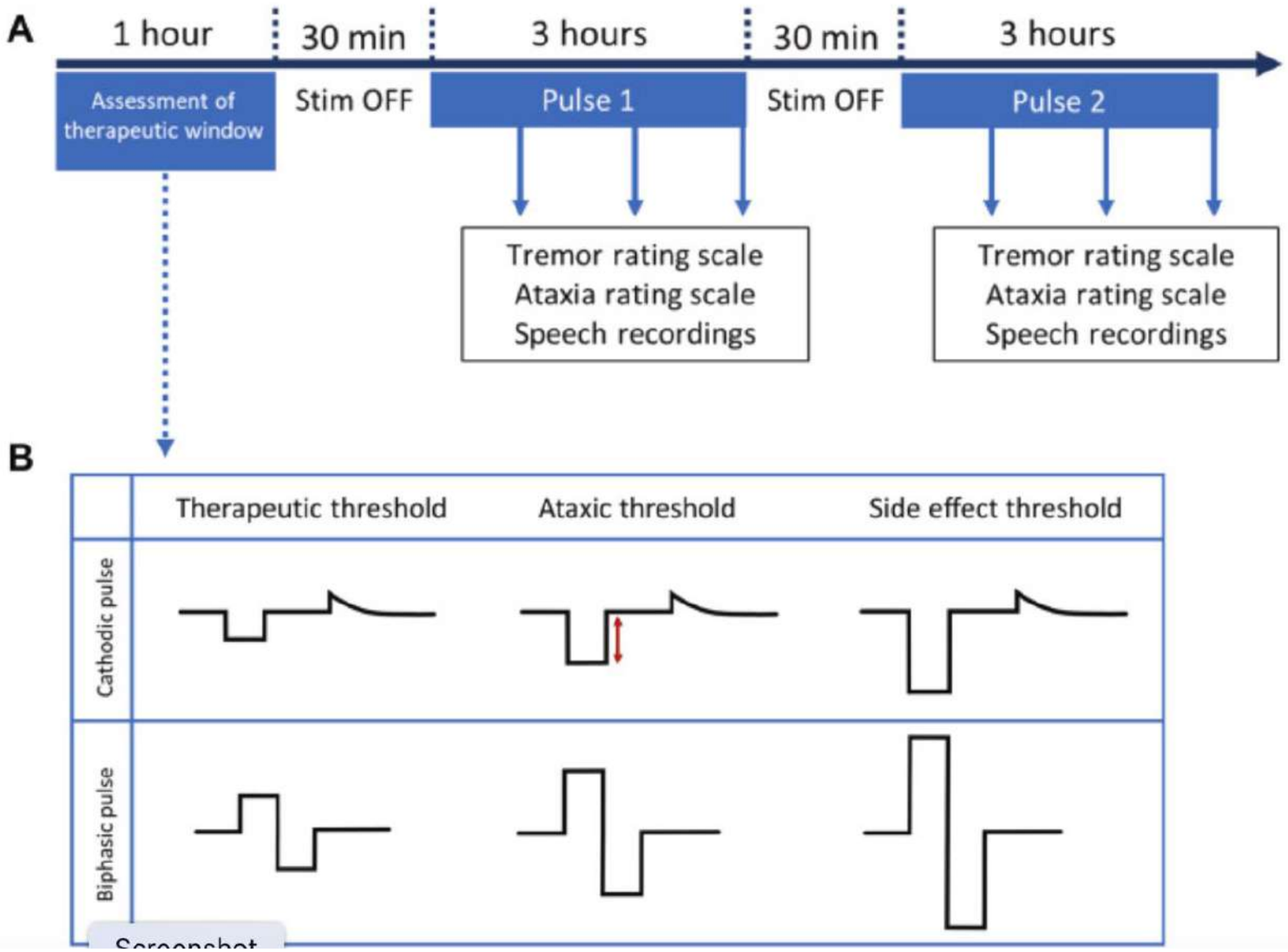
First published: 17 February 2023 | https://doi.org/10.1002/brb3.2926



Parkinsonism & Related Disorders
Volume 111, June 2023, 105435

Acute stimulation with symmetric biphasic pulses induces less ataxia compared to cathodic pulses in DBS for essential tremor

Alexandra Boogers [a b], Jana Peeters [a], Tine Van Bogaert [a], Jan Rusz [c], Camelia Bogaert-Miclaus [d], Griet Loret [d], Philippe De Vloo [e f], Wim Vandenberghe [b g], Bart Nuttin [e f], Myles Mc Laughlin [a]



Comparative Effectiveness of Transcutaneous Afferent Patterned Stimulation Therapy for Essential Tremor: A Randomized Pragmatic Clinical Trial

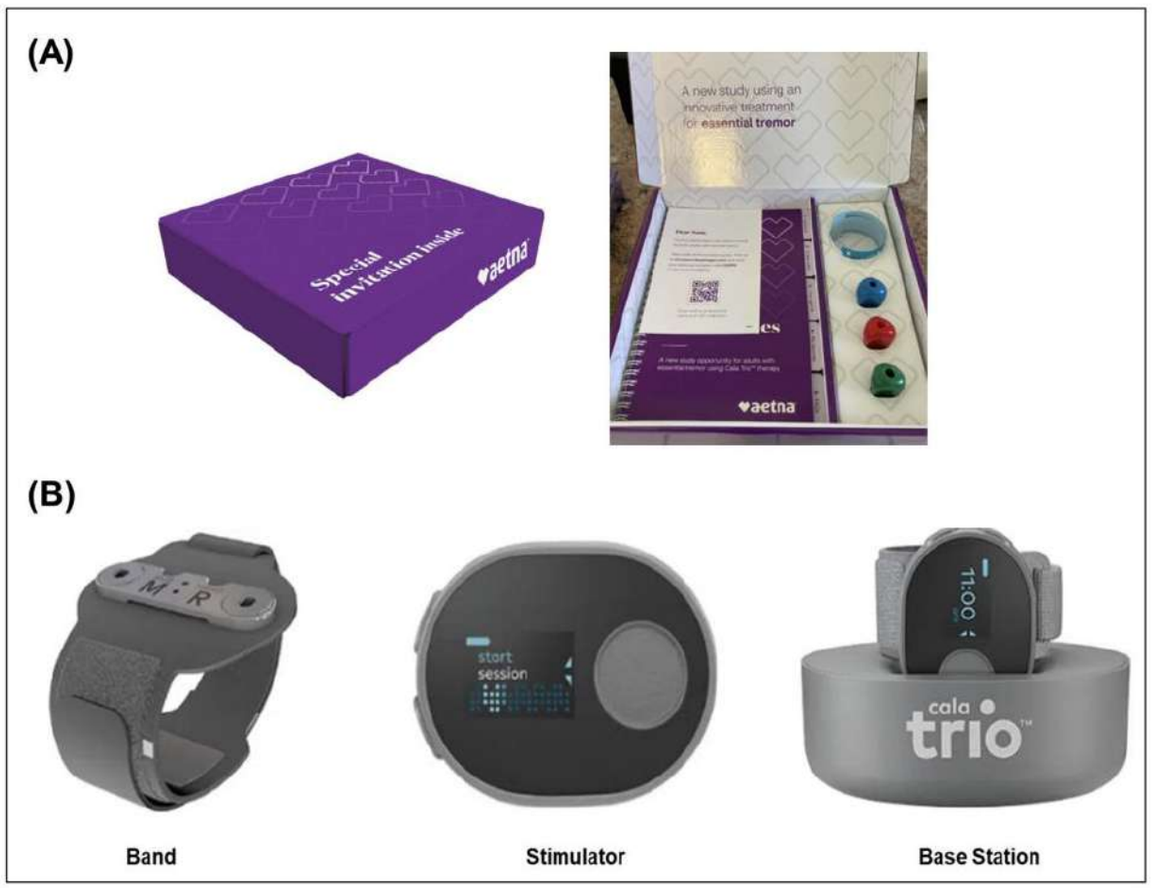
Tremor and Other Hyperkinetic Movements

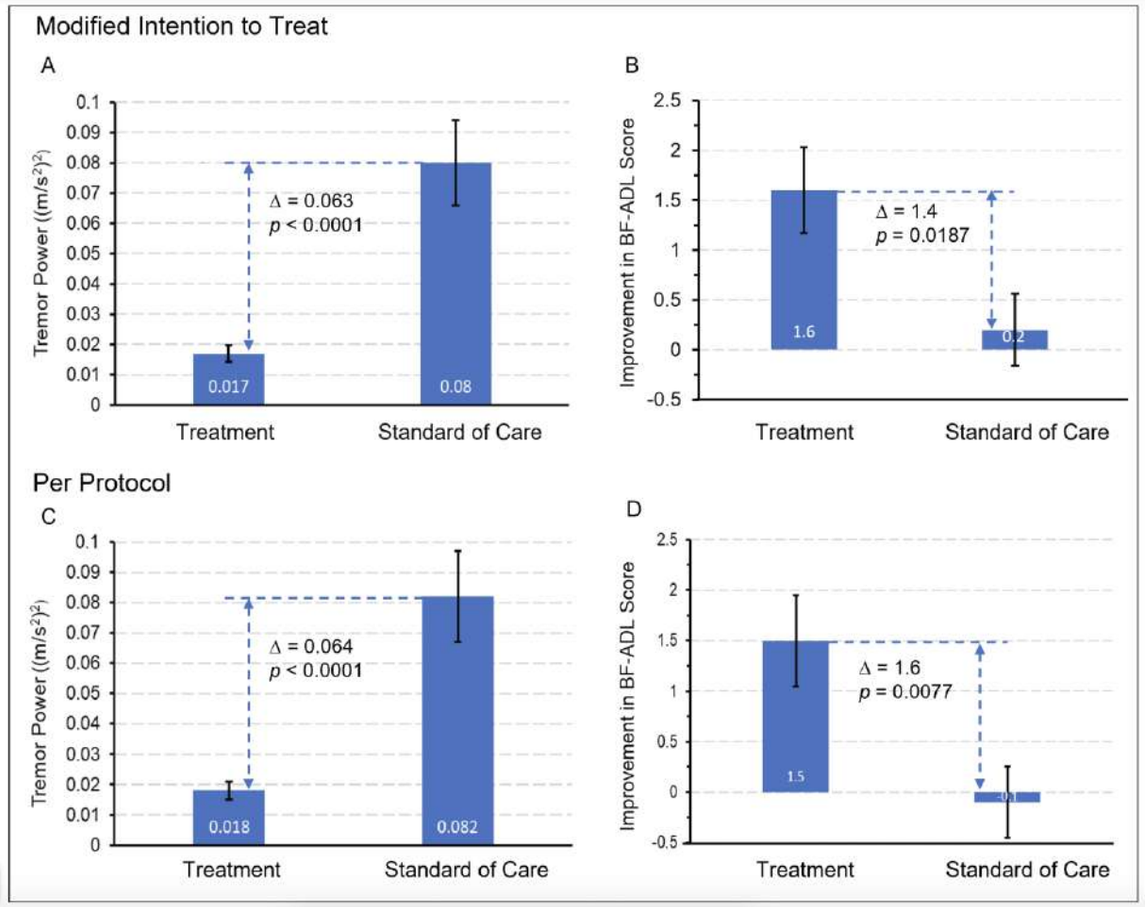
ARTICLE

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DINGWEI DAI
HAN KIM
JOAQUIM FERNANDES
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*Author affiliations can be found in the back matter of this article



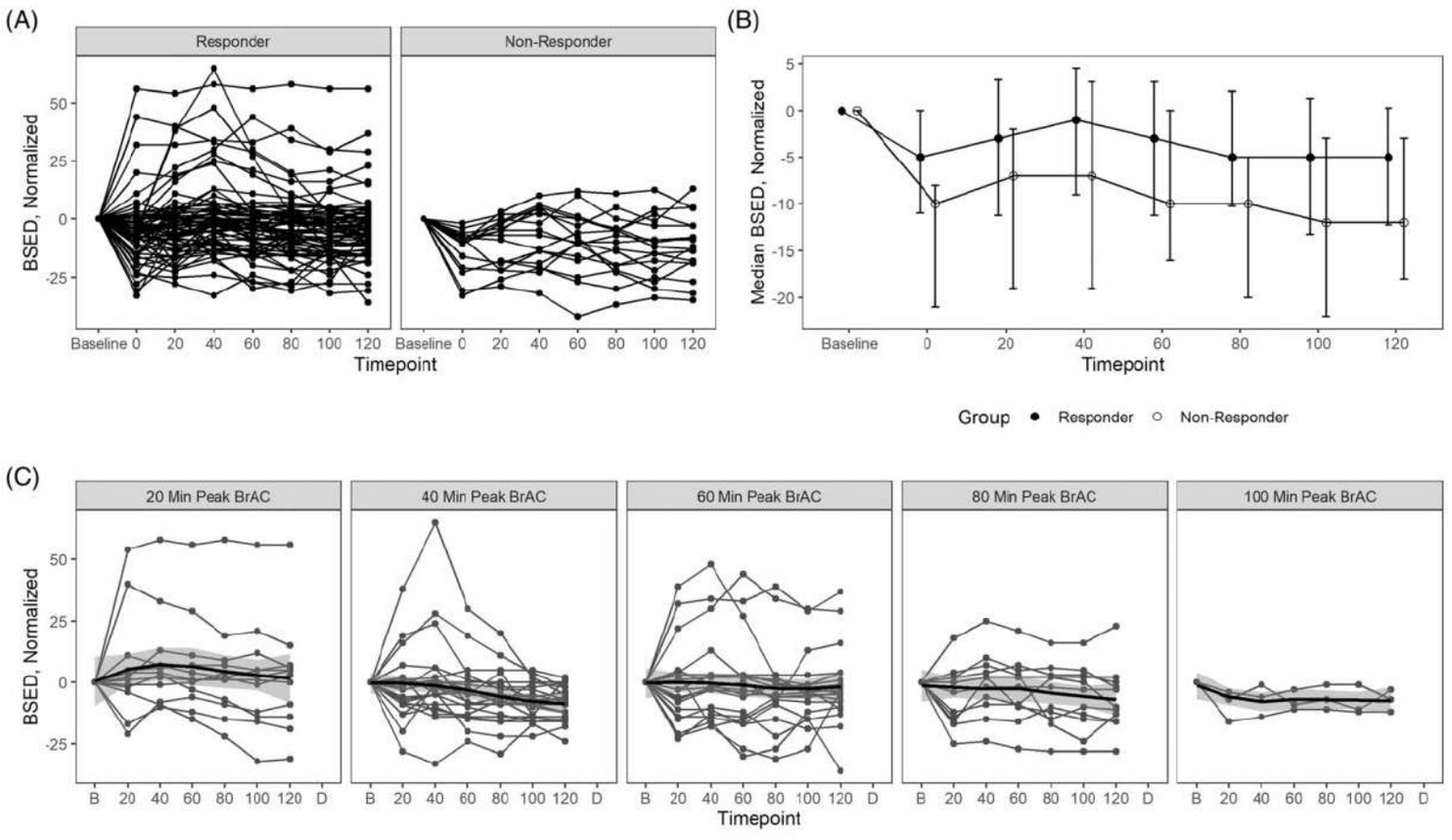


ANNALS of Clinical and Translational Neurology
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AMERICAN NEUROLOGICAL ASSOCIATION

RESEARCH ARTICLE

Objective response to ethanol in essential tremor: results from a standardized ethanol challenge study

Patrick McGurrin[1,2,†], Gina Norato[3,†], Johanna Thompson-Westra[2,4], Gayle McCrossin[2,5], Emily Lines[4], Codrin Lungu[6], Sanjay Pandey[7], Sule Tinaz[8], Bernhard Voller[9], Vijay Ramchandani[10], Mark Hallett[2] & Dietrich Haubenberger[2,3,11]



- 80% alcohol responsive using our objective definition
- Change in breath alcohol concentration levels after ethanol administration,
- Self-reported response does not correlate well with objective response.



Michael Okun @MichaelOkun · Feb 15

Is there a **new drug** on the horizon for **essential tremor**? New Randomized Phase 2 trial of SAGE-324/BIIB124 results are out in @MDJ_Journal.

Key points:

- The drug works as a **positive allosteric modulator** of **GABA-A** receptors.
- The design was a **double-blind, randomized,**

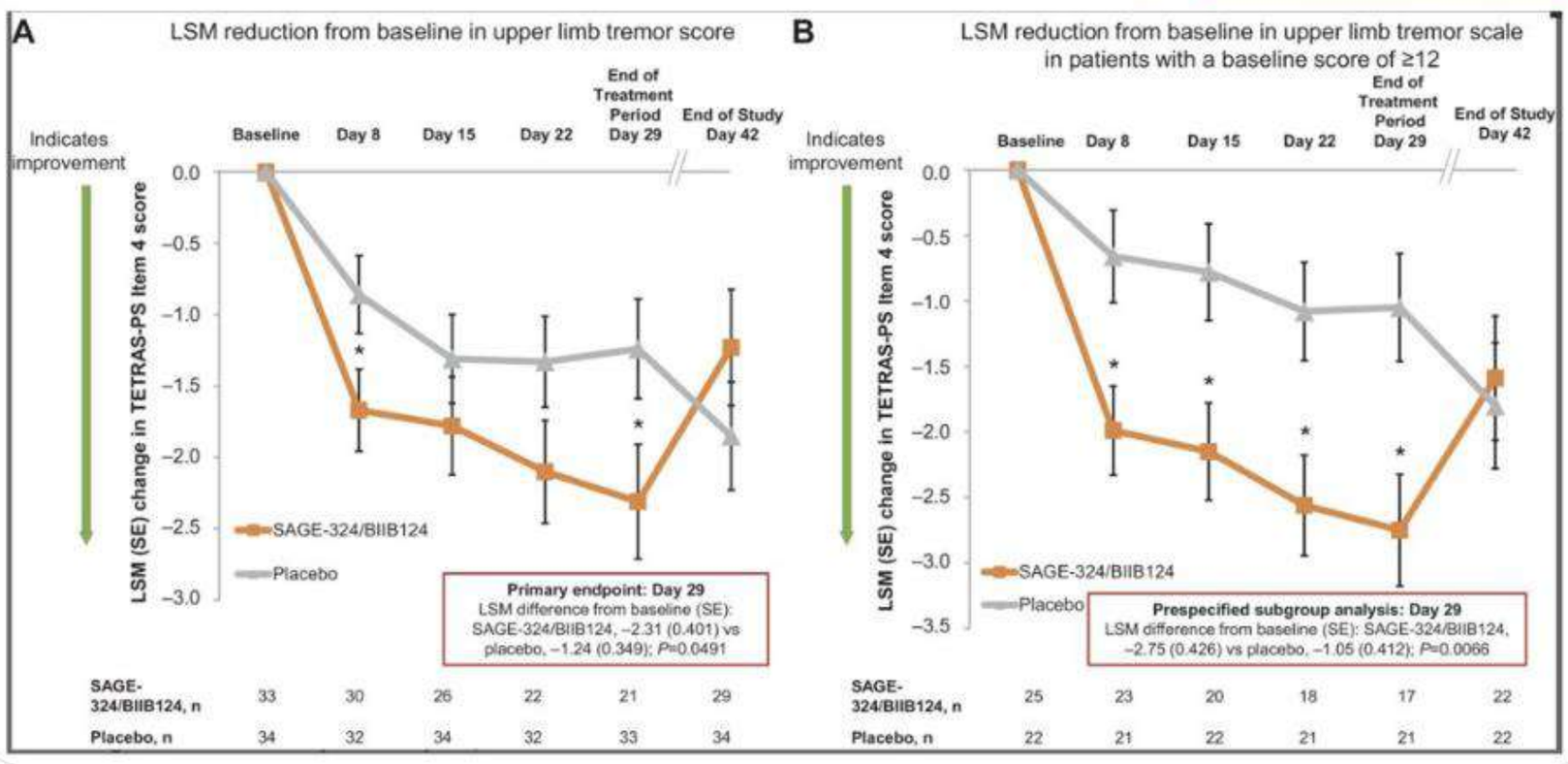
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BRIEF REPORT | Open Access

A Randomized Phase 2 KINETIC Trial Evaluating SAGE-324/BIIB124 in Individuals with Essential Tremor

Rodger J. Elble MD, PhD, William G. Ondo MD, Kelly E. Lyons PhD, Min Qin PhD, S
Bonnie Hersh MD, TinaMarie Lieu PhD, Dimitrios Arkilo MD, Rosalind Chuang M

Movement Disorders



1 23 78 8.6K



Michael Okun @MichaelOkun · Feb 5

Can you diagnose **ANO3** related **tremor**, **dystonia** and **gait** related disorders? Be careful as there are many possibilities for symptoms in this genetic disorder. Percetti and colleagues **broaden the spectrum** of possible presentations for the ANO3 gene mutation in a new paper in

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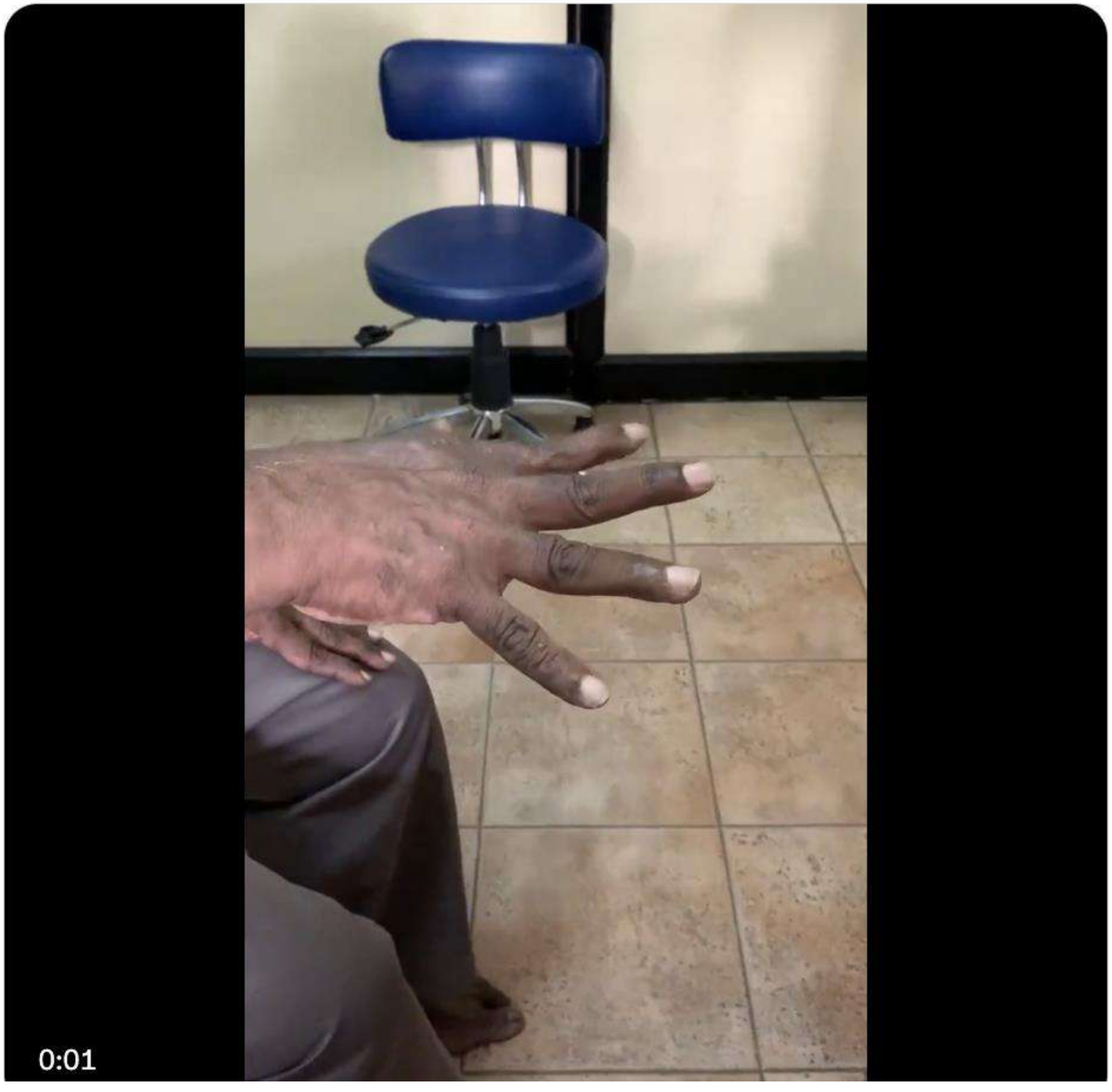


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Michael Okun @MichaelOkun · Mar 27

Can you recognize a **re-emergent tremor** in the setting of **Parkinson's disease**? 'One type of postural tremor are **rest tremors that re-emerge** after a variable delay while maintaining posture.' Described by Jankovic, physiology by @muthu100680 and example video by Boby.
Nice review
Show more

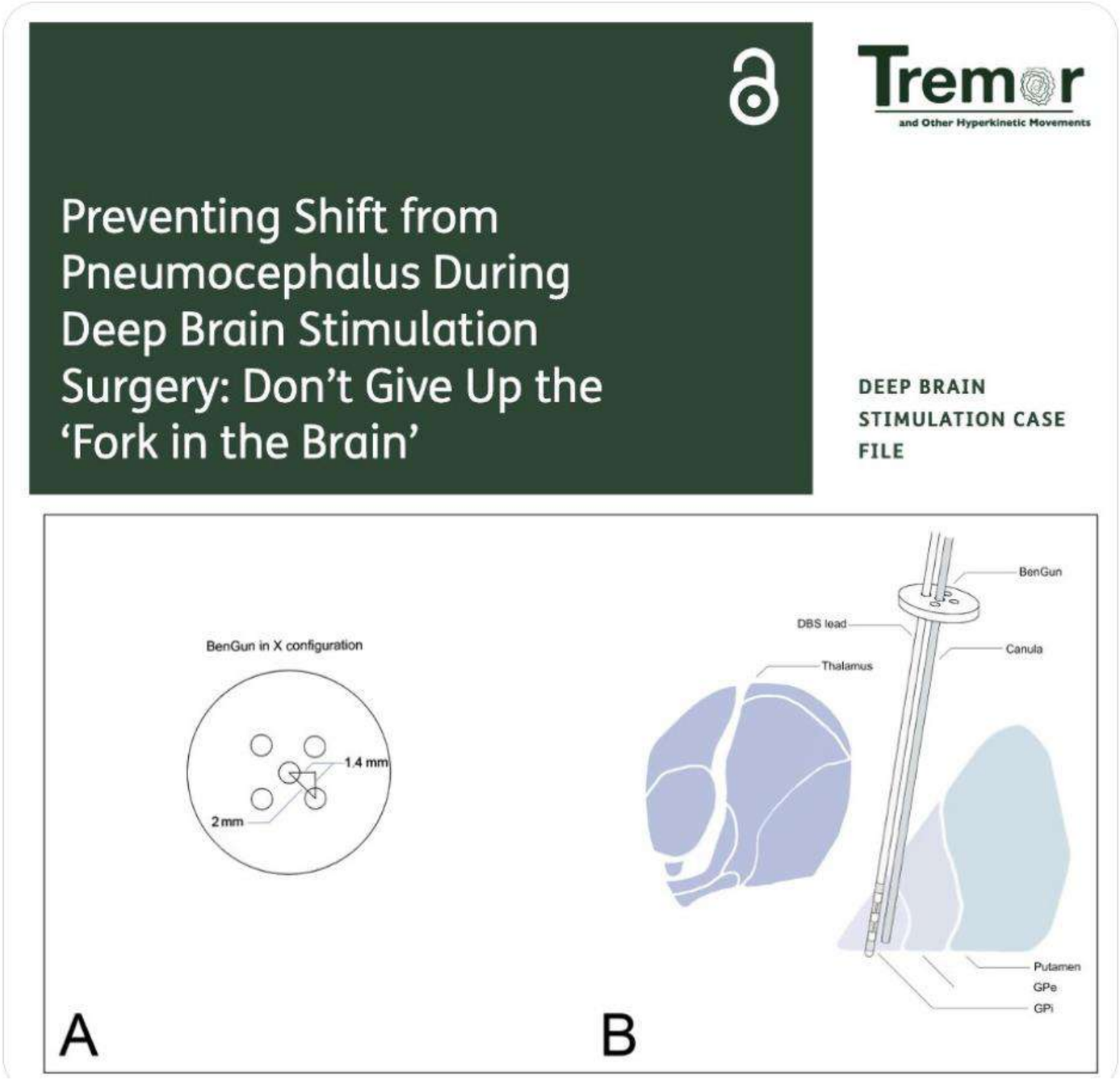


Michael Okun @MichaelOkun · Apr 14

What role does **Yogi Berra** play in **deep brain stimulation** (DBS)? Do you know how to **prevent shift from air**? Do you give up the **fork**? Alfonso Enrique Martinez-Nunez a fellow @FixelInstitute presents a case and discussion for the DBS Case Files as part of @tremorjournal.

Key Points:

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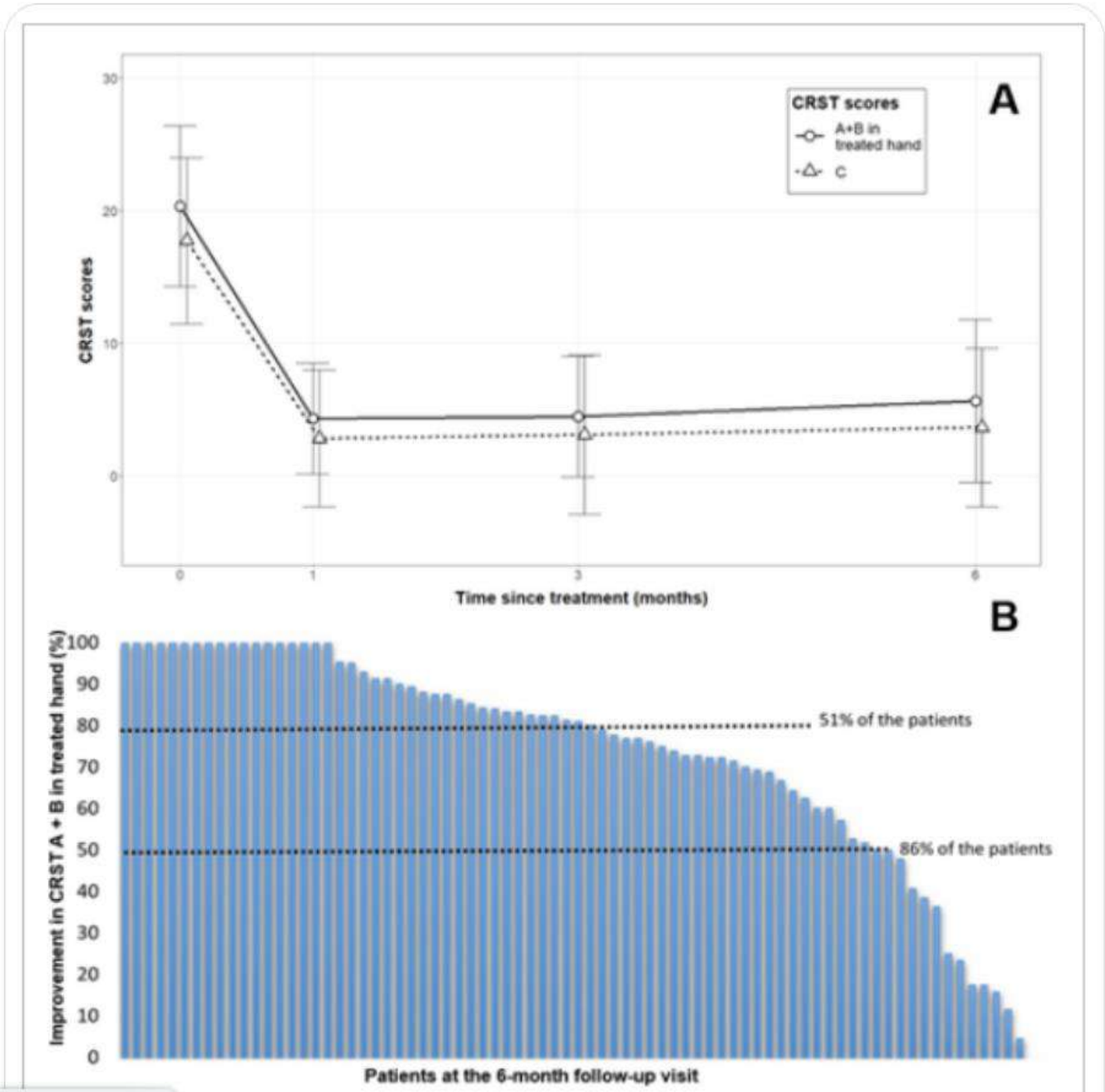
Michael Okun @MichaelOkun · Apr 20

Does **lesion location** or **lead location impact** your **outcome** from f**ocused ultrasound** or **DBS**? You bet it does. Lot's of papers on this for DBS and classical thalamotomy, and now one for FUS by Arcadi, Rodríguez-Oroz and colleagues in @MDJ_Journal.

Key Points:

- 127 people

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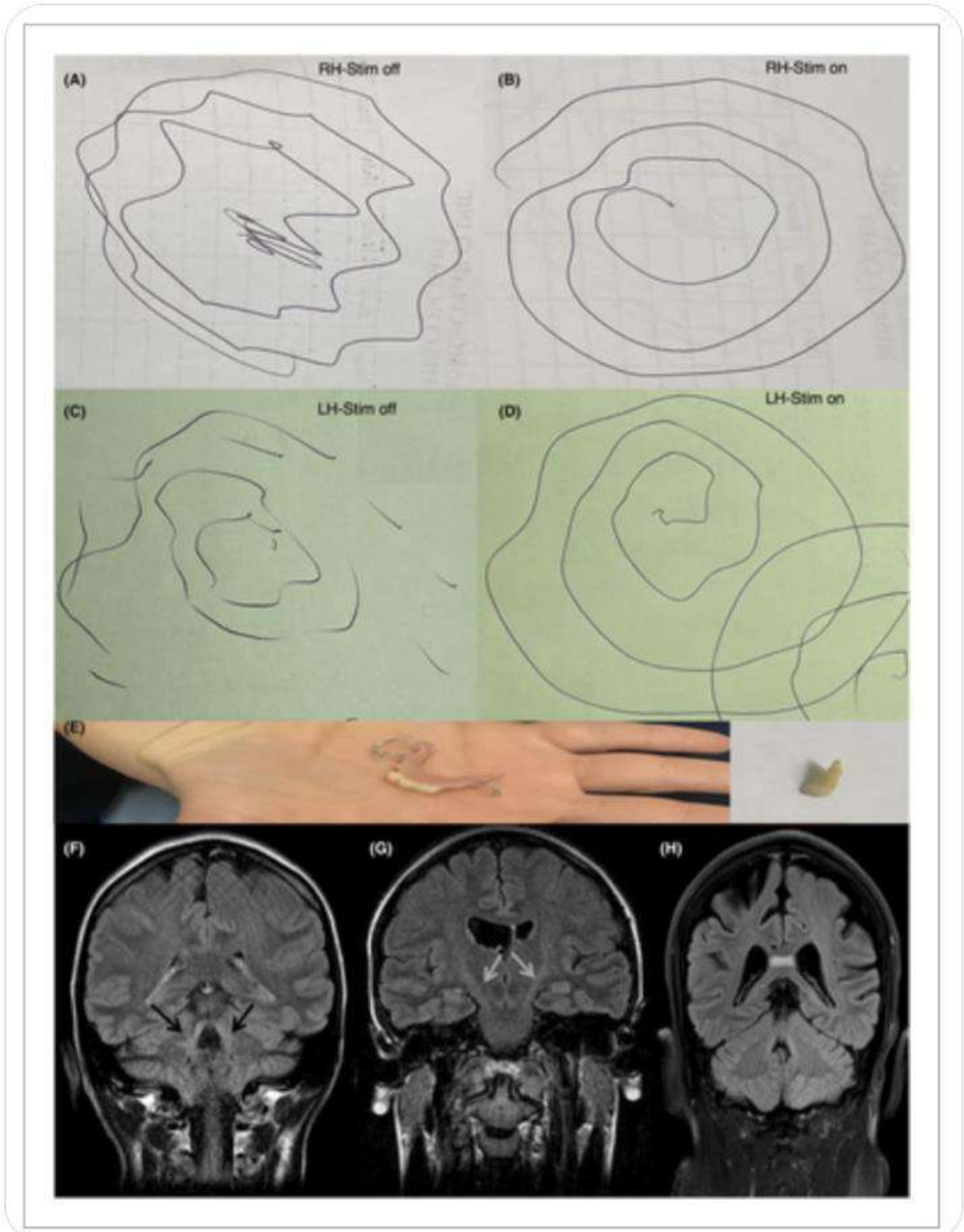




Michael Okun @MichaelOkun · May 9

Does **DBS** help for **dystonic tremor**? How about in **POLR3A-related disorders**? Yau and colleagues @ANA_journals have published a nice series followed by an important discussion. This group provides some data on thalamic vs. pallidal (GPi) DBS in this circumstance were the syndrome

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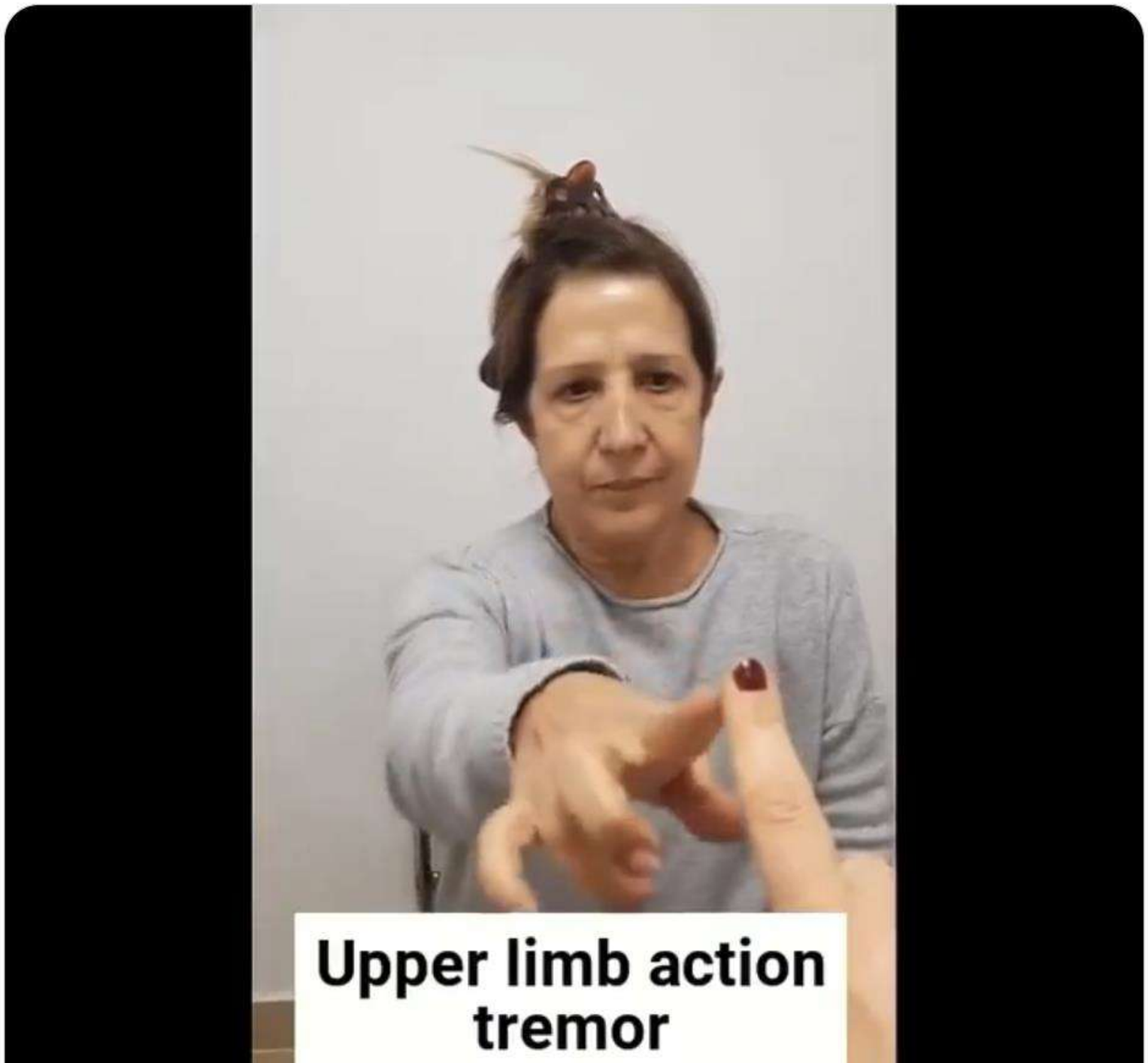
Screenshot

The **genetics of tremor** are getting more complicated everyday. Check out this **KCNQ2 gene variant** which presented in combined tremor syndrome @tremorjournal by Giulia Paparella and colleagues.

Key points:

- This woman had a **family history** of tremor.
- There was a novel **heterozygous**

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Michael Okun @MichaelOkun · Jun 22

Can you observe **tremor** in the setting of **spinocerebellar ataxia**? You bet you can. Check out this great scoping review and video from Mukherjee and Pandey in @tremorjournal.

Key Points:

- The authors point out that we frequently encounter **tremor in ataxia syndromes**.

- Action

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Michael Okun

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Michael Okun @MichaelOkun · Jul 13

Looking for a **master class in essential tremor** and **essential tremor versus Parkinson's disease**? Look no further as Binit Shah and Jeff Elias @UVA have a new piece in JAMA Insights.

Key Points:

- ET is frequently diagnosed in **primary care settings** based only history and

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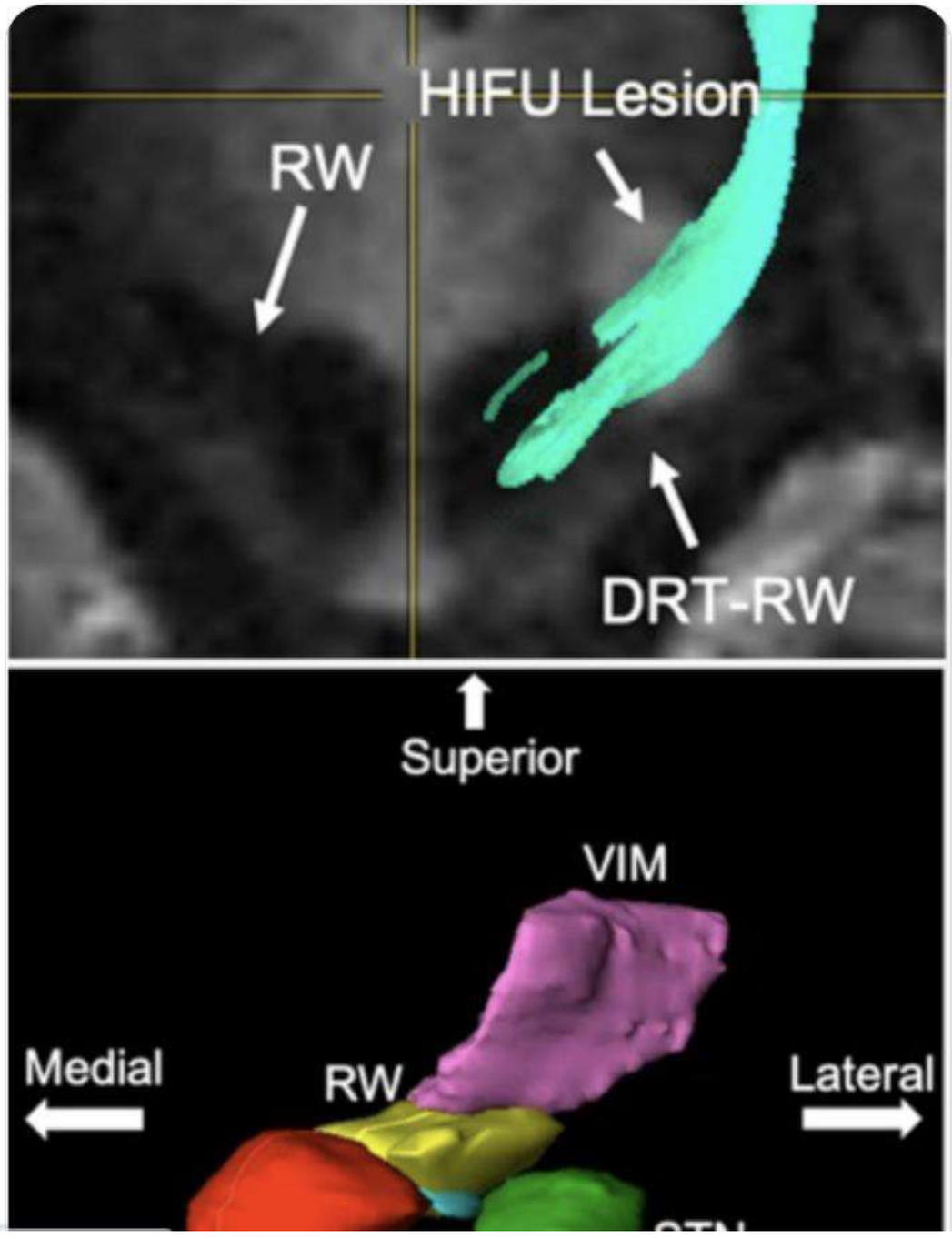


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ASSFN @ASSFNeurosurg · Jul 11

An article in @NeurosurgeryCNS describes a novel tractography method for targeting the dentatorubrothalamic tract rubral wing in high-intensity focused ultrasound, discussing its potential as a simple, well-demarcated method.

@AANS @CNS_Update
#ASSFN #neurosurgery #MedTwitter



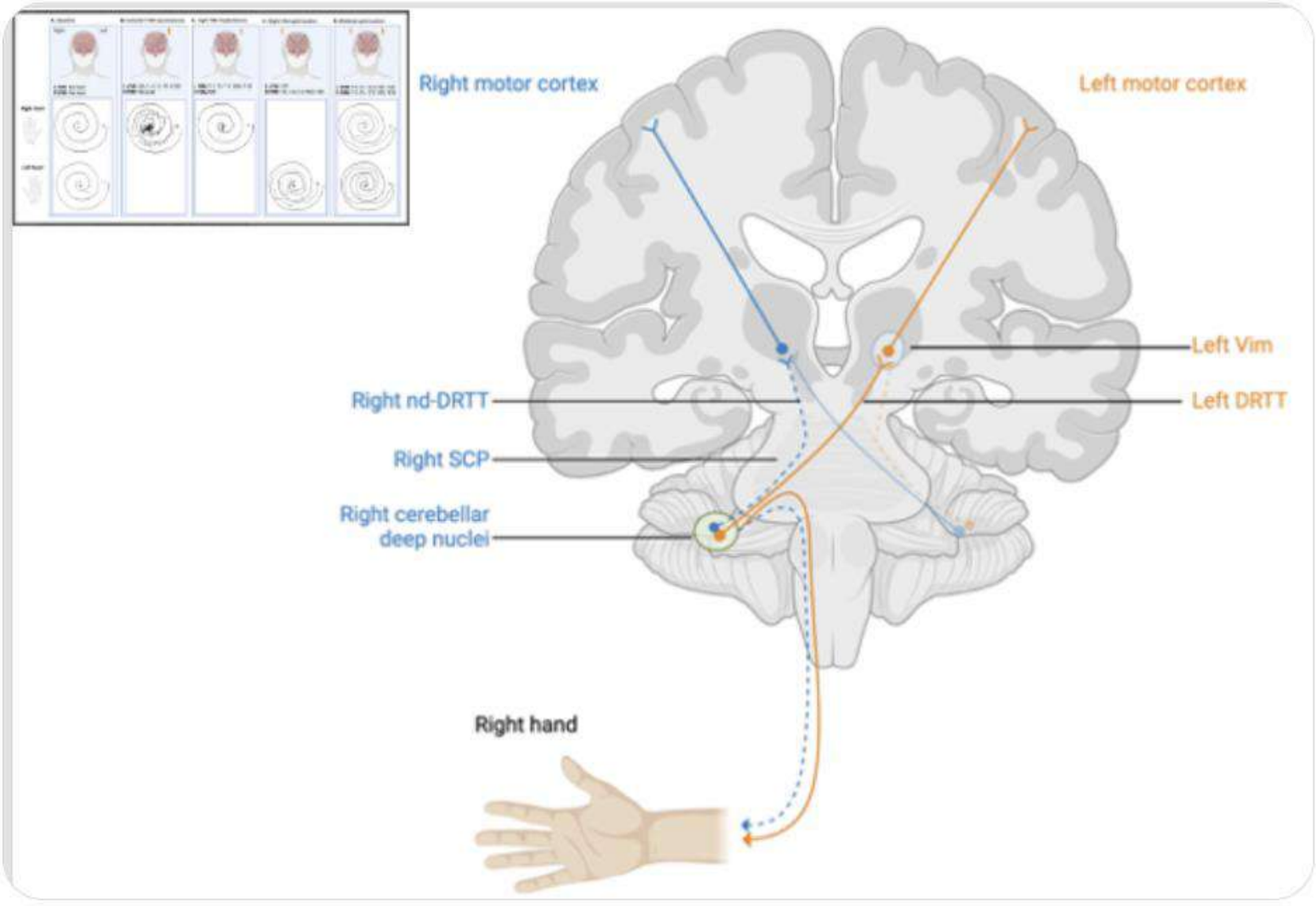


Michael Okun @MichaelOkun · Jul 6

Do you keep an '**eye on the first surgical side**' when you later add a DBS lead? Carpentier, Chan and @JWongggMD teach us to appreciate potential Impacts of adding a second DBS lead on ipsilateral symptoms. Check out the series @tremorjournal called the DBS Case Files.

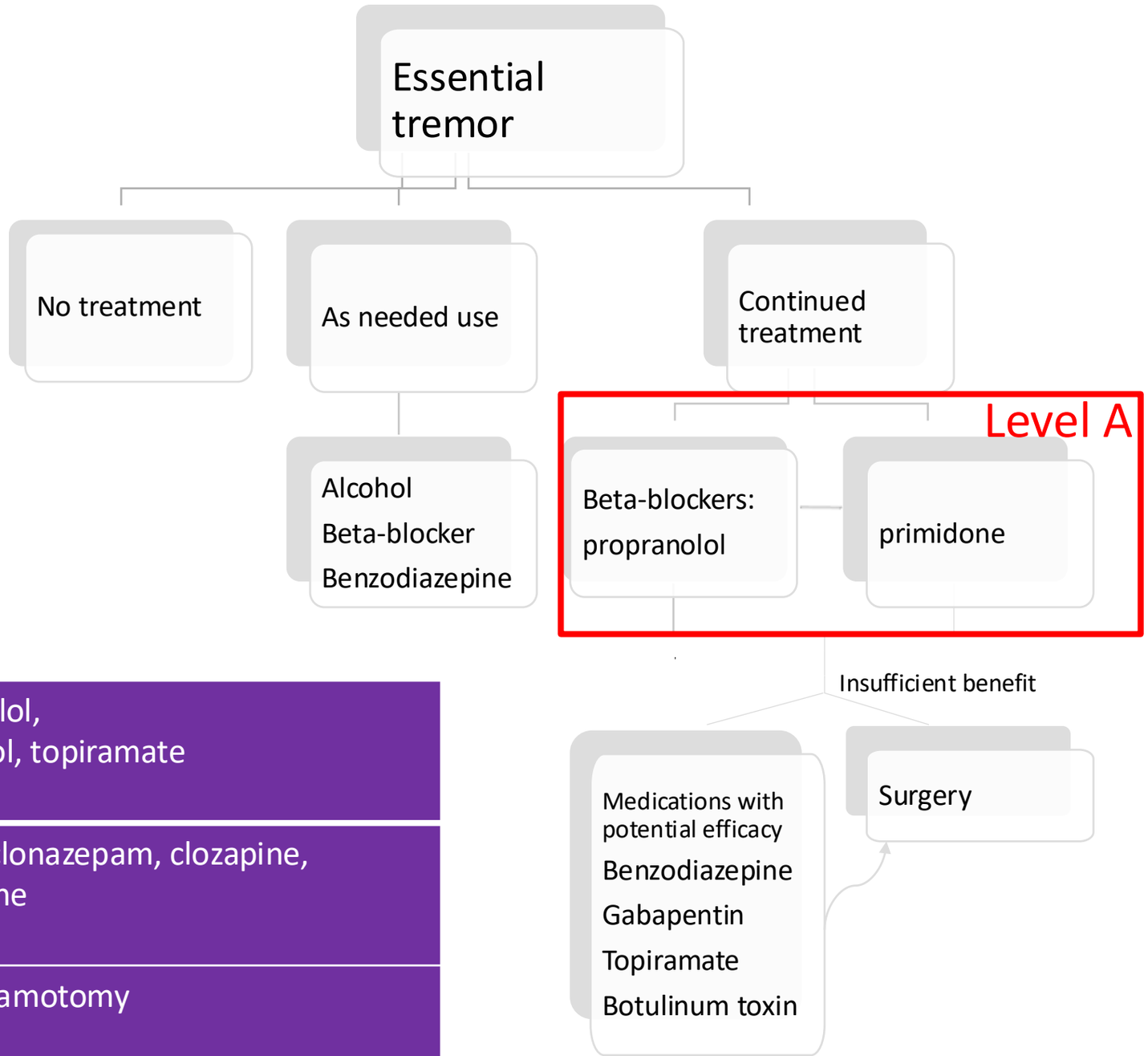
Key Points:

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9 27 2K

Treatment Approach



Level B	alprazolam, atenolol, gabapentin, sotalol, topiramate
Level C	botulinum toxin, clonazepam, clozapine, nadolol, nimodipine
Level U	Gamma knife thalamotomy
Surgery	DBS: ViM nucleus of thalamus, Thalamotomy

- Pahwa R, Lyons KE. Am J. Med. 2003;115:134. Zesiewicz et al. Neurology 2005;64:2008.

Tremor Circuits

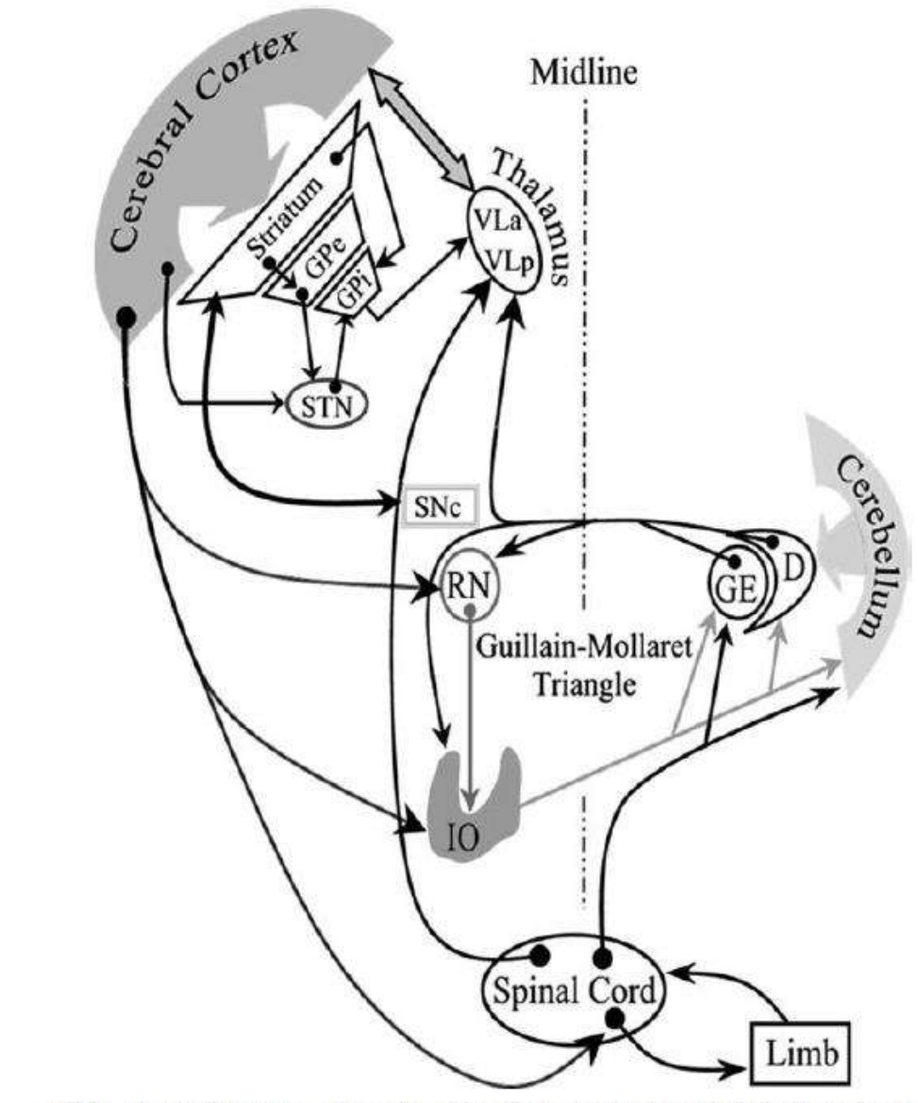


FIG. 1. Schematic diagram of motor pathways involved in tremor. Rest tremor is believed to be produced within the basal ganglia loop. Postural and intention tremors are probably generated within the olivor-cerebello-thalamo-cortical loop or the Guillain-Mollaret triangle (GPe and GPi, globus pallidus externa and interna, respectively; VLa and VLp, ventralis lateralis anterior and posterior, respectively [VLp, ventralis intermedius]; STN, subthalamic nucleus; SNc, substantia nigra pars compacta; RN, red nucleus; GE, globose-emboliform nuclei; D, dentate nucleus; IO, inferior olive).

1000g Loading Test

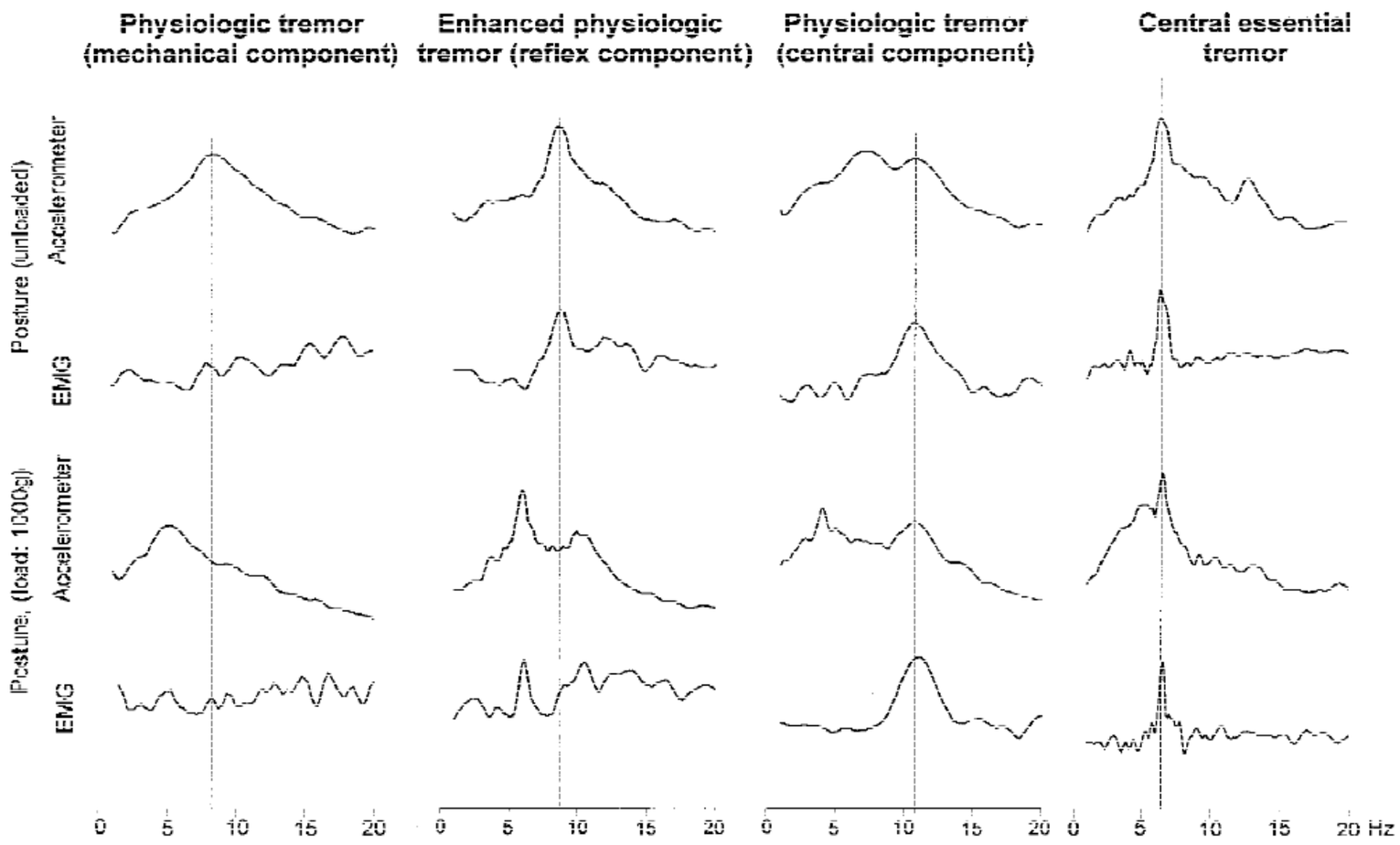


FIGURE 2. Spectral analysis of four different postural hand tremors with the accelerometer spectrum and the electromyographic spectrum of the wrist extensors (EMG) unloaded and with a load of 1000 g mounted on the back of the hand. The first example is a physiological tremor with a flat EMG spectrum and a load-dependent mechanical resonance peak. The second column is from a patient with thyrotoxic tremor who had a reflex-activated tremor because the EMG frequency peak decreased with the accelerometer peak during loading. The third example is from a normal subject having a central, frequency-invariant component in addition to the load-dependent mechanical component. The last is from a patient with a mild essential tremor displaying a frequency-invariant central component. This test can also be applied for diagnostic purposes.

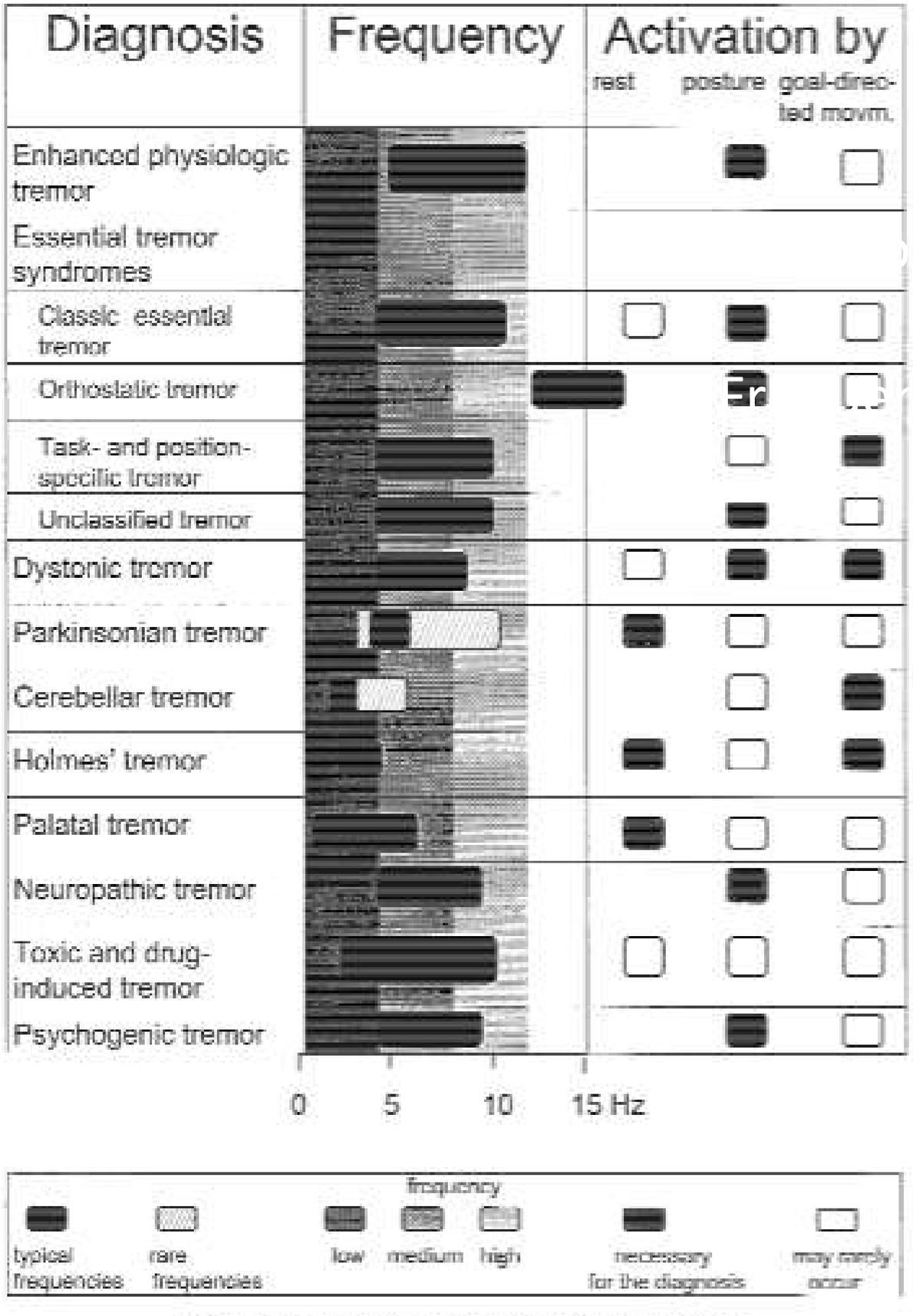


FIGURE 1. Frequency and activation characteristics of tremors.[44]

Deuschl, Muscle and Nerve, 2001

Parkinson's Disease Tremor

- Rest tremor 4-6Hz
  - asymmetric- focal/ hemi at onset
  - pill rolling upper limb
  - abduction-adduction leg or foot flexion extension with some inversion eversion
  - chin, jaw, tongue
  - attenuated during movement
  - reappears with new limb posture (”re-emergent”)
  - evident during walking (‘dependent”)

- Postural, action tremor 6-8Hz
  - may be asymmetric

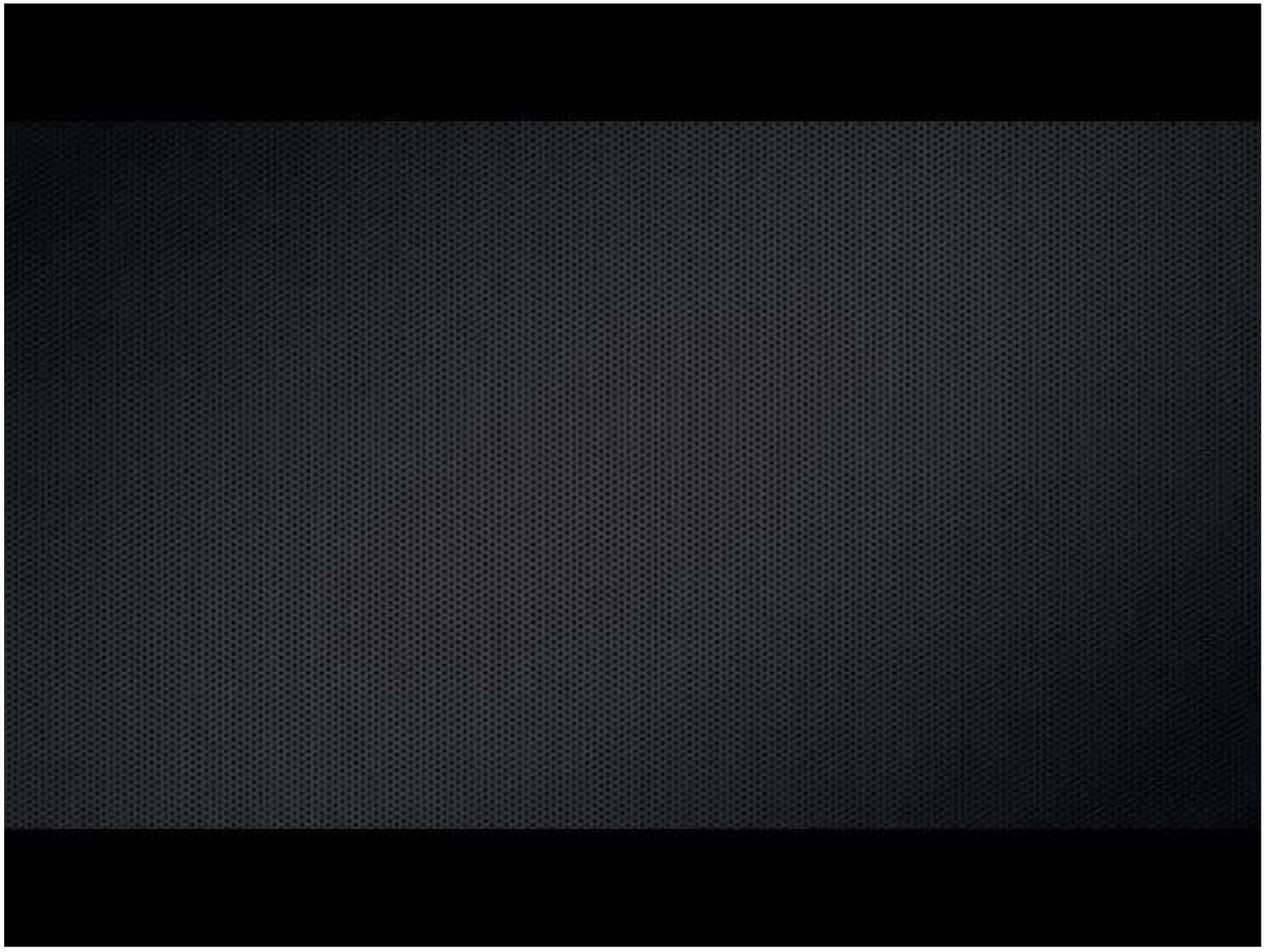
- Benign Tremulous PD
- (literature contaminated by dystonic tremor)







Chromosomal Aneuploidy
Jakob Disease
XYY



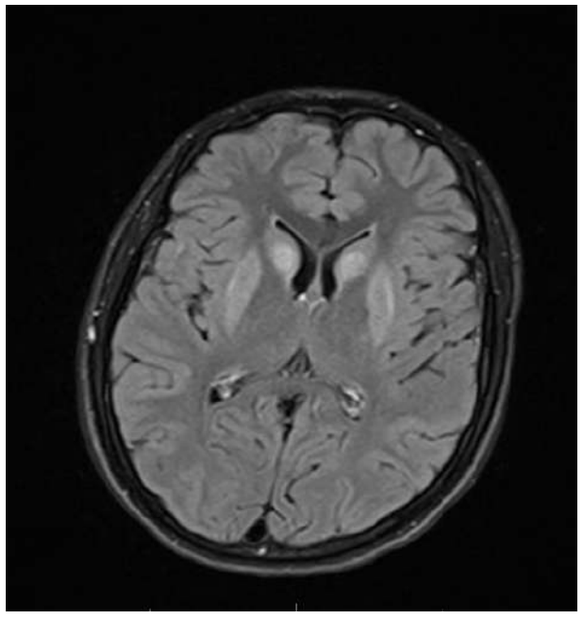


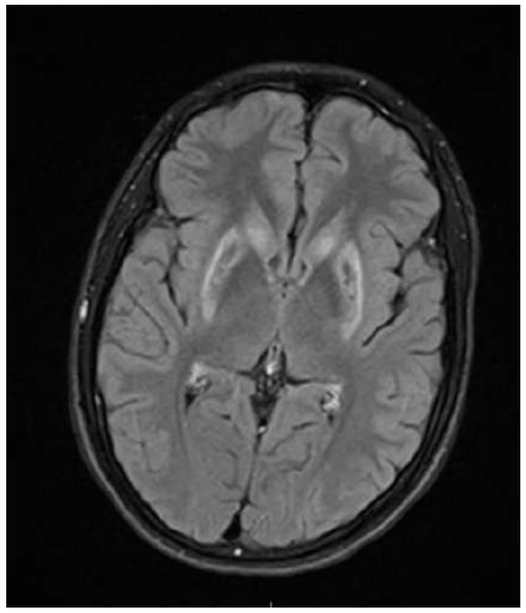
Myorythmia

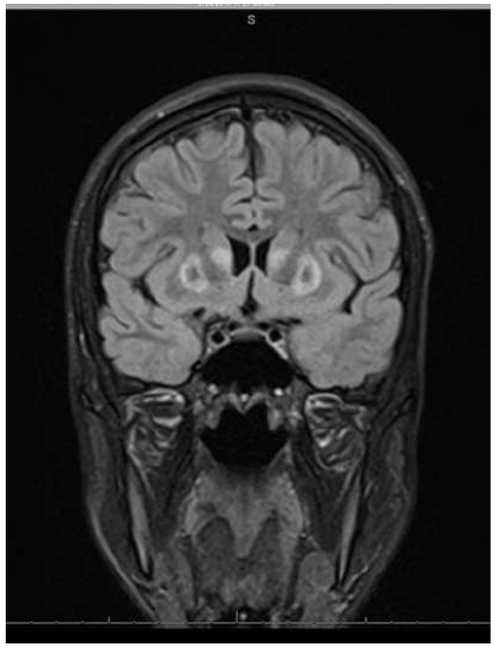


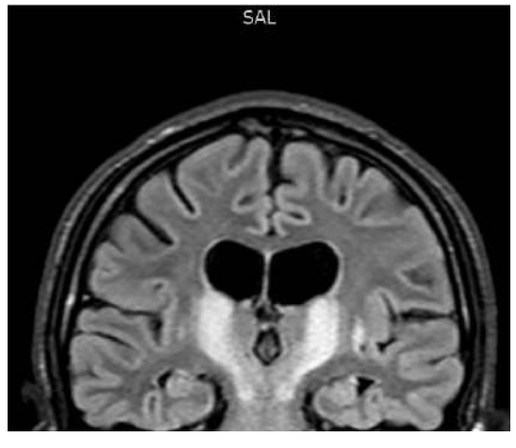
Myorhythmia in Whipple disease

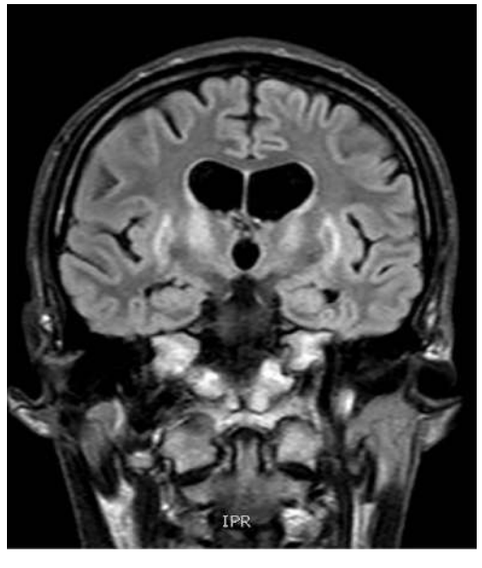
Wilson’s-Heptolenticular Degeneration “MRI’s”





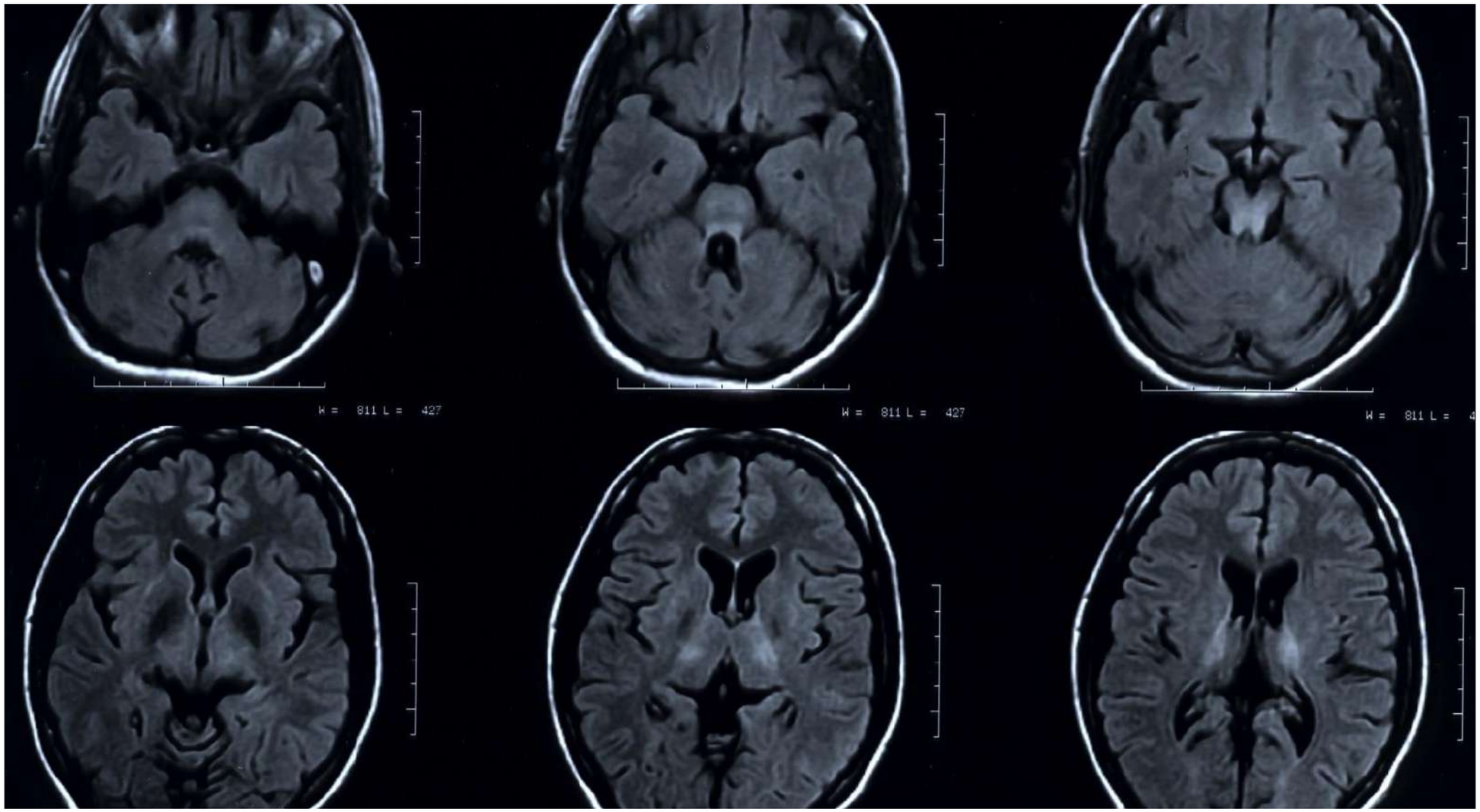




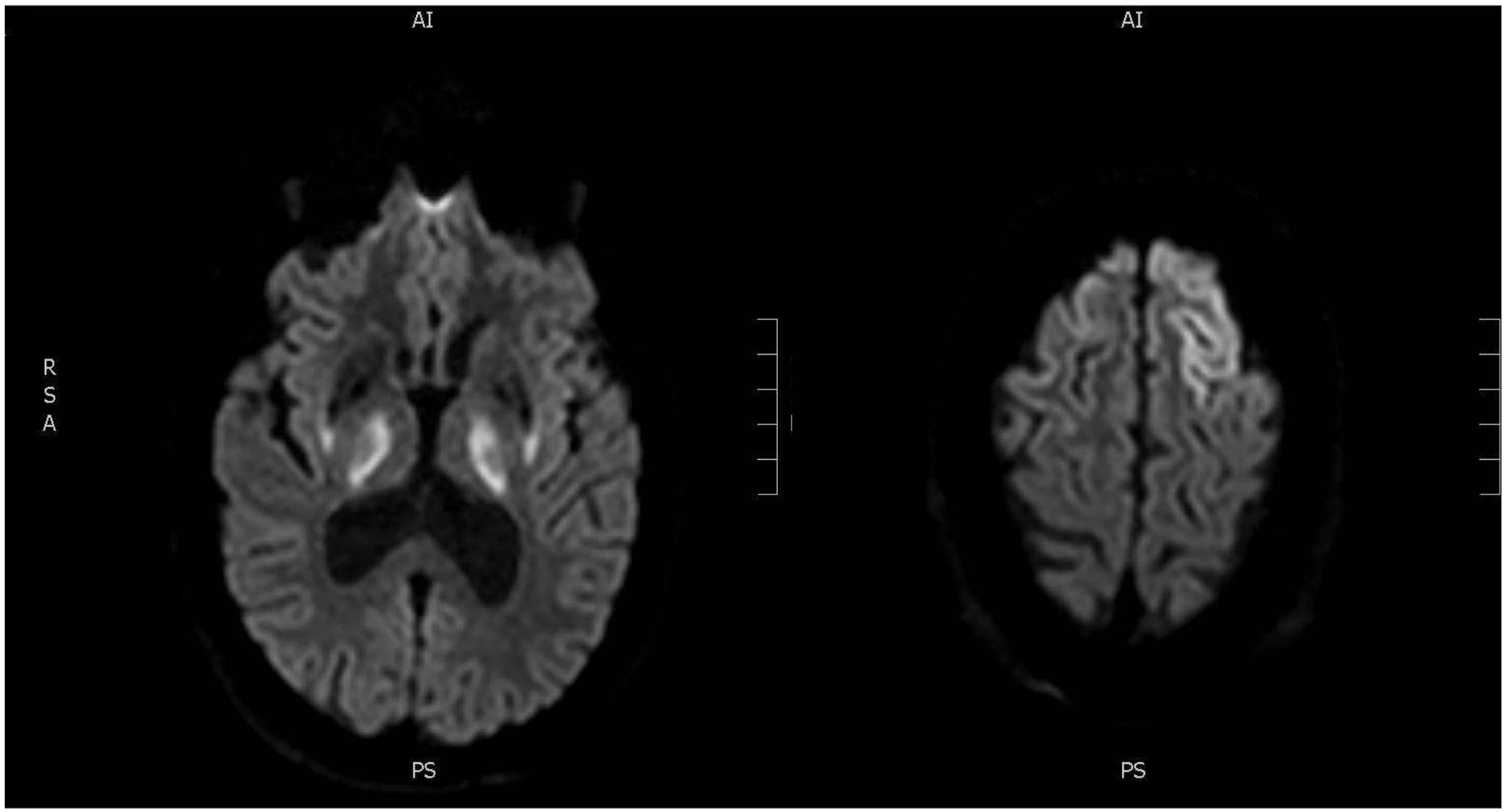




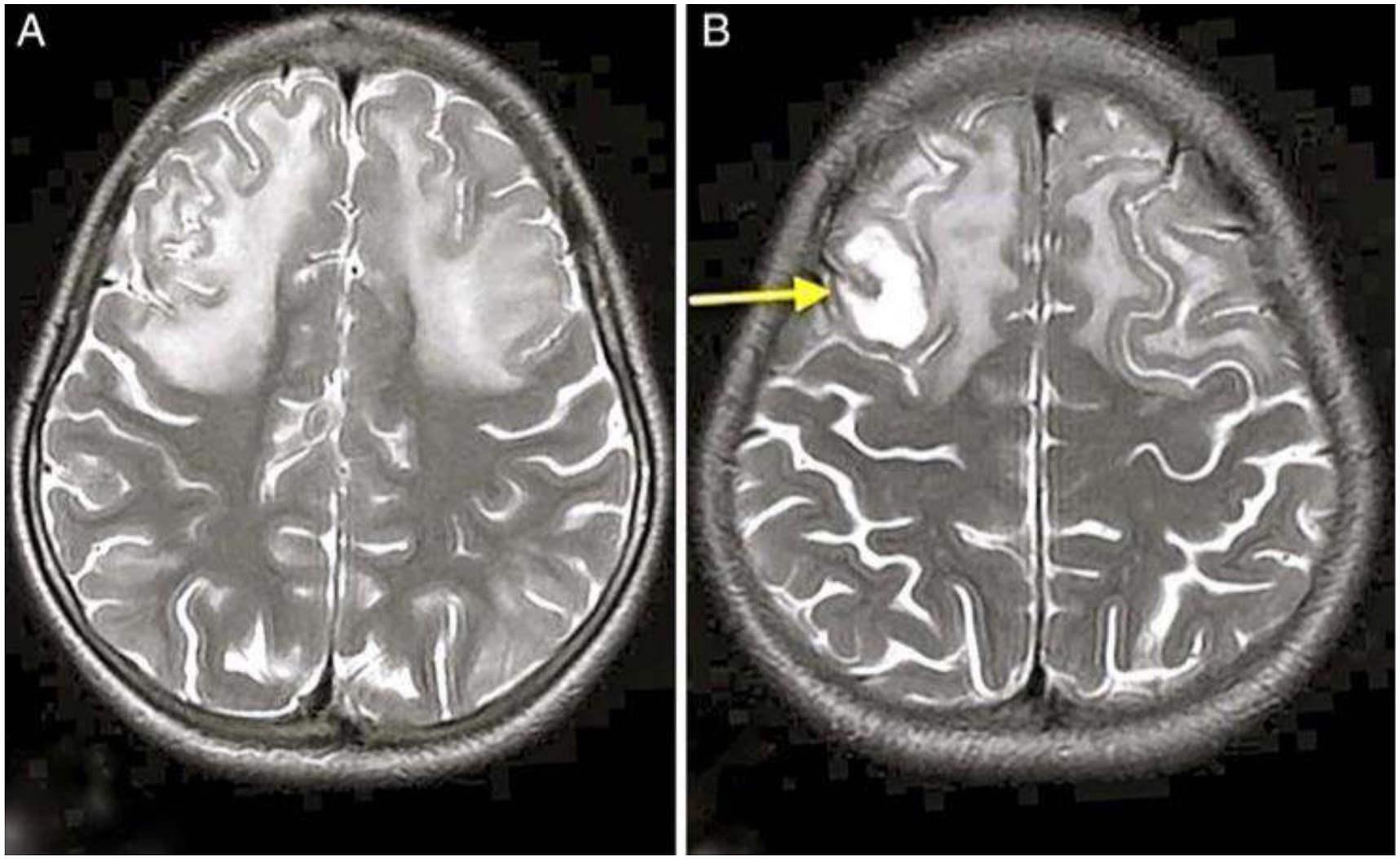
Wilson’s MRI’s



Wilson Disease MRI DWI



Wilson’s



Investigation and management of Wilson's disease: a practical guide from the British Association for the Study of the Liver

Cornerstones of good practice

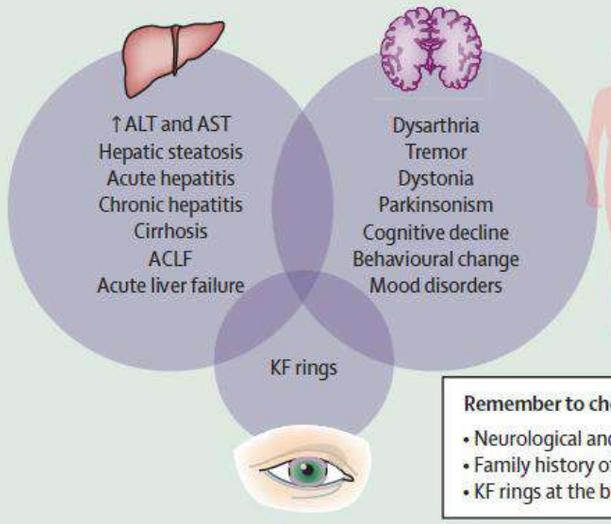
- Early recognition and diagnosis
- Prompt specialist referral and initiation of treatment
- Multidisciplinary working
- Patient adherence to medication

Clinical presentation

Acute liver failure

20% of hepatic presentations

- Coagulopathy
- ↑Bilirubin:ALP ratio
- Hepatic encephalopathy
- +/– underlying cirrhosis



Systemic manifestations

- Coombes-negative haemolytic anaemia
- Renal tubular acidosis
  Fanconi syndrome
- Chondrocalcinosis
  Osteoporosis
  Osteoarthritis

Remember to check for:

- Neurological and psychiatric symptoms
- Family history of liver disease and movement disorder
- KF rings at the bedside

Diagnostic work-up

- Adults with liver disease
- Children and adults with progressive postural tremor, dystonia, or parkinsonism

Routine investigations

- Full blood count
- Liver biochemistry
- Coagulation profile
- Serum caeruloplasmin

- Children with liver disease
- Adults with unexplained liver disease
- Adults with liver disease and movement disorder
- Children and adults with high-risk movement disorder
- Children and adults with unexplained haemolysis

Wider screen

- 24-h urine collection
- Slit lamp examination

- Ongoing diagnostic uncertainty
- Staging of liver disease severity
- Baseline assessments at diagnosis*

Selected additional tests

- Serum copper*
- Genetic testing*
- Liver imaging and TE*
- Neuroimaging*
- Liver biopsy
- Copper-65 absorption test

⚠
- Making a diagnosis can be challenging and often requires synthesis of results from wider screen and additional tests
- Consult a specialist centre early
- Delays in diagnosis can be life-threatening or lead to irreversible neurological disability

Initial management

- Penicillamine or trientine chelation therapy
- Monitor for paradoxical neurological worsening
- Early referral to transplant centre if acute liver failure suspected
- Offer family screening to first-degree relatives

Longer term management

- Regular follow-up every 6–12 months
- Monitor copper indices and check treatment adherence
- Multidisciplinary input
- HCC surveillance in cirrhosis

	Children	Adults without neurological or psychiatric symptoms	Adults with neurological or psychiatric symptoms	Maintenance dose (typically after 2 years)	Adverse effects
Penicillamine	125–250 mg per day slowly increasing by 125–250 mg per week to 20 mg/kg per day in two divided doses (maximum 1500 mg/day)	1000–1500 mg per day in two divided doses	125–250 mg per day, slowly increasing by 125–250 mg per week, to 1000–1500 mg per day in two divided doses	10–20 mg/kg per day in two divided doses	Early reactions: hypersensitivity reactions (fever and rash), proteinuria, bone marrow suppression (thrombocytopenia and neutropenia), altered sense of taste or smell, and paradoxical neurological worsening. Late reactions: lupus-like syndrome, Goodpastures syndrome, elastosis perforans serpiginosa, cutis laxa, and poor wound healing
Trientine	150–200 mg per day, slowly increasing by 150–200 mg per week to 400–1000 mg per day for trientine dihydrochloride (Cufence) or 225–600 mg per day for trientine tetrahydrochloride (Cuprior) in two divided doses	800–1600 mg per day for trientine dihydrochloride (Cufence) or 450–975 mg per day for trientine tetrahydrochloride (Cuprior) in two divided doses	150–200 mg per day, slowly increasing by 150–200 mg per week to 800–1600 mg per day for trientine dihydrochloride (Cufence) or 450–975 mg per day for trientine tetrahydrochloride (Cuprior) in two divided doses	800–1600 mg per day for trientine dihydrochloride (Cufence) or 450–975 mg per day for trientine tetrahydrochloride (Cuprior) in two divided doses	Urticaria or other rashes, arthralgia, myalgia, proteinuria, haematuria, sideroblastic anaemia, and paradoxical neurological worsening
Zinc salts	25 mg daily if patient <6 years; 25 mg three times daily if patients aged 6–16 years or <50 kg; 50 mg three times daily if patient >16 years or >50 kg	50 mg three times daily if patient >50 kg	50 mg three times daily if patient >50 kg	25–50 mg three times a day	Nausea, abdominal pain, gastritis, and paradoxical neurological worsening

Dosing for penicillamine and zinc salts are based on experience of the authors, and dosing for trientine dihydrochloride and trientine tetrahydrochloride on the basis of the summary of product characteristics by the manufacturer. The recommended doses of trientine dihydrochloride and tetrahydrochloride are expressed as mg of trientine base as opposed to trientine salt. Chelating agents and zinc salts should be taken on an empty stomach.

Table 2: **Dosing and adverse effects for penicillamine, trientine, and zinc salts**

Neuroimaging Correlates of Cognitive Deficits in Wilson's Disease

Samuel Shribman, MA,[1] Maggie Burrows, BA,[1] Rhian Convery, MSc,[2] Martina Bocchetta, PhD,[2]
Carole H. Sudre, PhD,[3,4,5] Julio Acosta-Cabronero, PhD,[6] David L. Thomas, PhD,[2,7,8] Godfrey T. Gillett, PhD,[9]
Emmanuel A. Tsochatzis, PhD,[10] Oliver Bandmann, PhD,[11] Jonathan D. Rohrer, PhD,[2] and Thomas T. Warner, PhD[1*]

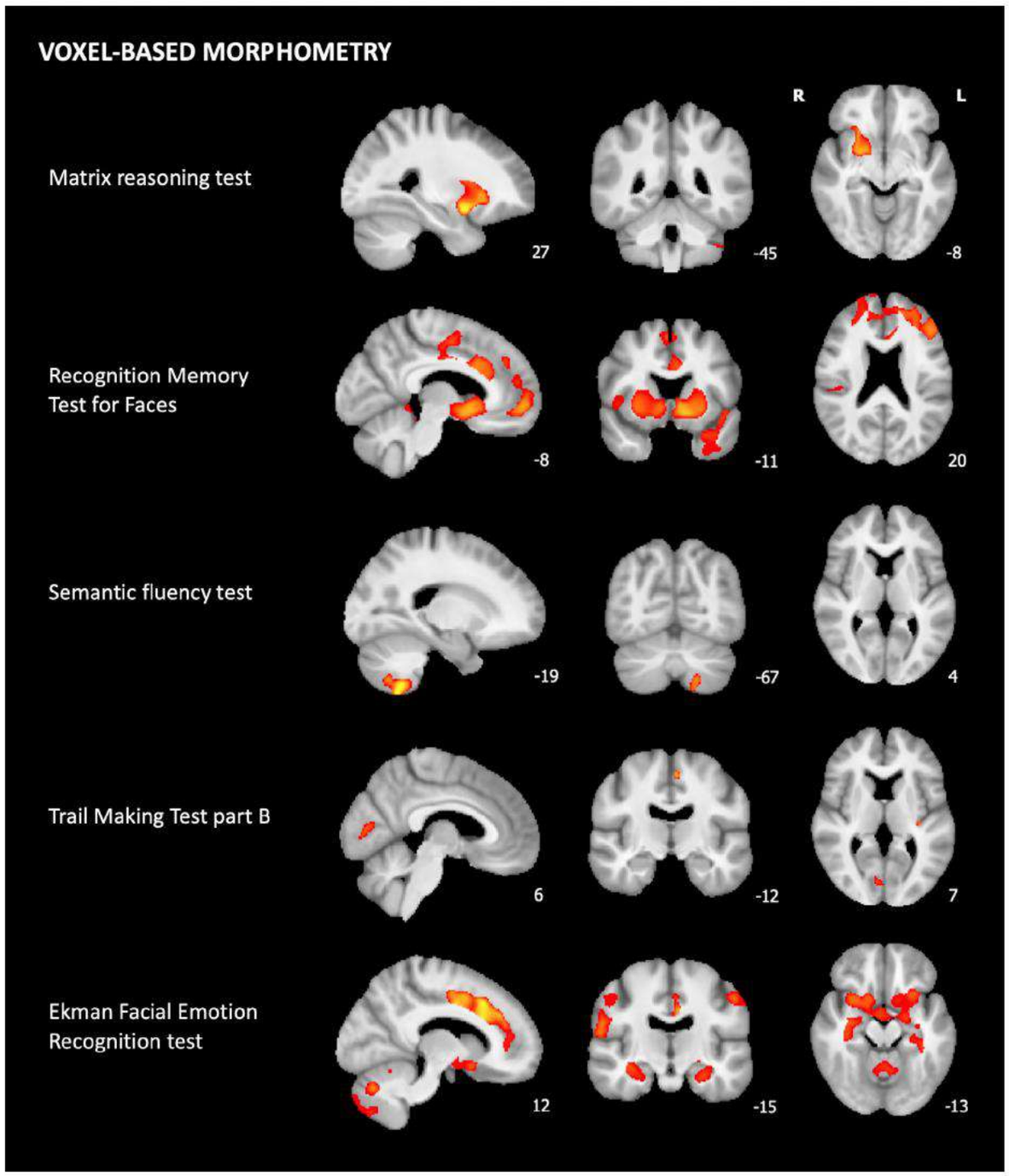


FIG. 2. Voxel-based morphometry for associations with neuropsychological test scores. Tissue maps show clusters where gray matter volumes decrease with worsening cognitive performance for FWE (family-wise error)-corrected *P*-values <0.05. Clusters are overlaid onto the study-wise mean template. For visualization, one slice in each of the sagittal (*x*), coronal (*y*), and axial (*z*) planes was selected, and Montreal Neurological Institute (MNI) coordinates are provided. [Color figure can be viewed at wileyonlinelibrary.com]

Neuroimaging

- Patients with neurological Wilson's almost always have an abnormal MRI
- The findings are "pleomorphic"

PNAS RESEARCH ARTICLE | GENETICS



Identification of *PSMB5* as a genetic modifier of fragile X–associated tremor/ataxia syndrome

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- PSMB5 knockdown results in suppression of CGG neurotoxicity
- Via RAN translation and RNA-mediated toxicity mechanisms
- Could this be a therapeutic strategy for FXTAS