No, it is not Parkinson's disease!

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Unité de troubles du mouvement André-Barbeau du CHUM
Université deMontréal

tremor in Parkinson

- pill rolling: involvesthe thumb and the index, can also be wrist flexion/ extension, supination/pronation of forearm
- can involve legs, mandible
    - rarely the head
- at rest: goes away with action
- can appear or be increased by distraction
- re-emergent tremor
- 60% of patients with PD have tremor
- patients can also have portural/action tremors of same or different frequencies than thie resting tremor

rest tremor - DDX

<u>iatrogenic</u>

- D2 blockers
- Ca channel blockers
- lithium
- valproate
- amiodarone

- vascular parkinsonism
- SCA 2 and 3
- RT can be present in association with other types of tremors (essential, dystonic, Holmes)

tremors in SWEDD's

- SWEDD: Scan Without Evidence of Dopaminergic Deficit
- 2 yr f\u in 34 patients with tremor
- clinical evaluation at 24 moths, scan on 12 patients with still undetermined dx

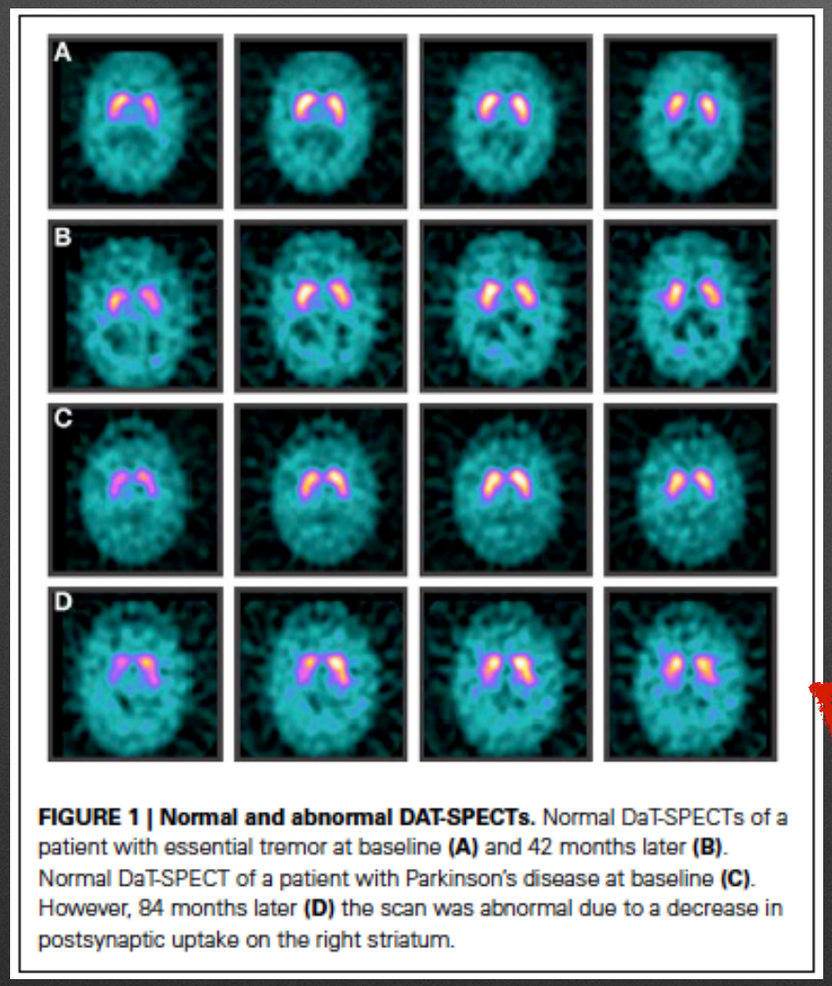
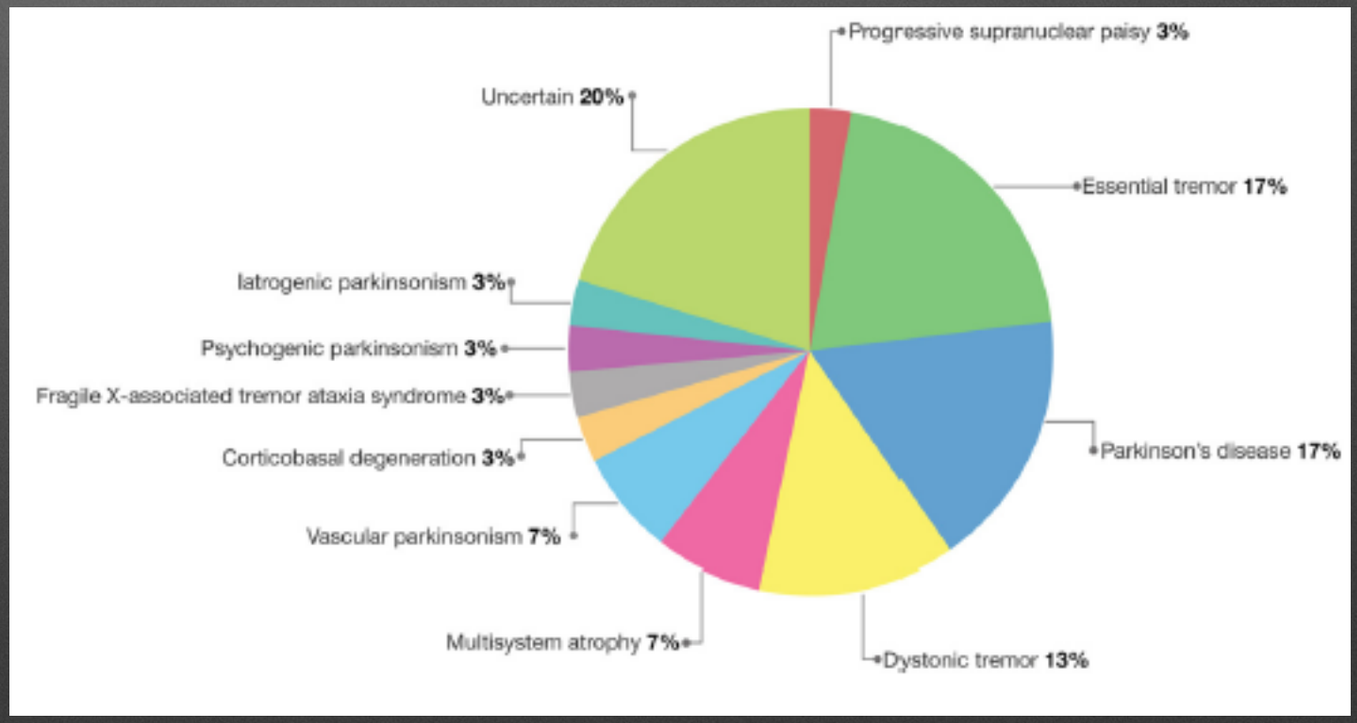


FIGURE 1 | Normal and abnormal DAT-SPECTs. Normal DaT-SPECTs of a patient with essential tremor at baseline **(A)** and 42 months later **(B)**. Normal DaT-SPECT of a patient with Parkinson's disease at baseline **(C)**. However, 84 months later **(D)** the scan was abnormal due to a decrease in postsynaptic uptake on the right striatum.



la différence est claire!

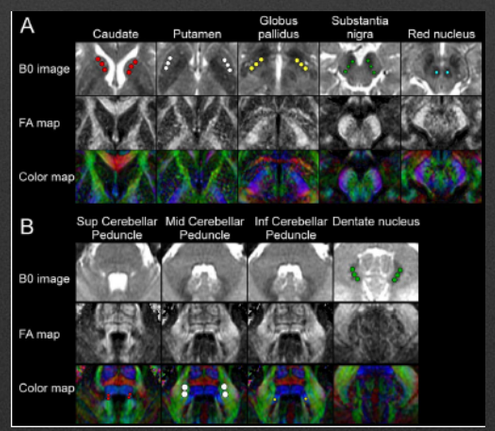
Diagnoses behind patients with hard-to-classify tremor and normal DaT-SPECT: a clinical follow up study

Manuel Menéndez-González[1,2,3], Francisco Tavares[4], Nahla Zeidan[5], José M. Salas-Pacheco[6] and Oscar Arias-Carrión[7]**

frontiers in aging neuroscience 2014;6:1-9

What is the link between ET and PD?

- 46% of patietns with PD have postural tremor
    - Gigante et al Eur J Neurol 2014
- prevalence of ET before the Dx of PD is te same as in the general population
    - Rana et al Int J Nsci 2014
- no alpha-synucléine variant (20 SNP's on 661 ET vs 1216 in 427 PD)
- differenciation between PD and ET with Tension Diffusion imaging



Distinguishing PD From ET

The final step of analysis was to determine how well the DTI measures distinguished PD from ET. The AUC was 0.96 (sensitivity, 92%; specificity, 87%) using DTI measures from the caudate and substantia nigra.

PRODOEHL ET AL *Movement Disorders*, Vol. 28, No. 13, 2013

treatment of tremor in PD

- dopaminergic agents
- anticholinergic agents
- thalamic surgeries

treatment of rest tremor other than PD

- stop causative agents

- tardive:
  - tetrabenazine
  - clozapine?

definition

rythmic oscillation of a body part

- which body part?
- what frequency?
- what context?

body part

head

- dystonia
- ET

mandible

- Parkinson
- dystonia
- hereditary geniospasm

palate

- essential
- secondary (cerebellar lesion)
- GFAP mutation (associate to Alexander disease)

lower limbs

- orthostatic tremor
- Parkinson

frequency

low frequency: < 4 Hz

- Holmes tremor

mid frequency: 4 to 7 Hz

- rest tremor of PD

high frequency: > 7 Hz

- ET
- orthostatic tremor (13-18 Hz)

context of tremor

Table 1 | Classification of tremors according to moment of occurrence

Moment of occurrence	Features	Example of underlying disorder
A. At rest	Best judged in a body part that is fully supported against gravity	Parkinson disease
B. With action		
Postural	Occurs in body part that assumes a posture against gravity	Physiological; enhanced physiological (stress, endocrine disorders or intoxications); essential tremor
Kinetic		
Simple	Occurs during entire movement trajectory	Essential tremor
Intention	Progressively increases towards intended target	Cerebellar ataxia
Task specific	Occurs only during specific activities	Dystonic writing tremor
Isometric	Occurs during voluntary muscle contractions against a stationary resistance	Physiological; associated with other types of tremor
C. Combinations	Various	Severe essential tremor; atypical parkinsonism; dystonic tremor; rubral (Holmes) tremor

The above classification was proposed by a Consensus Statement of the Movement Disorder Society.[17]

essential tremor

- essential = essence of the syndrome, ≠ nécessary
- benign essential tremor = not associated to a deadly disease, ≠ no handicap
- 1% of the population de > 65 yrs
- 27% of patients with ET will seek medical attention
- progression very slow
- familial histoiry suggestive of a dominant inheritance
- usually upper limbs (95%), but can also involve the head (30%), the voice (20%), the mandible (10%), the tongue (20%), the trunk (5%) and the lower limbs (10%)
- relatively symmetrical
- postural and action

Table 1 Summary of diagnostic criteria for essential tremor according to TRIG, Movement Disorders Society, and Bain et al.[5,6]

Core criteria[5]
1. Bilateral postural and kinetic tremor of the hands and forearms (but not rest tremor) (TRIG, MDS, Bain et al.)
2. Absence of other neurologic signs (TRIG, Bain et al.)
3. May have isolated head tremor with no signs of dystonia (MDS, Bain et al.)
Duration and level of certainty[6]
1. Definite ET: duration >5 years + comprehensive exclusion of other causes + no stepwise deterioration (TRIG)
2. Probable ET: duration >3 years + same criteria as definite ET (TRIG)
3. Possible ET: no duration criterion + type I: some other neurologic symptoms allowed; type II: monosymptomatic or isolated tremors of uncertain relation to essential tremor (TRIG)
Secondary criteria[5]
1. Positive family history (present in 30%–60% of patients) (Bain et al.)
2. Beneficial alcohol response (present in 50%–75% of patients) (Bain et al.)

Abbreviations: ET = essential tremor; MDS = Movement Disorders Society; TRIG = Tremor Investigation Group.

ET: dx criteria

Tremor Investigation Group Criteria [18]	**Movement Disorder Society Consensus Criteria [7]**
Inclusion criteria: 1. Bilateral postural tremor, with or without kinetic tremor, in the hands that is visible and persistent 2. Duration longer than 5 years	Inclusion criteria: 1. Bilateral, largely symmetric postural or kinetic tremor of the hands that is visible and persistent 2. Additional or isolated head tremor in the absence of abnormal posturing
Exclusion criteria: 1. Other abnormal neurologic signs (with the exception of the presence of tremor and Froment's sign. The full neurologic examination should be normal for age) 2. Presence of known causes of enhanced physiologic tremor 3. Concurrent or recent exposure to tremorogenic drugs or the presence of a drug withdrawal state 4. Direct or indirect trauma to the nervous system within 3 months preceding the onset of tremor 5. Historic or clinical evidence of psychogenic origins of tremor 5. Convincing evidence of sudden onset or evidence of stepwise deterioration	Exclusion criteria: 1. Other abnormal neurologic signs, especially dystonia 2. The presence of known causes of enhanced physiologic tremor, including current or recent exposure to tremorogenic drugs or the presence of a drug withdrawal state 3. Historic or clinical evidence of psychogenic tremor 4. Convincing evidence of sudden onset or evidence of stepwise deterioration 5. Primary orthostatic tremor 6. Isolated voice tremor 7. Isolated position-specific or task-specific tremors, including occupational tremors and primary writing tremor 8. Isolated tongue or chin tremor 9. Isolated leg tremor

tremor in ET, an isolated symptom? ATTENTION: controversial

<u>complex syndrome</u>

- clinical cerebellar symptoms
  - intention tremor
  - dysmetria and overshoot
  - difficulty with the tandem
  - abnomalities of the vestibulo-ocular system
- diminished survival (littérature variable)

ET
the non-motor syndrom

ET (vs normal population)

- hyposmia 4.5% (idem)
- constipation 21.7% (idem)
- RBD 43.5% (vs 0.5%)
- depression 17.6 - 21.7% (vs 5%)
- more MCI (69.2%) and higher rate of conversion form normal to MCI 25% within 2 yrs, but conversion to dementia (8.4% within 2 yrs, idem)
- anxiety (25%)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Tremor and Other Hyperkinetic Movements

Articles

Mild Cognitive Impairment, Dementia, and Affective Disorders in Essential Tremor: A Prospective Study

Gary Sinoff[1,2*†] & Samih Badarny[2,3†]

[1] Department of Gerontology, University of Haifa, Haifa, Israel, [2] Faculty of Medicine, Technion Institute, Haifa, Israel, [3] Movement Disorders Clinic, Neurology Department, Carmel Medical Center, Haifa, Israel
[†] These authors contributed equally to this work.


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Tremor and Other Hyperkinetic Movements

Articles

Increased Prevalence of Non-motor Symptoms in Essential Tremor

Annie Lacerte[1], Sylvain Chouinard[1], Nicolas Jodoin[1], Geneviève Bernard[2], Guy A. Rouleau[1,3] & Michel Panisset[1*]

[1] André-Barbeau Movement Disorders Unit Service of Neurology, Centre Hospitalier de l'Université de Montréal and Department of Medicine, Université de Montréal, Montréal, Québec, Canada, [2] Division of Pediatric Neurology, Montreal Children Hospital, McGill University, Montréal, Québec, Canada, [3] CENUM, Centre de recherche du Centre Hospitalier de l'Université de Montréal, Montréal, Québec, Canada

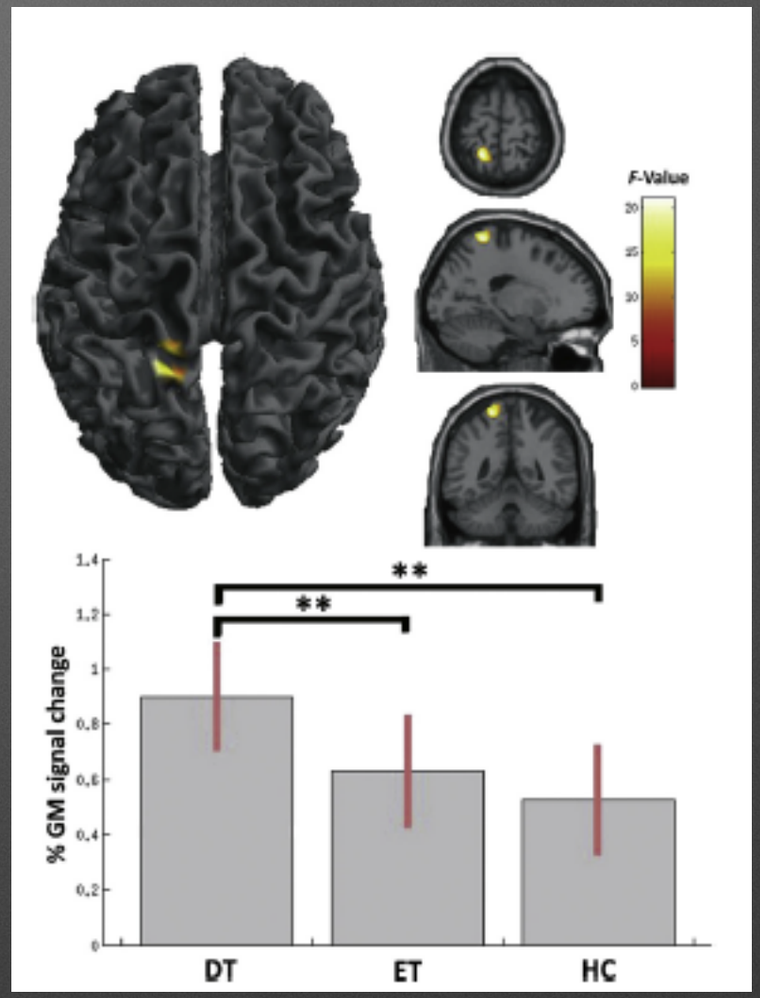
ET, a degenerative disease of an abnormal cerebello- thalamique oscillation? ATTENTION: controversial

<u>pathologic syndrome</u>

- Lewy bodies, Torpedoe cells, gliosis of Bermann
  - Louis et al Brain 2007, Louis et al Lancet Neurol 2010, Louis et al Park and Rel Dis 2011
- no difference between TE, PD forme tremblante, and normal controls for the loss of Purknjie neurons
  - Rajput et Rajput, Park and Rel Dis 2011, Shill, Adler & Beach, Park and Rel Dis 2012, Rajput et al Park and Rel Dis 2012

isolated tremor of the head

- ET or dystonic tremor?
- dystonic tremor = thickening of sensori-motor and of primary motor cortex
- ET= atrophy of anterior cerebellar cortex



A. Cerasa et al. / Parkinsonism and Related Disorders 20 (2014) 314–317

postural tremor: DDX

- physiologic tremor
- toxic (mercury, e.g.)
- metabolic
- fragile X
- neuropathy
- Parkinson

<u>iatrogenic</u>

- valproate
- T4
- lithium
- tricyclic antidepressants

<u>stimulating agents</u>

- adrenergic agonists (salbutamol, e.g.)
- cocain
- cafein
- amphetamine
- nicotine

AAN guidelines 2011

- propranolol, primidone (Level A, established as effective);
- alprazolam, atenolol, gabapentin (monotherapy), sotalol, topiramate (Level B, probably effective)
- nadolol, nimodipine, clonazepam, botulinum toxin A, deep brain stimulation, thalamotomy (Level C, possibly effective)
- gamma knife thalamotomy (Level U, insufficient evidence)

1) levetiracetam, 3,4-diaminopyridine should not be considered (Level B)
2) flunarizine (Sibelium) may not be considered (Level C)
3) pregabalin, zonisamide (Zonegan/Tremode), or clozapine (Level U, insufficient evidence)

treatments for ET

Table 1 Recommended drugs for essential tremor

Drug	Mean or median effective daily dosage	Estimated percentage improvement in tremor amplitude
Propranolol	40–240 (320) mg/d	32–75
Primidone	<62.5 –750.0 mg/d	42–76
Topiramate	100–333 mg/d	30–41

Table 2 Drugs for essential tremor with probable or weak efficacy

Drug	Mean or median effective daily dosage	Estimated percentage improvement in tremor amplitude [ref.]	Percentage improvement by accelerometry [ref.]
Atenolol	50–100 mg/d	24–38 [21, 22]	37 [23]
Sotalol	80–240 mg/d	29–51 [21, 22]	–
Gabapentin	1200–1800 mg/d	39 [24]	77
Alprazolam	0.75–1.5 mg/d	48–60 [25, 26]	–

Table 3 Drugs for essential tremor with uncertain efficacy (likely not efficacious)

Level C possibly effective (daily dosage of the respective studies) [ref.]	Agents with recommendations against use	Inadequate evidence to confirm or exclude efficacy
Clonazepam (0.5–4.0 mg) [27]	Acetazolamide/methazolamide	Olanzapine
Clozapine (18–75 mg) [28]	Amantadine	Pregabalin
Flunarizine (10 mg) [29]	Carisbamate	Tiagabine
Nadolol (120–240 mg) [30]	Isoniazid	Sodium oxybate
Nimodipine (120 mg) [31]	Levetiracetam	Zonisamide
Botulinum toxin (depending on injected muscles)	Pindolol	
	Trazodone	
	3,4-Diaminopyridine	
	Mirtazapine	
	Nifedipine	
	Verapamil	

ET: treatment for the upper limbs

- botulinum toxin
  - objective improvement (accélérometer)
  - no subjective improvement
  - 30-70% weakness
- thalamotomy or thalamic stimulation
  - target = dentato-rubro-thalamic tract
  - stimulation: détérioration 73% within 5 yrs
- STN or zona incerta stimulation
- radio surgery (gamma knife)
- MRI guided ultrasound surgery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journal homepage: www.elsevier.com/locate/clineuro

Does lesioning surgery have a role in the management of multietiological tremor in the era of Deep Brain Stimulation?

Srinivas Dwarakanath[b], Abu Zafar[a], Ravi Yadav[a], A. Arivazhagan[b], M. Netravathi[a], S. Sampath[b], Pramod Kumar Pal[a,*]

[a] Department of Neurology, National Institute of Mental Health and Neurosciences (NIMHANS), Hosur Road, Bangalore 560029, Karnataka, India
[b] Department of Neurosurgery, National Institute of Mental Health and Neurosciences (NIMHANS), Hosur Road, Bangalore 560029, Karnataka, India

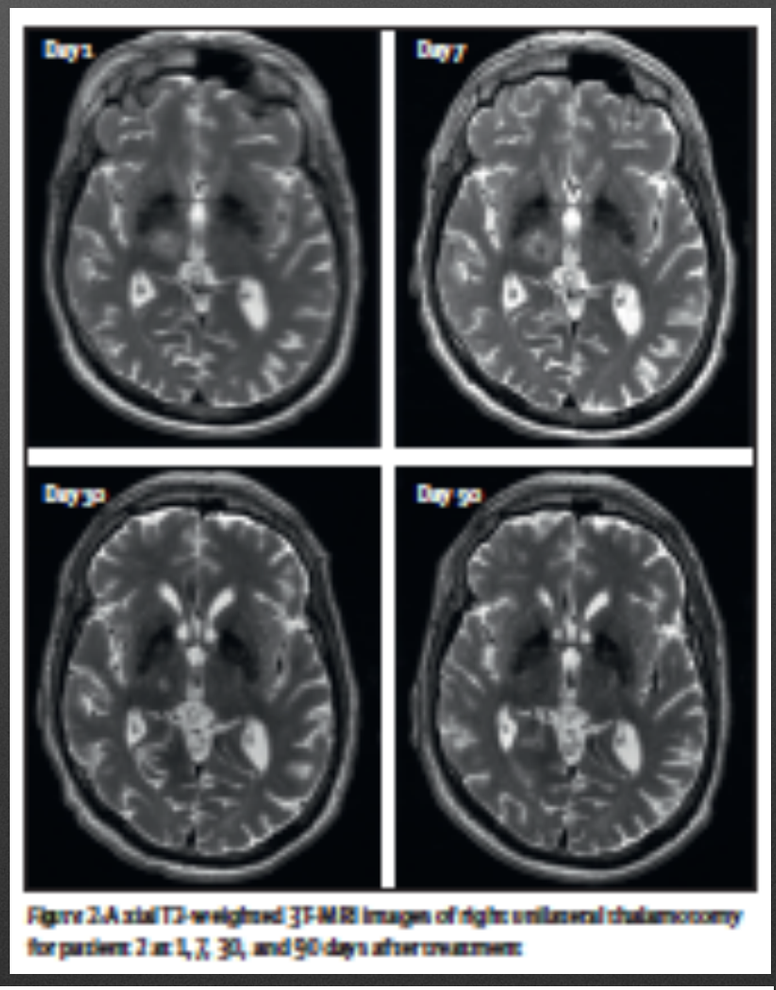


Figure 2: Axial T2-weighted 3T-MRI images of right unilateral thalamotomy for patient 2 at 1, 7, 30, and 90 days after treatment

Nir Lipsman, Michael L Schwartz, Yuexi Huang, Liesly Lee, Tejas Sankar, Martin Chapman, Kullervo Hynynen, Andres M Lozano

Lancet Neurol 2013; 12: 462–68

dystonic tremor

- dystonic tremor: tremor of a limb that is affected by dystonia
- tremor associated to dystonia: tremor in a limb that is not affected by dystonia, but in a patient with dystonia
  - irregular amplitude and variable («jerky») frequency
  - position-specific, specific to a task (nul position)
  - improved by a «geste antagoniste»
  - worse in mouvements that go against the direction of the torsion of dystonia
- controversial: tremor with characteristics of dystonic tremor, but in a patients without dystonia

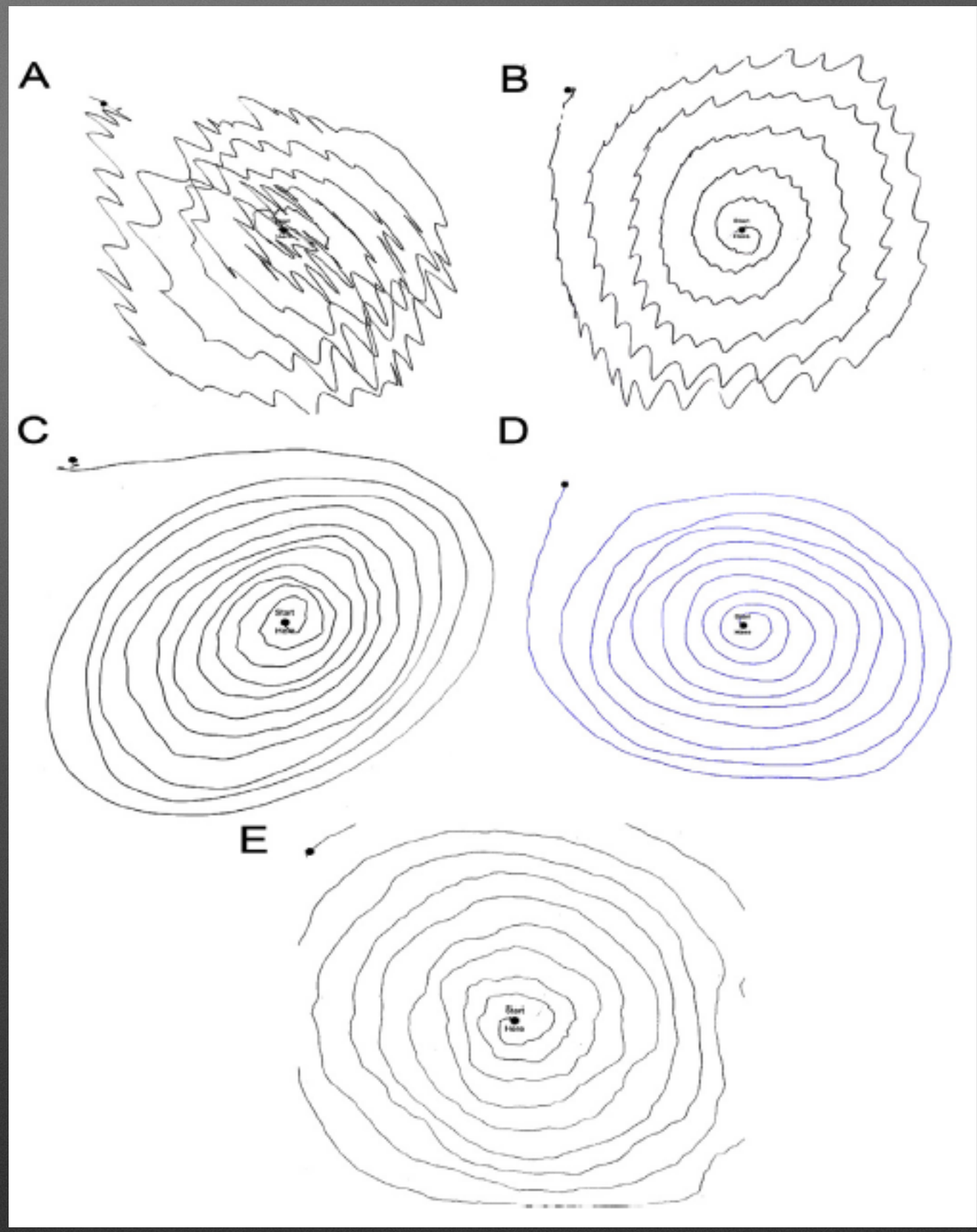
The spiral axis as a clinical tool to distinguish essential tremor from dystonia cases

Monika Michalec[a], Nora Hernandez[a], Lorraine N. Clark[b,c], Elan D. Louis[a,b,d,e,*]

Parkinsonism and Related Disorders 20 (2014) 541–544

- A, B, C, D = ET
- E = DT

- ET = one axis
- TD = no predominant axis



dystonic tremor

- 17% of patients with dystonia
- mainly in cervical dysotnia
- 10% = DT and 5% TAD, 2% = DT and TAD
- manifestations of DT and of TAD are very similar

Tremor in primary adult-onset dystonia: prevalence and associated clinical features

Giovanni Defazio,[1] Angelo Fabio Gigante,[1] Giovanni Abbruzzese,[2] Anna Rita Bentivoglio,[3] Carlo Colosimo,[4] Marcello Esposito,[5] Giovanni Fabbrini,[4] Arianna Guidubaldi,[3] Paolo Girlanda,[6] Rocco Liguori,[7] Lucio Marinelli,[2] Francesca Morgante,[6] Lucio Santoro,[5] Michele Tinazzi,[8] Paolo Livrea,[1] Alfredo Berardelli[4]

J Neurol Neurosurg Psychiatry 2013;**84**:404–408.

55,4% of patients with dystonia (473)

- 41% head tremor
- 30%tremor of an upper limb
- very rare: sup or middle part of the face
- mandible (open-close or latero-lateral)
- 21% combination head and uper limb
  - postural 100%
  - action 73,6%
  - rest 40,7%

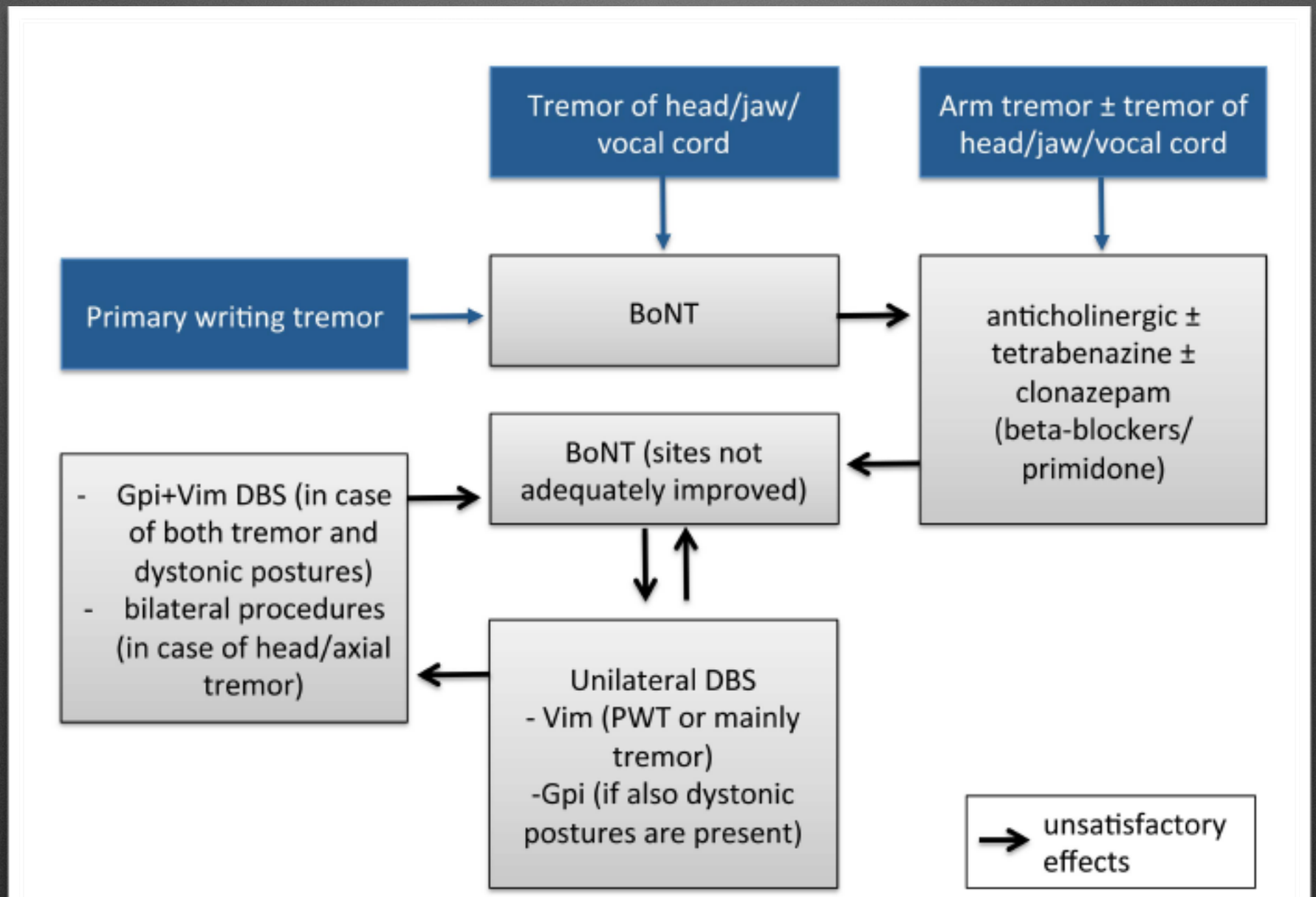
Rest and other types of tremor in adult-onset primary dystonia

Roberto Erro,[1] Ignacio Rubio-Agusti,[1,2] Tabish A Saifee,[1] Carla Cordivari,[3] Christos Ganos,[1,4] Amit Batla,[1] Kailash P Bhatia[1]

J Neurol Neurosurg Psychiatry 2014;**85**:965–968. doi:10.1136/jnnp-2013-305876

DT: treatment algorythm

Fasano et al JNNP 2014

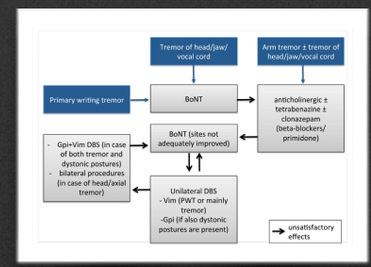


treatment of dystonic tremor

- mild to moderate efficacy
  - anticholinergics
  - tetrabenazine
  - clonazepam
  - beta-blockers
  - primidone
- levodopa only efficacious in DRD
- botulinum toxin mainly for hean and voice tremor

- lesioning surgeries
  - thalamotomy
  - focused ultrasound thalamotomy
  - radiosurgery (gamma-knife, cyber-knife)
- deep brain stimulation
  - thalamus
  - globus pallidus
  - sub-thalamic nucleus
  - combination of targets

Fasano et al JNNP 2014



ET or DT?

<u>new nomenclature : primary postural tremors</u>

- DT si sometimes so rythmic taht it is impossible to differenciate from ET
- tremor may be the only manifestation of dystonia (dystonia gene associated tremor) Deuschl, Bain, Brin. Mov Dis 1998;13:2-23
- ET is a syndrome that is common to many diseases
- mild dystonia often not diagnosed in cases of ET
- the specificity of geste antagonistes, nul position, irregularity, task-specificity, overflow is unknown

<u>electrophysiology</u>

- not specific (TCMCS and H-reflex)

likely one of the principal reasons why discovery of ET genes remain elusive

Defining Dystonic Tremor

Rodger J. Elble*

Current Neuropharmacology, 2013, *11*, 48-52

primary writing tremor

- the most common task specific tremor
  - primary bowing tremor has been described
- good response to botulinum toxin injections and thalmaic surgeries

differences from ET

- More often in people from Africa, in men, older (47 vs 39 years)
- less likely to have a familai history
- less responsive to medications and to alcohol
- evolution to addition of other task-specific tremor, resting or mixed tremor, but not to postural tremor

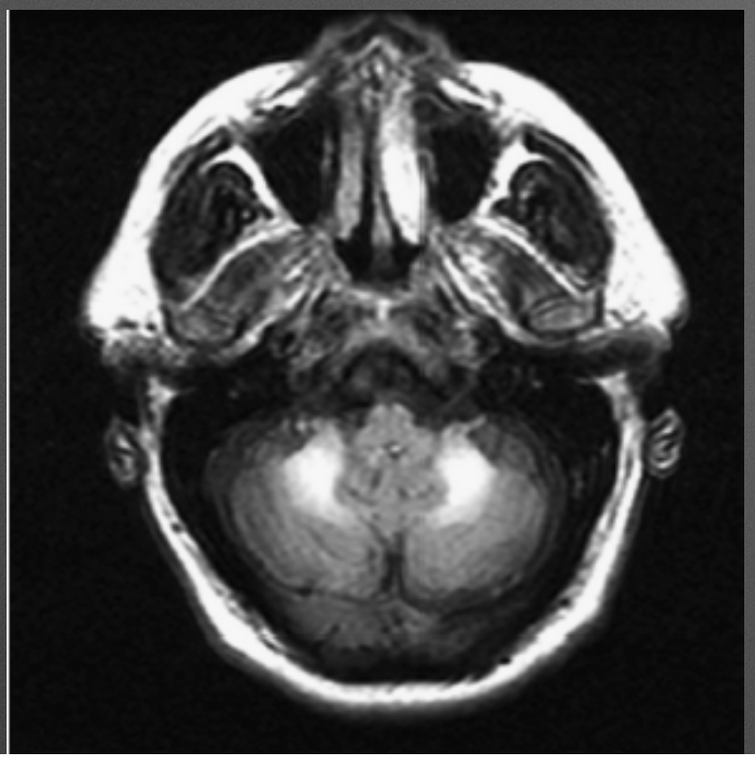
Citation: Lee A, Chadde M, Altenmüller E, et al. Characteristics of task-specific tremor in string instrument players. Tremor Other Hyperkinet Mov. 2014; 4. doi: 10.7916/D86Q1V9W

orthostatic tremor

- 4.5 to 40 years before obataining the dx
- 30% unsteadiness
- progressive or stable
- imporvement with alcohol, bent posture, walking, sitting
- no familial hx
- treatment =
    - clonazepam 1mg die (0.25 to 3.5)
    - gabapentin

- pure or associated to other movement disorders (ot-plus)
    - 30%
    - PD, LBD, vascular parkinsonism, PSP, primary FOG, RLS, ET, multifocal action tremor, focal dystonia, oro-facial dyskinesia

FXTAS



- tremor of FXTAS
  - essential-like 35%
    - small amplitude
  - cerebellar 29%
  - resting 12%
  - unilateral

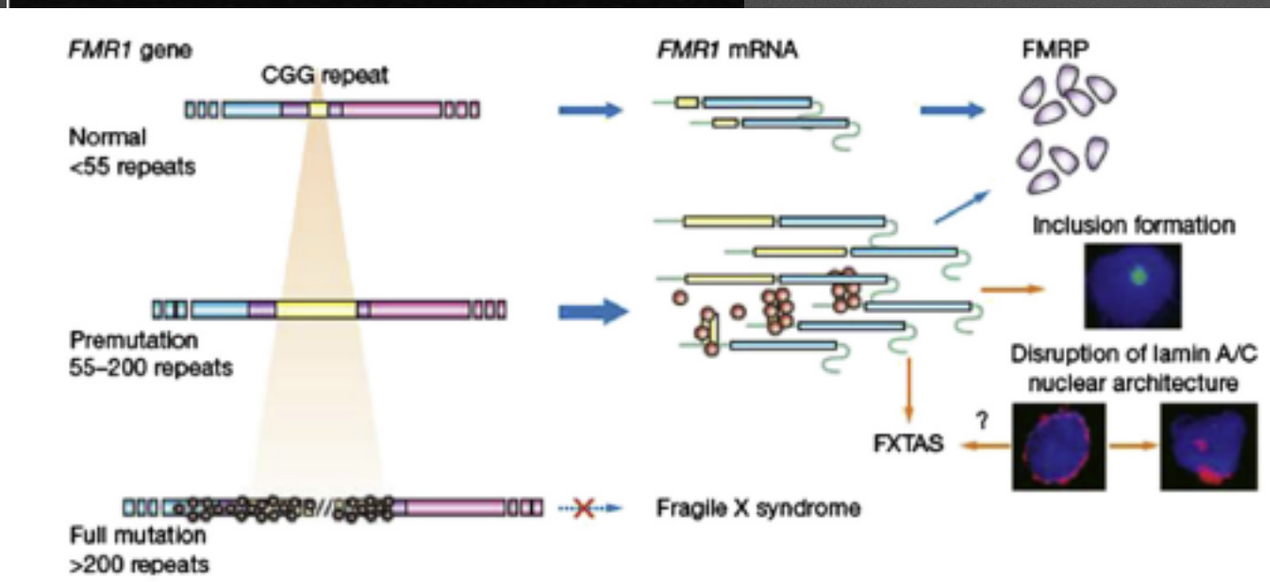


Fig. 3. Clinical and pathogenic effects of expanded CGG repeats in the *FMR1* gene. The repeat expansion ranges are located in the left portion of the figure. In individuals with the premutation, there is an increase in *FMR1* mRNA, which leads to inclusion formation and FXTAS. In individuals with a full mutation, the promoter and CGG repeat is methylated, the gene is silenced, and fragile X syndrome occurs. (*From* Hagerman PJ, Hagerman RJ. Fragile X-associated tremor/ataxia syndrome–an older face of the fragile X gene. Nat Clin Pract Neurol 2007;3(2):107–12; with permission.)

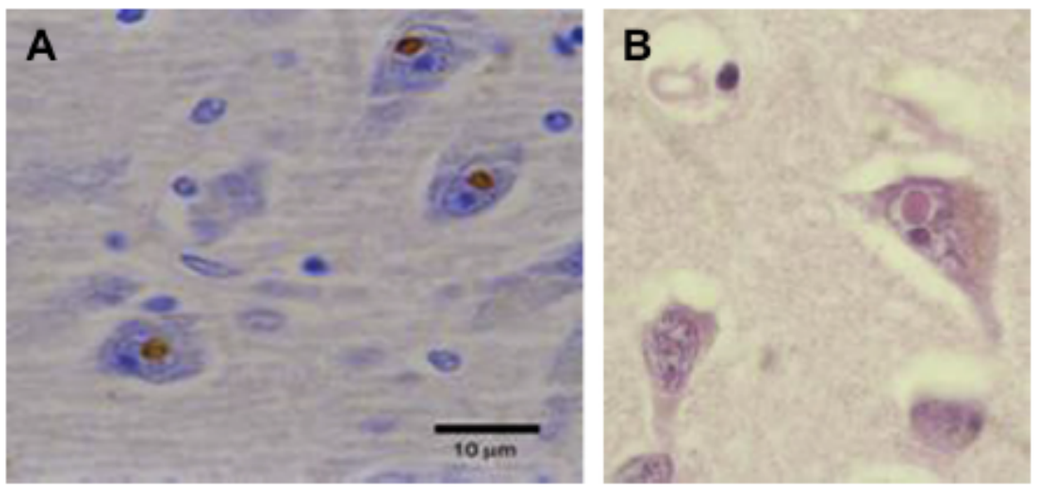


Fig. 2. FXTAS pathology. (*A*) Eosinophilic neuronal intranuclear inclusions. (*B*) Intranuclear inclusions stained with antiubiquitin antibodies.

Hall & O'Keefe Neurol Clin 31 (2013) 1073–1084

Holmes tremor

- rest and intention
- 4-5 Hz
- can be impossible differentiate from a termor due to a lesion of the dorso-lateral thalamus (usually associated to dystonia)

treatment

- levodopa high doses
- trihexyphenidyl ad 12 mg
- clonazepam ad 4 mg
- clozapine ad 75 mg
- levitiracetam
- htalamic stimulation or two targets (variable)

tremor associated to a neuropathy

- treatment of the neuropathy
- propranolol
- pregabalin
- thalamic stimulation

mandibular tremor

- ET
- iatrogenic
- Parkinson
- DT
- tremor associated to dystonia
- tremor associated to dental work

funcitonal (psychogenic) tremor

- 55% of functional movement disorders
- remission 20-60%
- treatment by a multidisciplinary team
  - psychotherapy
  - physiotherapy
  - medical PRN

- acute onset
- highly variable
- coherence: tremor of different segments with same rythm
- «inconsistence»
- increased amplitude with weigh
- distractibility and «entrainment»
- suggestibility
- inability to double-task
- pause of tremor during a rapid action
- spontaneous remissions
- other symptoms (false neurological signs, hypersensitvity to stimuli [startle])

functional tremor

no difference in severity, but difference in variability inbetween the 10 spirals

Increased variability in spiral drawing in patients with functional (psychogenic) tremor

Christopher W. Hess[a], Annie W. Hsu[a], Qiping Yu[a], Robert Ortega[b] Seth L. Pullman[a,*]

Human Movement Science 38 (2014) 15–22

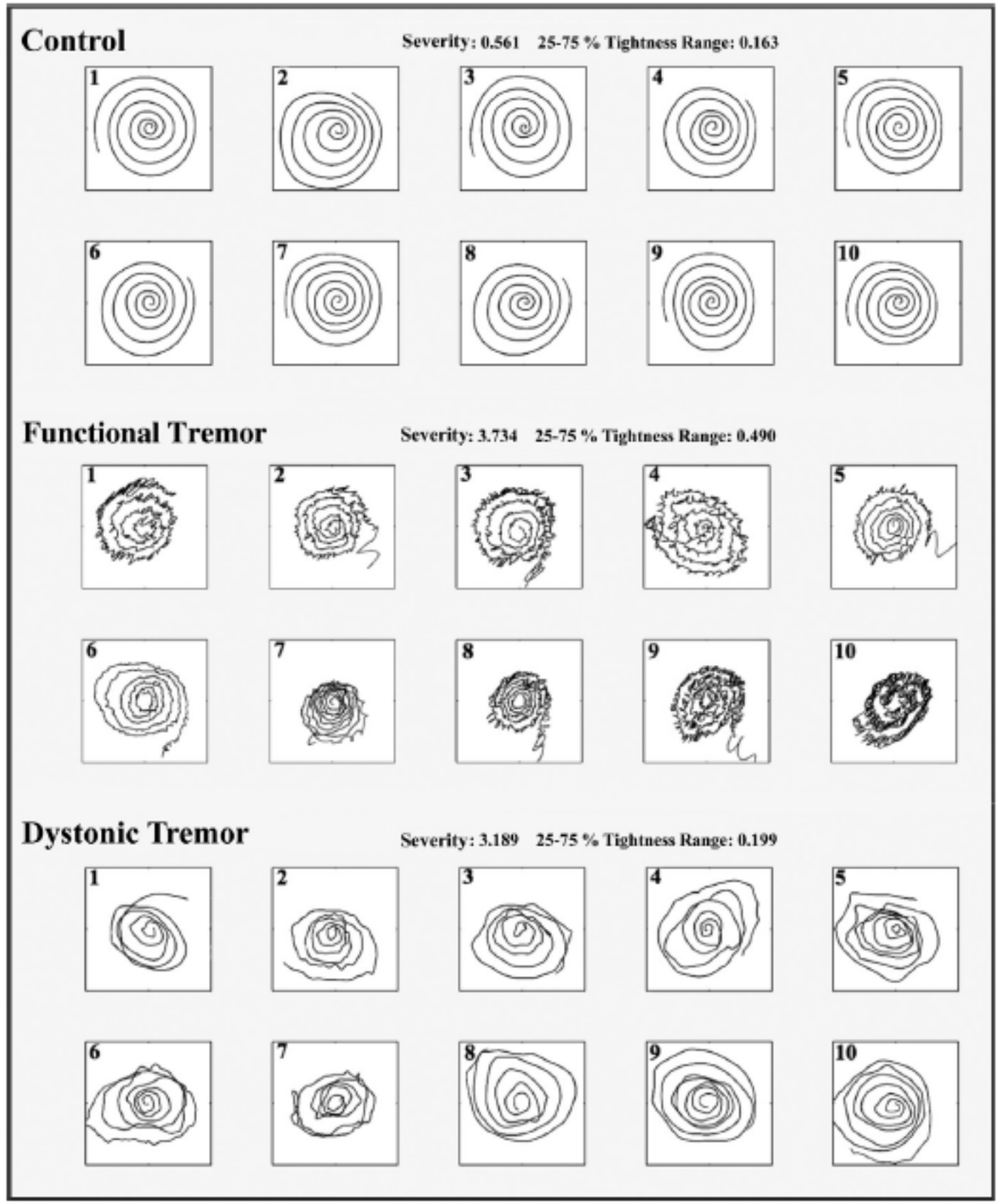


Fig. 2. Representative spiral drawings from a participant in each of the subject groups. Ten spirals are drawn for each participant. The spiral severity and tightness indices were determined for each spiral and the range between the 25th and 75th percentile of spiral tightness (25–75%^{ile} tightness range) was calculated across 10 spirals. Note that while both tremor groups reveal severely abnormal spirals, the variability between spirals is greater in the middle functional tremor set.

tremors in MS

- postural/action/ intention
- medications usually useless

<u>botulinum toxin</u>

- significant improvement 6 and 12 weeks post injection
- weakness 42%

<u>thalamotomy or thalamic stimulation</u>

- remains the best treatment

tremor in MSA-P

- 80% of patients
- rest (33%)/postural (50%)/action (20%)/intention (20%)
- symmetrical or asymmetrical
- irregular «jerky» or myoclonic (cortical minipolymyoclonus)
    - stimulus-sensitive myoclonus in the upper limbs (30%)
    - supportive for a Dx of MSA
- pill rolling < 10%
- head, tongue, chin, lips, legs: rare
    - supportive for a Dx of PD
- LD, amantadine, propranolol, clonazepam, but not anticholinergics

tremor in PSP

- PSP-P
  - not described in the literature
  - cases of ET have been described to evolve to PSP
    - 11 cases have evolved within 5-49 years to parkinsonism or dementia
    - none were diagnosed wiht PSP
    - all had a pathological dx of PSP

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Essential Tremor Followed by Progressive Supranuclear Palsy: Postmortem Reports of 11 Patients

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Abstract

For many years, clinicians have commented on the development of signs of parkinsonism among their essential tremor (ET) patients but the links between ET and parkinsonism are not well understood. We report 11 of 89 ET patients (12.4%) who were prospectively collected at the Essential Tremor Centralized Brain Repository over the course of its first 9 years. All patients had longstanding ET (median duration = 38 years); there was a 5- to 49-year latency from the onset of ET to the development of either parkinsonism or dementia. Despite the presence of parkinsonism or dementia during life, none had been diagnosed clinically with progressive supranuclear palsy (PSP). All 11 received the postmortem diagnosis of PSP. The prevalence of PSP in this ET sample (12.4%) is clearly larger than the population prevalence of PSP (0.001% to 0.0065%). It is also 2 to 5 times the proportion of normal cases with incidental PSP in 2 prior autopsy series. This case series raises the questions of an association between ET and PSP, whether ET patients are at increased risk of developing PSP, and what the proportion of ET patients who develop presumed PD or AD in life actually have PSP (i.e. ET+PSP).