Movement Disorders translational research to bridge into clinical practice

Essential tremor
45 min

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

Stockholm September 2012

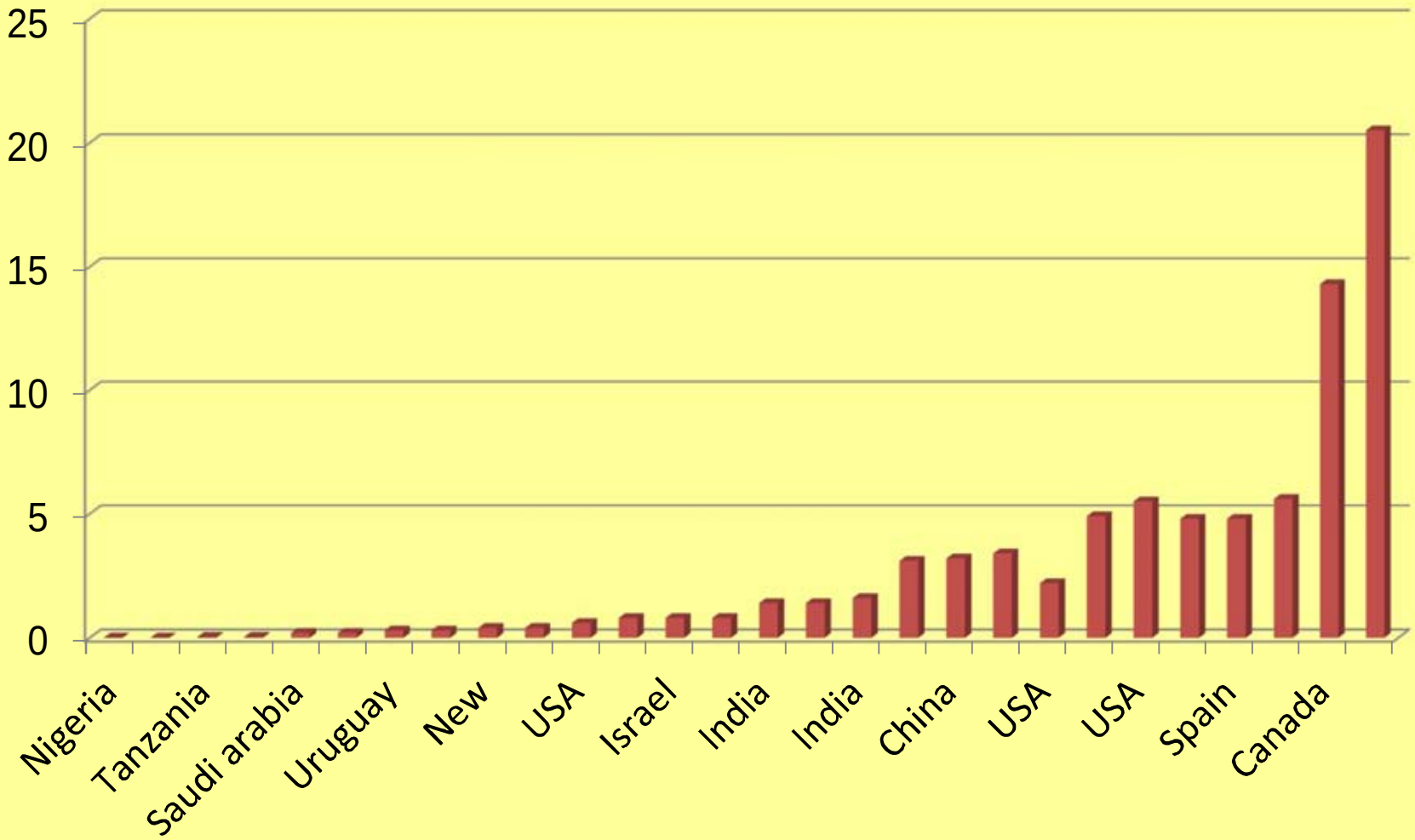
Clinical Classification

1998 MDS Classification

- Bilateral action tremor of the hands and forearms (but not rest tremor)
- Absence of other neurologic signs with the exception of the cogwheel phenomen
- May have isolated head tremor with no signs of dystonia

3 years: probable ET, >5 years: definite ET

The prevalence of tremor in different studies worldwide: are these all the same tremors?



Louis and Ferreira 2010

The border to dystonic tremor

(Ferraz et al. 1994)

- 22,7% of idiopathic dystonias have a significant tremor
- 21,5% of symptomatic dystonia have a significant tremor

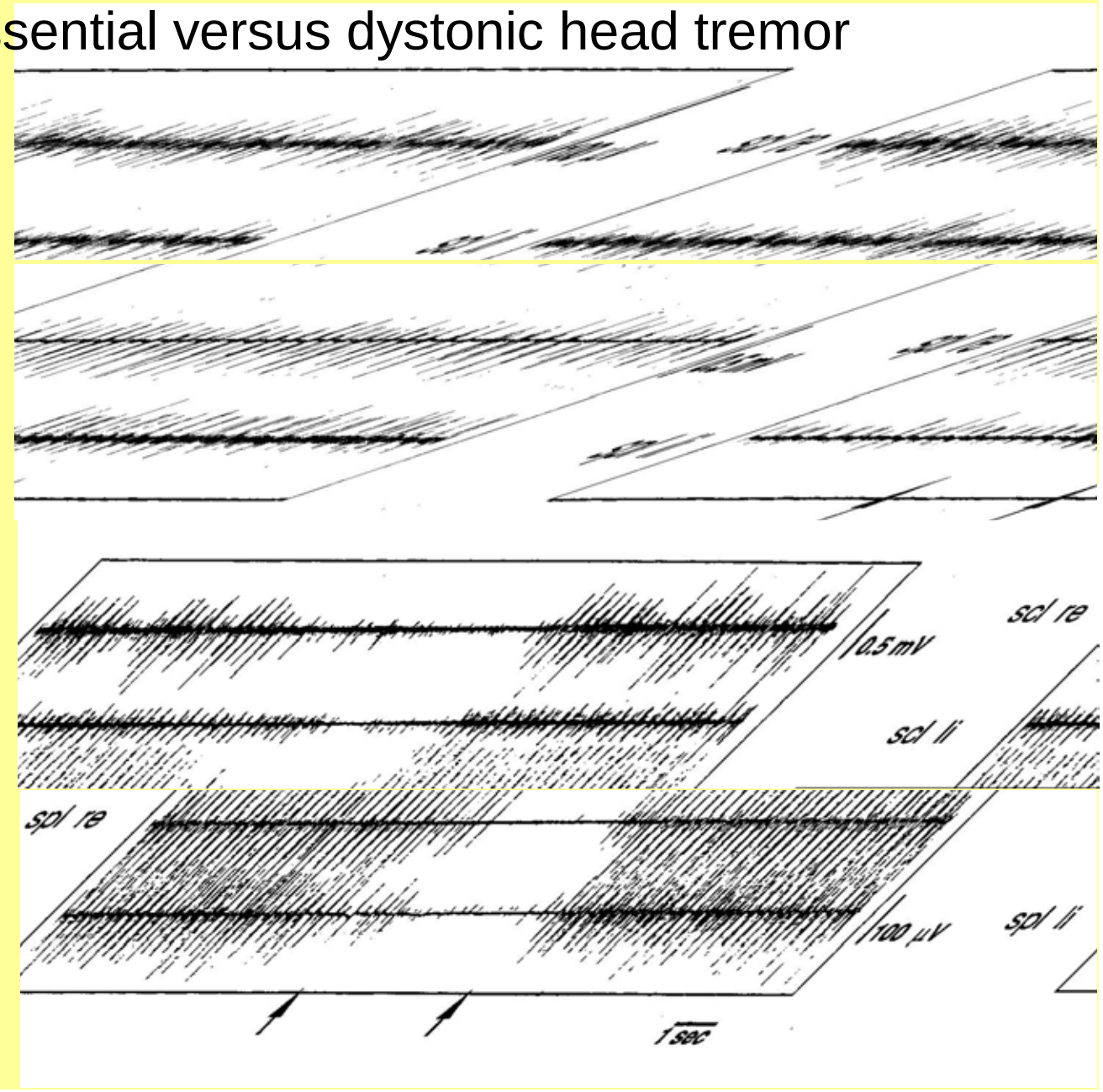
Similar percentage for focal, segmental and generalized dystonia

Essential or dystonic tremor

The diagnostic significance of the ‘geste antagonistique’ for detecting essential versus dystonic head tremor

Essential head tremor

Dystonic head tremor



Quantification of sensory trick: impact on tremor amplitude and frequency in 60 patients with head tremor (Masuhr et al. 2000)

	Definition	No of patients	Clinical positive geste	Reduction of tremor (peak power)
Tremulous Cervical dystonia	Head tremor and torticollis	34 patients	+	83%
Dystonic head tremor	Head tremor without torticollis	14 patients	+	90%
Essential head tremor	Head tremor without torticollis	12 patients	-	6%

Differential diagnosis between dystonic an essential tremor

	Dystonic tremor	**Essential tremor**
Onset	Gradual onset (over years)	Gradual onset (over decades)
Family history	rare	frequent
Focal tremor	yes	no
Gestes antagonistiques	yes	no
Alcohol-sensitivity	unknown	yes
Distractability	low	low
Variability	Task-consistent	low
Co-contraction	May occur	rare
Finger tremor	frequent	frequent

Clinical evidence for a subdivision?

Do we have sufficent evidence for separating ET-cases beyond the general definition?

ORIGINAL RESEARCH

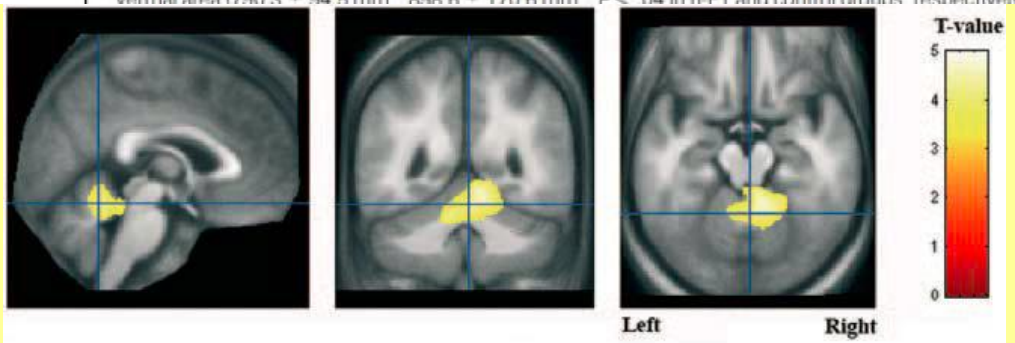
Essential Head Tremor Is Associated with Cerebellar Vermis Atrophy: A Volumetric and Voxel-Based Morphometry MR Imaging Study

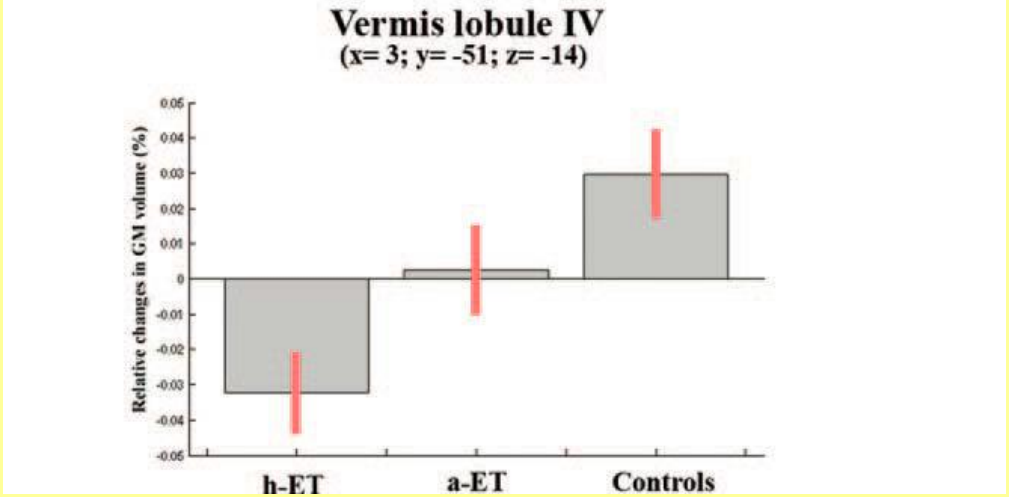
A. Quattrone
A. Cerasa
D. Messina
G. Nicoletti
G.E. Hagberg
L. Lemieux
F. Novellino
P. Lanza
G. Arabia
M. Salsone

BACKGROUND AND PURPOSE: Our aim was to investigate the presence of brain gray matter (GM) abnormalities in patients with different forms of essential tremor (ET).

MATERIALS AND METHODS: We used optimized voxel-based morphometry (VBM) and manually traced single region-of-interest analysis in 50 patients with familial ET and in 32 healthy subjects. Thirty patients with ET had tremor of the arms (a-ET), whereas the remaining 20 patients had both arm and head tremor (h-ET).

RESULTS: VBM showed marked atrophy of the cerebellar vermis in the patients with h-ET with respect to healthy subjects ($P_{corrected} < .001$). Patients with a-ET showed a trend toward a vermal GM volume loss that did not reach a significant difference with respect to healthy controls ($P_{uncorrected} < .01$). The region-of-interest analysis showed a reduction of the cerebellar volume (CV) in the h-ET group (98.2 ± 13.6 mm^3) compared with healthy controls (110.5 ± 15.5 mm^3, $P < .012$) as well as in the entire vermal area (790.3 ± 94.5 mm^2, 898.6 ± 170.6 mm^2, $P < .04$ in h-ET and control groups, respectively)





Voice tremor:
Possible hints at the differential diagnosis

ET-voice tremor

Vocal

speech

ET voice tremor
an intervention

before

after

Dystonic
voice tremor

Vokal

speech

Clinical Classification

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2013 MDS Classification (work in progress)

- Axis 1 (Syndromic classification): bi-brachial symmetrical postural and kinetic tremor syndrome of both arms with or without head tremor, with or without additional symptoms
- Axis 2 (Etiologic classification): Clinically isolated tremor with or without additional symptoms to be defined

Long-term course of ET: Disease progression, another tool?

- Mean annual increase of tremor severity: 12% worsening (Putzke et al. 2006).
  - Factors with severity at initial visit: older age, longer disease duration, voice tremor.
  - Factors with progression after initial visit: asymetrical tremor, longer follow-up
- Mean annual increase in tremor severity: 3,1 – 5,3%. Median annual increase: 1,8%-2,0% (Louis et al 2011)

Does pathology help to define ET?

19 cases since the 1930-ies - inconsistent pathology

Rajput et al 2004: 20 cases - inconsistent pathology

Controlled studies (57 cases):
Louis et al. (5 papers reporting a total of 33 patients):
2 types of pathology:

- ET with Lewy bodies
- ET without Lewy bodies, Purkinye cell ↓, Torpedos ↑

Shill et al. 2008 (1 paper on 24 patients):

- Significant cerebellar pathology and atrophy of the locus coeruleus but no Lewy bodies

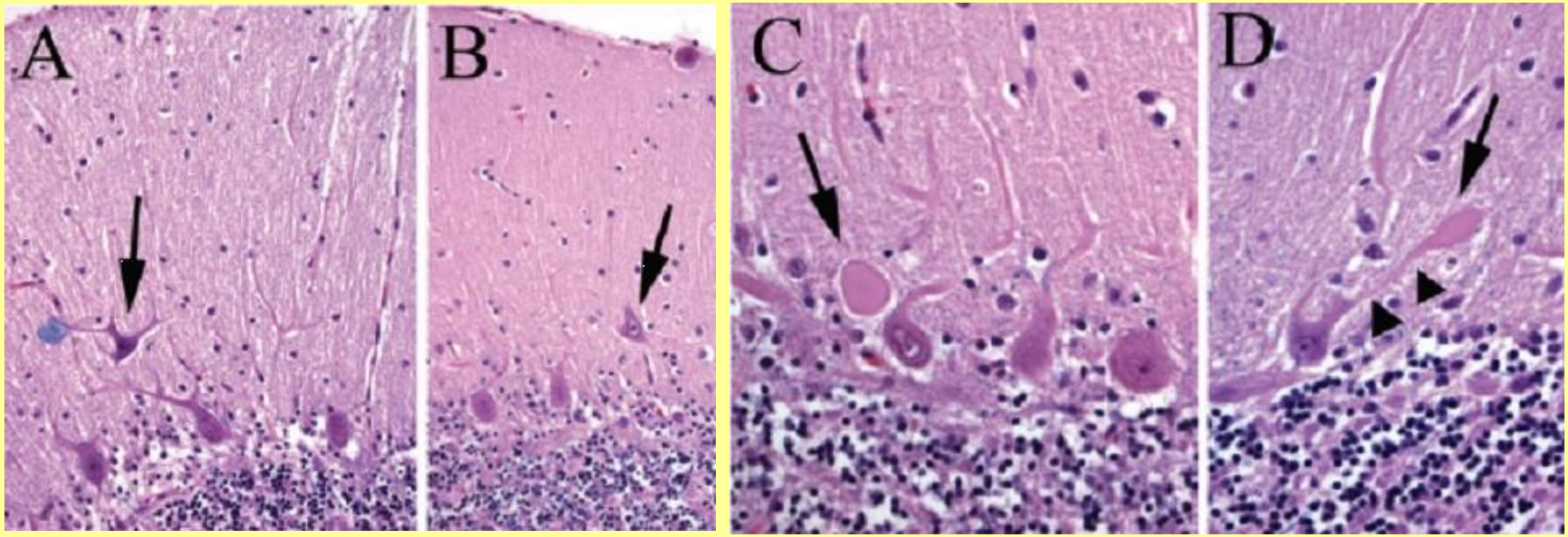
Rajput et al. 2012 (12 ET, 6 controls, 41 PD)

- Purkinye-cell loss is age-dependent, not ET-specific

Is this the pathology?

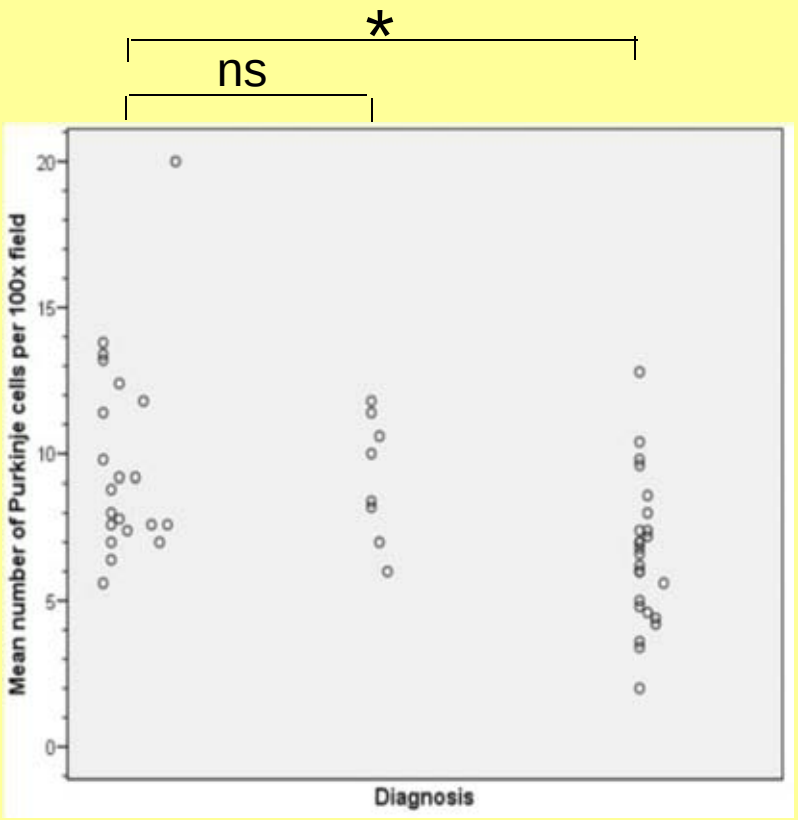
Purkinje cells

Torpedoes

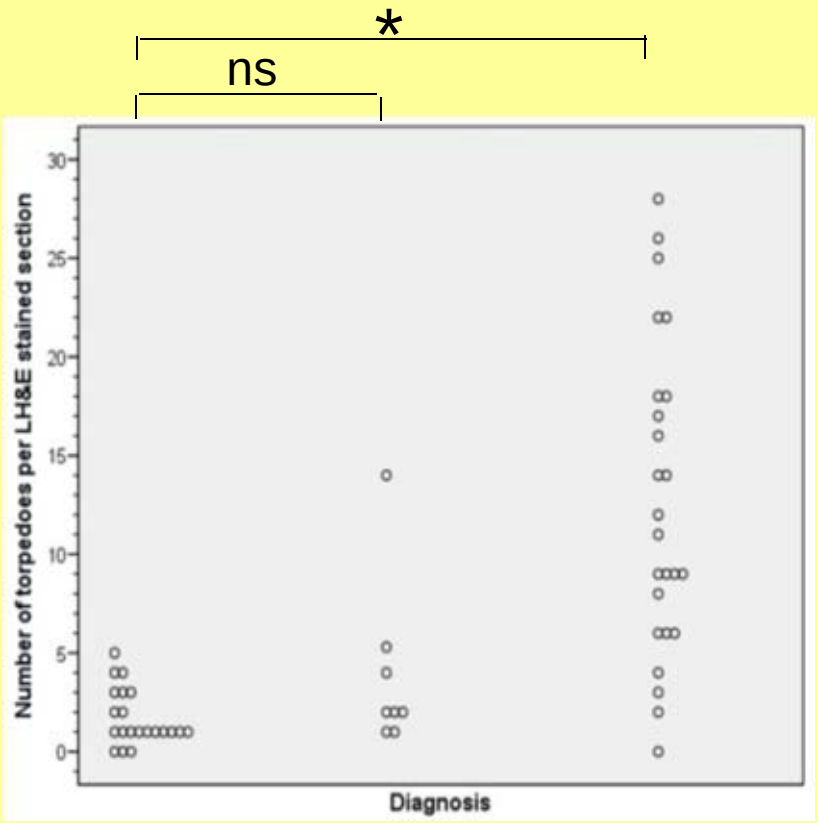


Louis et al. Brain 2007

Mean number of Purkinje cells



torpedoes



controls ET with LB ET without LB

controls ET with LB ET without LB

25 cases without Lewy bodies
8 cases with Lewy bodies

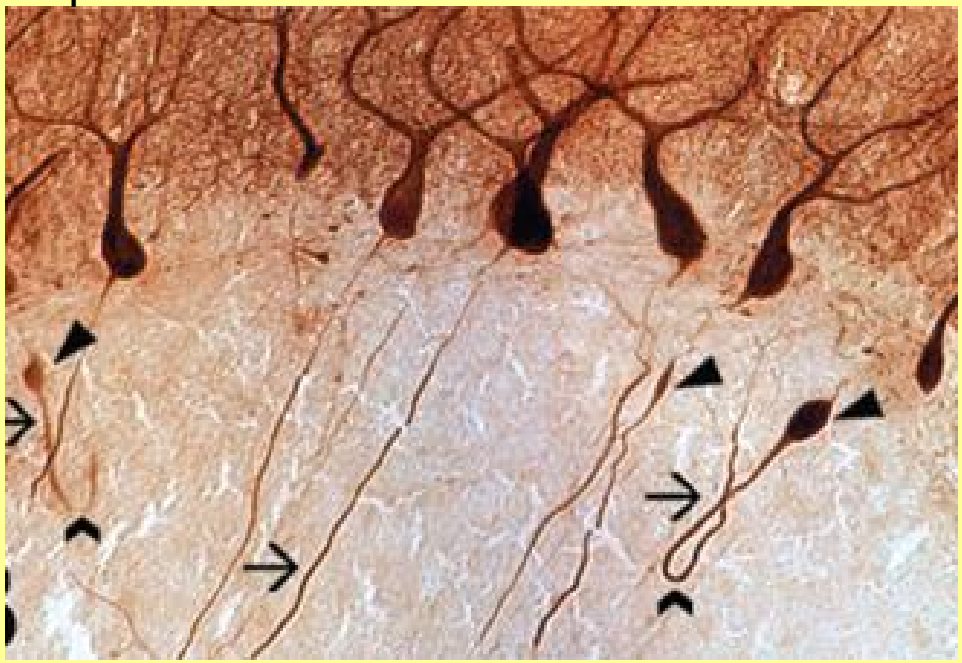
Louis et al. Brain 2007

Brain Advance Access published September 12, 2013
doi:10.1093/brain/awt238 Brain 2013: Page 1 of 11 | 1
BRAIN
A JOURNAL OF NEUROLOGY

Purkinje cell axonal anatomy: quantifying morphometric changes in essential tremor versus control brains

Rachel Babij,[1] Michelle Lee,[1] Etty Cortés,[2] Jean-Paul G. Vonsattel,[2,3] Phyllis L. Faust[3] and Elan D. Louis[1,2,4,5]

Torpedos on axons with recurrent collaterals

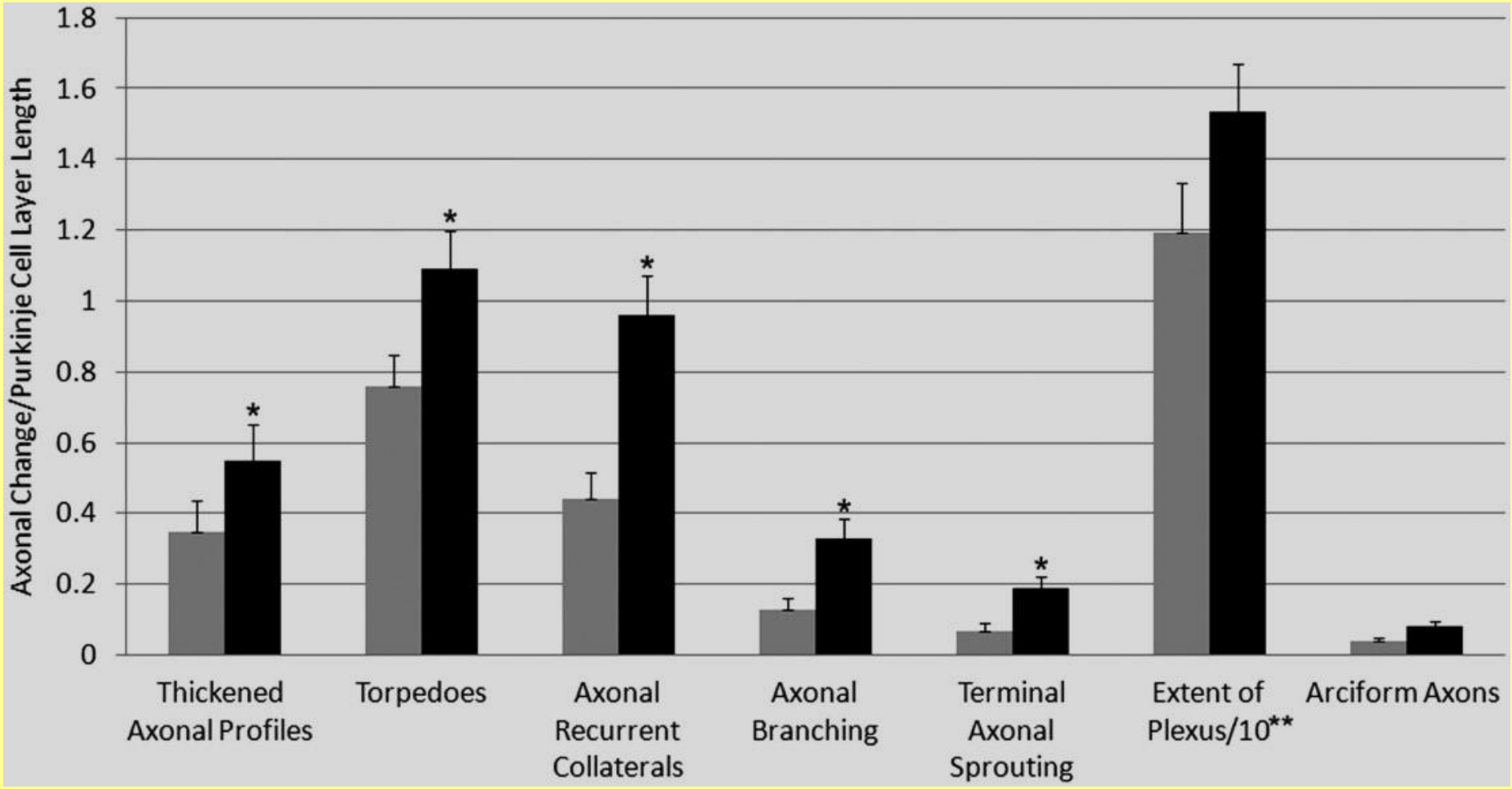


Quantitative measures

	ET-Cases	Controls	significance
Purkinye cell count	6.6 ± 1.7	9.9 ± 3.1	P < 0.001
Torpedo count (Bielschowsky)	25.0 ± 27.7	9.2 ± 9.5	P<0.001
Age	87.8 ± 71	77.4 ± 12.0	P < 0.001

Essential tremor: 49 cases
Controls: 39 cases

Babij et al. 2013



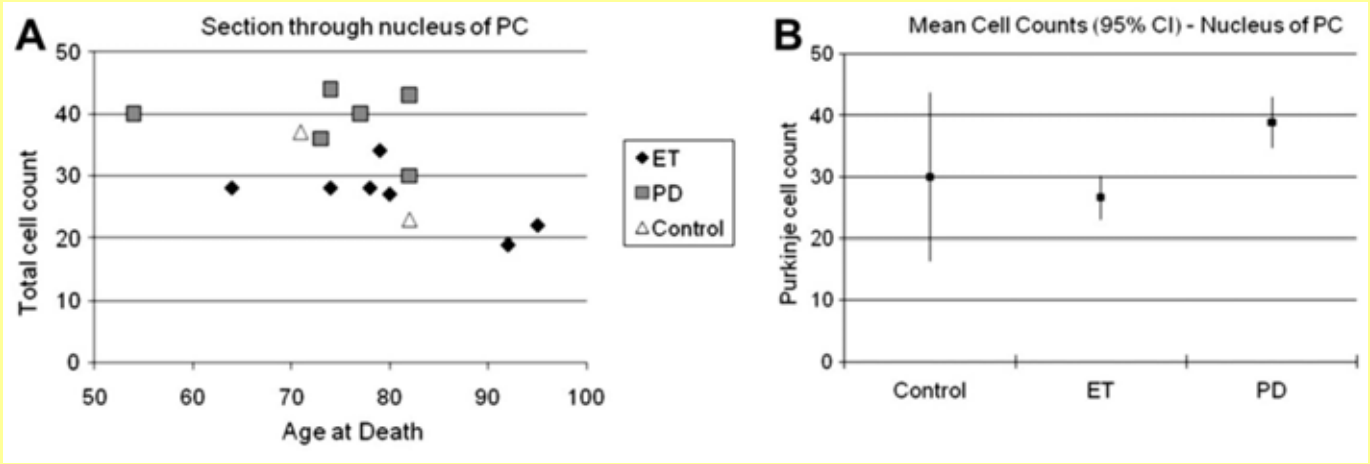
Babij et al. 2013

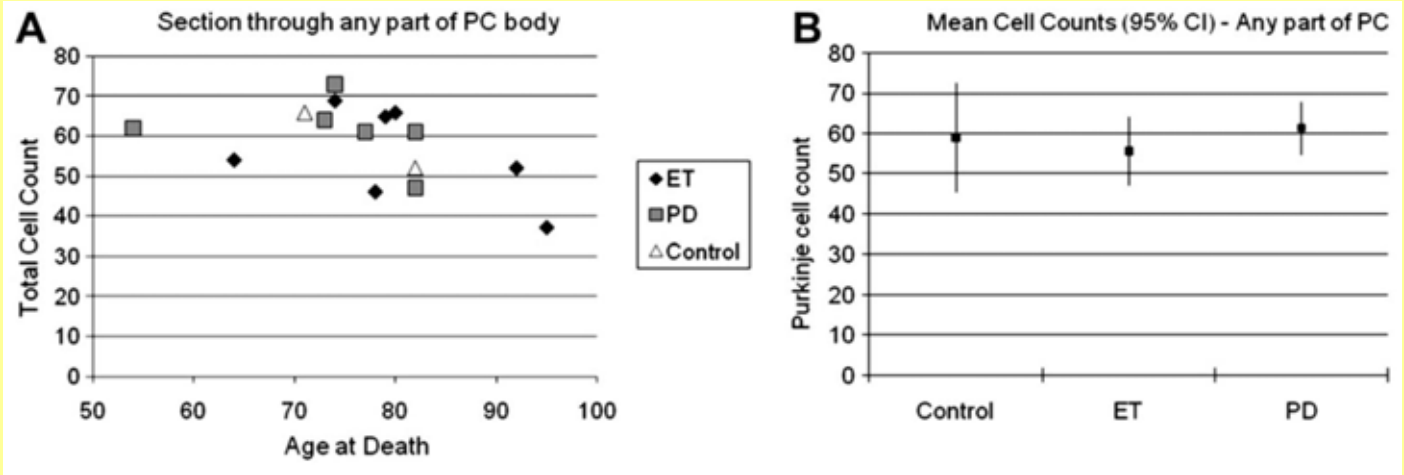
Cerebellar Purkinje cell loss is not pathognomonic of essential tremor

A.H. Rajput*, C.A. Robinson, M.L. Rajput, A. Rajput

Saskatchewan Health Region, University of Saskatchewan, Room 1663, Royal University Hospital, Saskatoon, Saskatchewan S7N 0W8, Canada

Parkinsonism and Related Disorders 17 (2011) 16–21





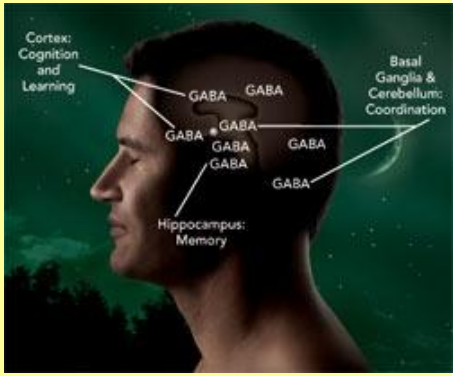
Pathology continues to be inconsistent

	ET comes with Lewy pathology	ET comes with obvious cerebellar pathology
Louis et al. 2009	Yes	Yes
Shill et al. 2008	No	Some cases
Rajput et al. 2011	No	No

Does genetics help to redifine ET? Candidate genes

- ETM1: (FET1) (4 of 6 cohorts positive)

  DRD3: Dopamine receptor D3 may involved in regulation of locomotion. DRD3 is expressed in Purkinje cells



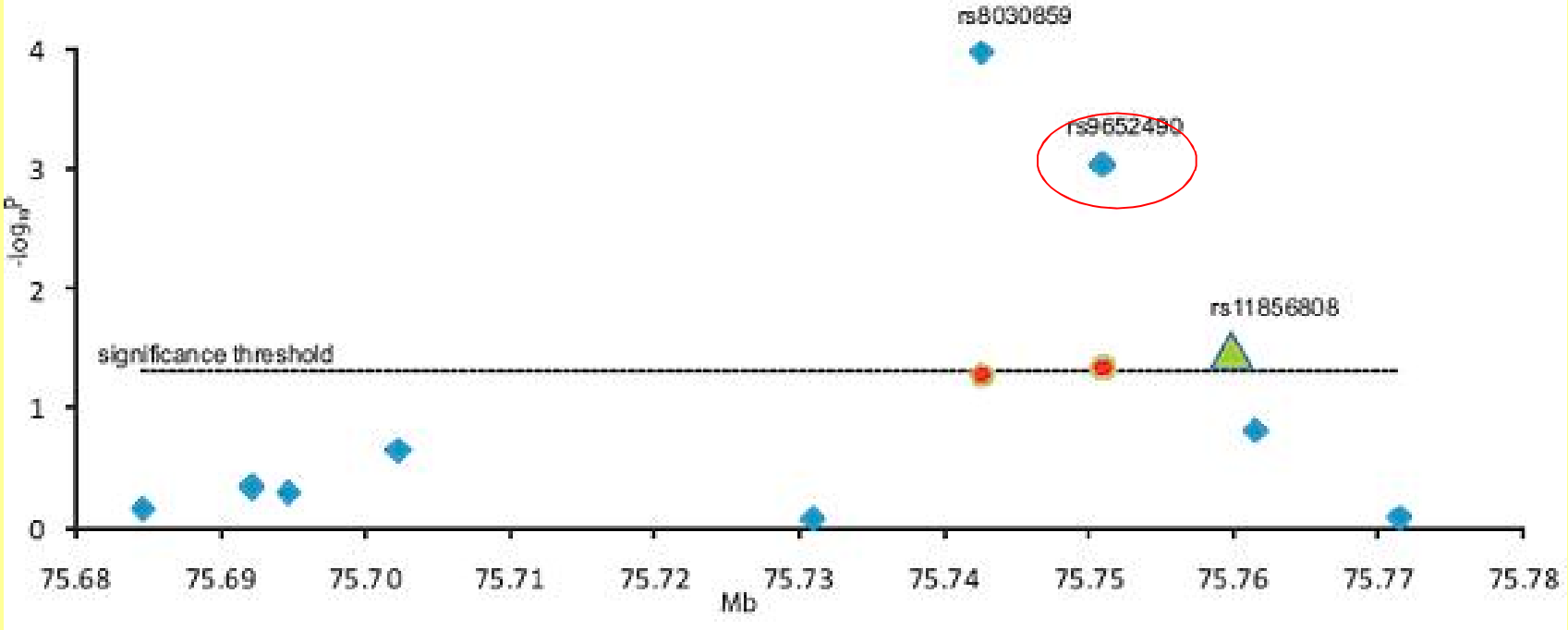
- ETM2: (5 of 7 cohorts)

  HS1-BP3 gene: HS1-BP3 protein binds to proteins that are expressed in neurons and Purkinje cells and regulates Ca2+ calmodulin-dependent protein kinase activation of tyrosine and tryptophan hydroxylase

- GABA A receptor α1 & GABA transporter subtype 1 knock out mice (2 negative studies)

Replication studies failed for most of the loci except for ETM 2.

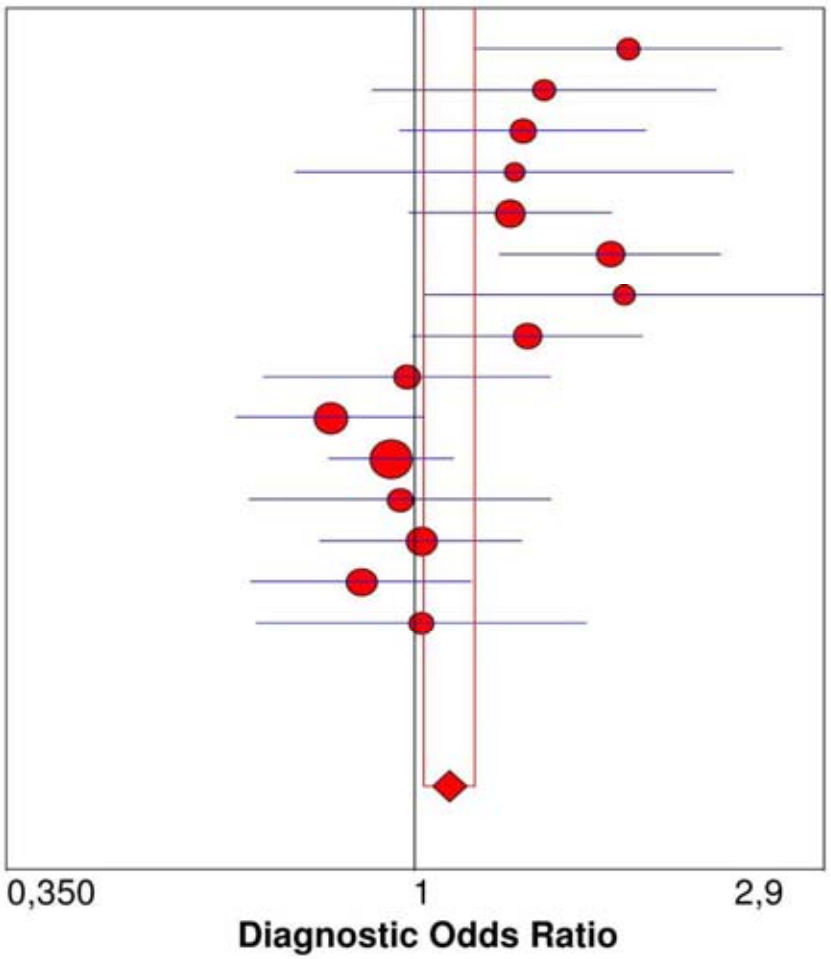
Genome.-wide association studies:
The LINGO1-gene (Steffanson, Nat Med 2009)



Stefansson et al. 2009: 450 cases, 300 follow-up, 15.000 controls.
Significant association on chromosome 15q24.3

(SNP: rs9652490(G))

Lingo1 metaanalysis



	Diagnostic OR (95% CI)	
Stefansson, 2009 Ref 2	1,73	(1,16 - 2,56)
Stefansson. 2009 Ref 2	1,39	(0,90 - 2,16)
Stefansson. 2009 Ref 2	1,32	(0,96 - 1,81)
Stefansson. 2009 Ref 2	1,29	(0,74 - 2,26)
Tan, 2009 Ref 43	1,28	(0,98 - 1,65)
Thier, 2010 Ref 40	1,65	(1,24 - 2,19)
Thier. 2010 Ref 40	1,71	(1,02 - 2,86)
Clark, 2010 Ref 42	1,33	(0,99 - 1,79)
Zuo, 2010 Ref 44	0,98	(0,68 - 1,42)
Vilarino-Guell, 2010 Ref 39	0,80	(0,63 - 1,02)
Vilarino-Guell, 2010 Ref 41	0,94	(0,80 - 1,10)
Wu, 2011 Ref 45	0,96	(0,65 - 1,42)
Bourassa, 2011 Ref 38	1,02	(0,78 - 1,32)
Lorenzo-Betancor, 2011 Ref	0,87	(0,66 - 1,16)
Radovica, 2012 Ref 46	1,02	(0,66 - 1,55)

Pooled Diagnostic Odds Ratio = 1,09 (1,02 to 1,17)

Kuhlenbäumer et al (in preparation)

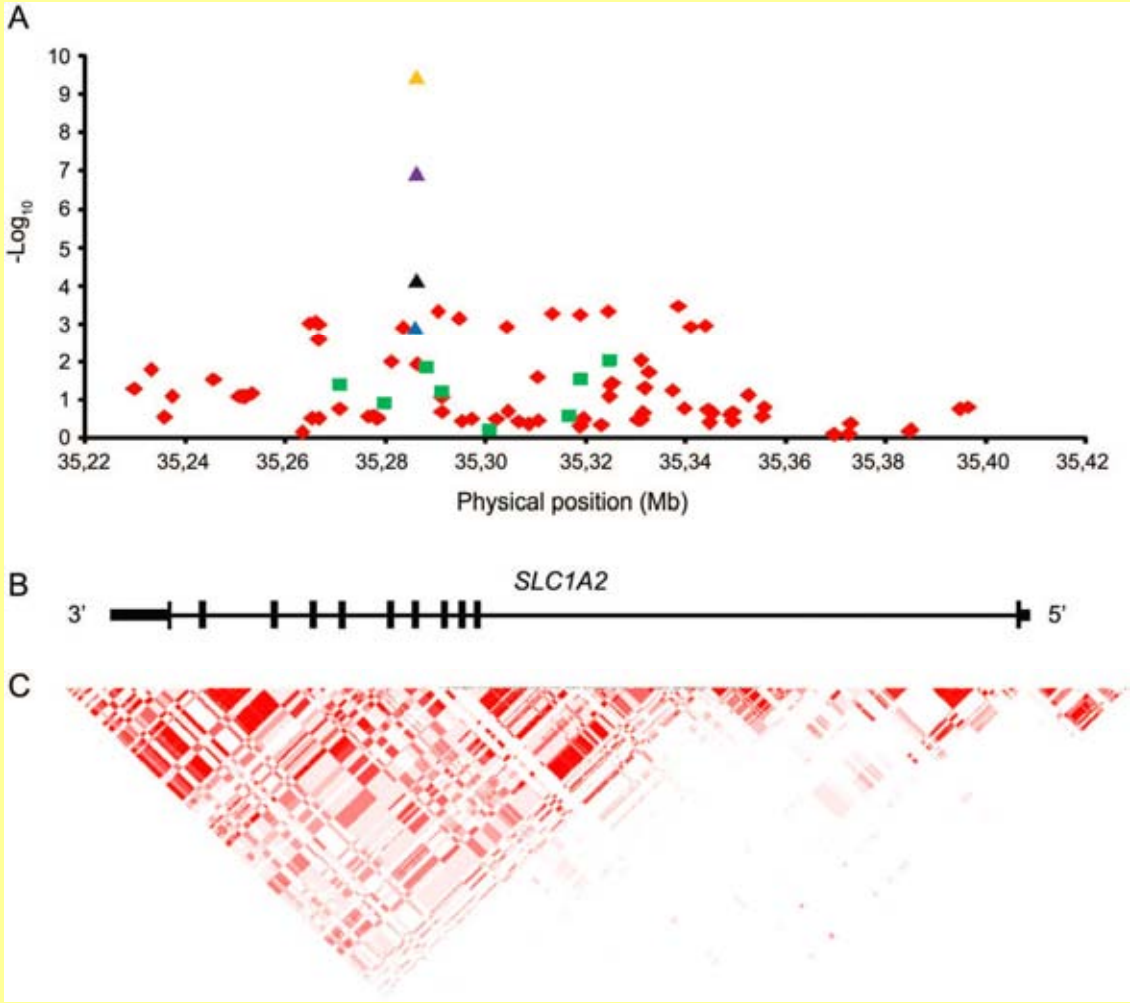
Excitatory amino-acid transporter 2 (EAAT2) = solute carrier family 1 member 2 (SLC1A2)

Thier et al. 2012

990 subjects and 1,537 control subjects from Kiel, Innsbruck, Tübingen, Odense

1.Step: Assoziation von rs3794087, $p=6.95 \times 10^{-5}$, OR=1.46).
2. Step: Association of rs3794087, $p=1.25 \times 10^{-3}$, OR=1.38).

SLC1A2 / EAAT2 important transmembraneous glutamate transporter



Exome Sequencing Identifies *FUS* Mutations as a Cause of Essential Tremor

Nancy D. Merner,[1,2] Simon L. Girard,[1,2] Hélène Catoire,[1,2] Cynthia V. Bourassa,[1,2] Véronique V. Belzil,[1,2] Jean-Baptiste Rivière,[1,2] Pascale Hince,[1,2] Annie Levert,[1,2] Alexandre Dionne-Laporte,[1,2] Dan Spiegelman,[1,2] Anne Noreau,[1,2] Sabrina Diab,[1,2] Anna Szuto,[1,2] Hélène Fournier,[3] John Raelson,[3] Majid Belouchi,[3] Michel Panisset,[2,4] Patrick Cossette,[1,2] Nicolas Dupré,[5] Geneviève Bernard,[2,4] Sylvain Chouinard,[2,4] Patrick A. Dion,[1,2,6] and Guy A. Rouleau[1,2,4,7,*]

The American Journal of Human Genetics *91*, 313–319, August 10, 2012

Exom-Sequenzierung: FUS/TLS
(fused in sarcoma/translocated in liposarcoma)

- A family with a FUS p.Gln290* Mutation as the cause of ET
- For 270 additional cases only 2 missense mutations
- FUS mutations found in ALS are different and do have more severe functional consequences.

- Confirmation: 1 other family, several attempts failed

Does epidemiology help to define essential tremor?

Epidemiological data are inconsistent: Two large epidemiological studies in New York and Spain

- Prevalent dementia increased in ET (OR= 1.84, 95% CI = 1.13-2.98, p = 0.01). (Thawani et al. 2009)
- Prevalent dementia not increased in the whole population but in those ET with onset >65 y (Bermejo-Pareja et al. 2007)
- Incident dementia increased in ET with onset > 65 y (Benito-Leon et al. 2011)
- Higher mortality in ET (Louis et al., 2007)

Longevity in ET

Table 2. Age of parents at death

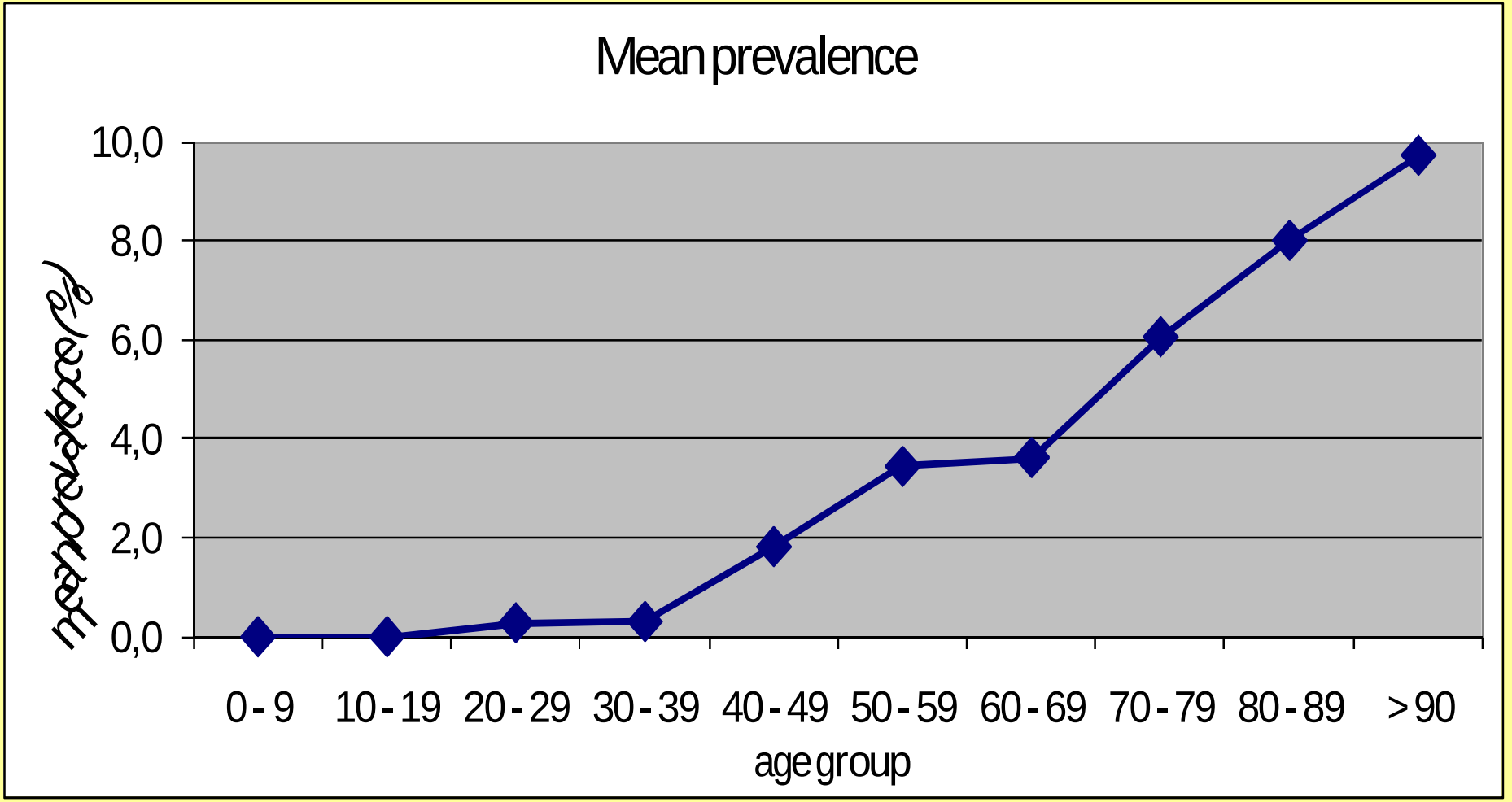
Variable	Parents of PD patients with tremor	Parents of PD patients without tremor	Parents of ET patients without tremor	Parents of ET-PD patients with tremor	Parents of ET-PD patients without tremor
Number	47	572	145	58	146
Median age at death of mothers (yr)	85	82	80*	83	80
Median age at death of fathers (yr)	84†	73†	70*	82†	62†

PD Parkinson's disease.
ET Essential tremor.
ET-PD Combined essential tremor and Parkinson's disease.
* $p < 0.05$.
† $p < 0.005$.

Jankovic 1995

The influence of age

(mean values of 10 studies)



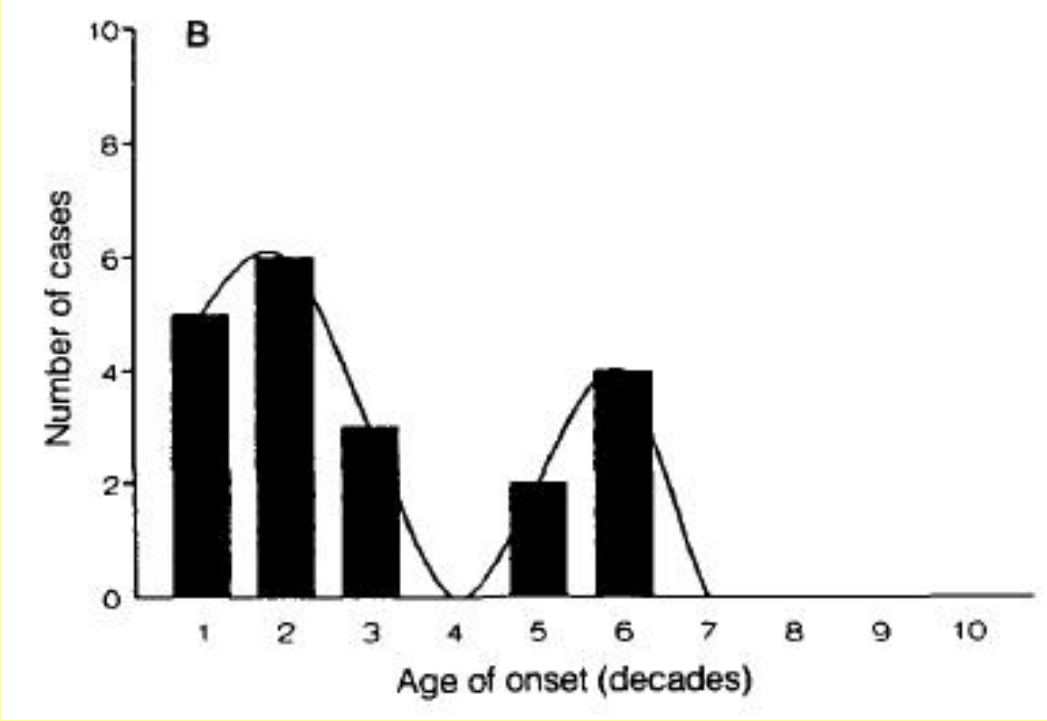
data from Louis and Fereirra MDJ 2010

When is full penetrance reached in hereditary ET?

Brain (1994), **117**, 805–824

A study of hereditary essential tremor

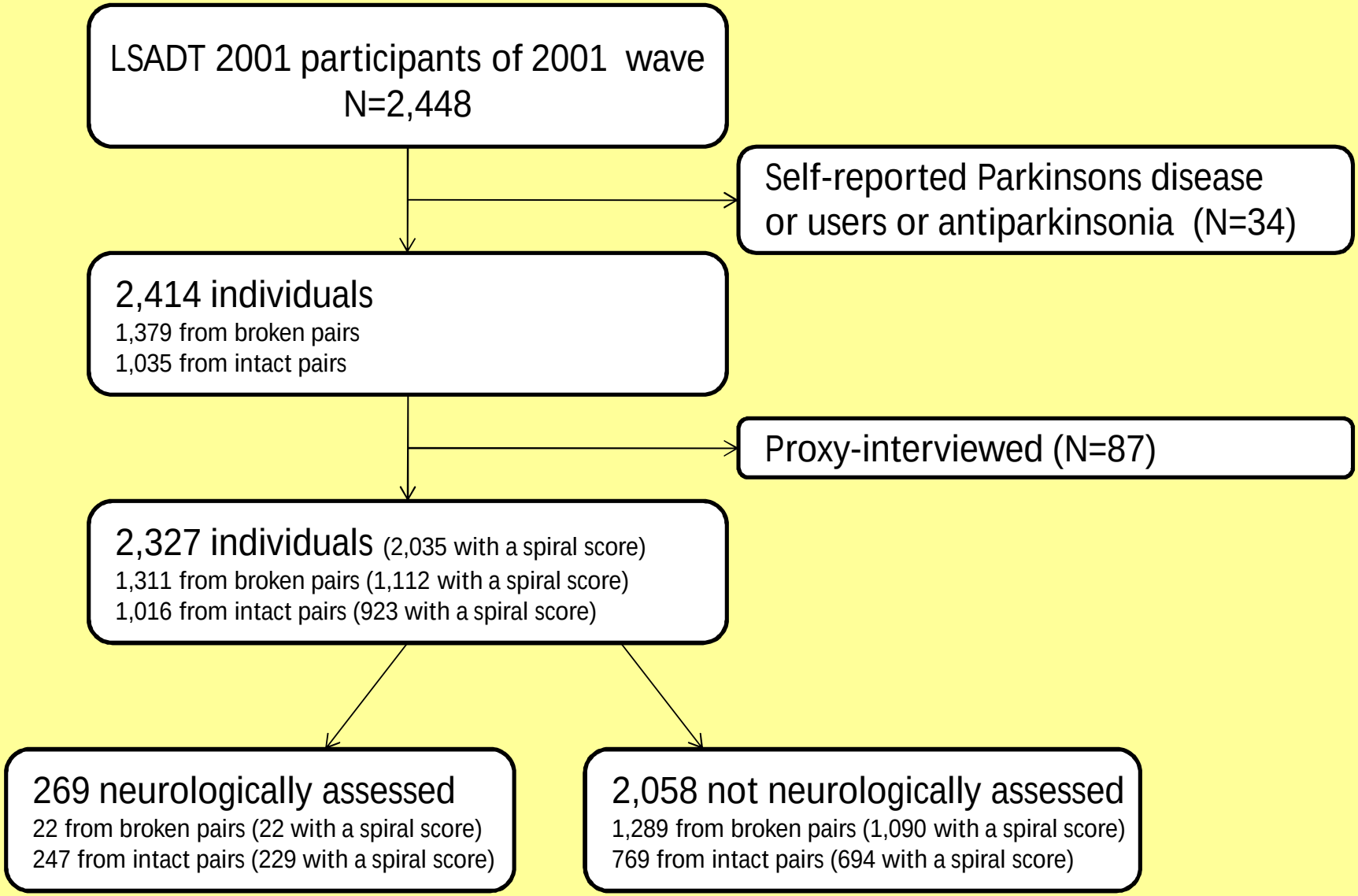
P. G. Bain,[1] L. J. Findley,[2] P. D. Thompson,[1] M. A. Gresty[1], J. C. Rothwell,[1]
A. E. Harding[1] and C. D. Marsden[1]



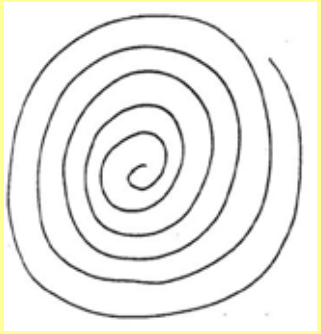
Preliminary conclusions

- Clinical analysis suggests subtyping
- Pathology inconsistent
- Biochemistry inconsistent
- ET prevalence is increasing with age
- Hereditary ET (the core group) is fully penetrant above the age of 65
- May or may not be associated with prevalent and incident dementia
- May or may not be associated with shorter life expectancy

Tremor in the elderly:
Results from a danish cohort of aging twins



Grad 0



Grad 1

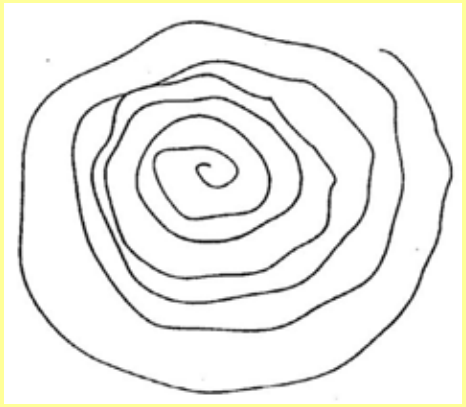
Grad 2

ASSESSING TREMOR SEVERITY

A Clinical Handbook

Peter G Bain
Leslie J Findley

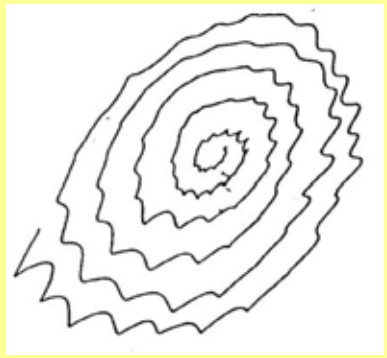
Grad 3



Grad 4

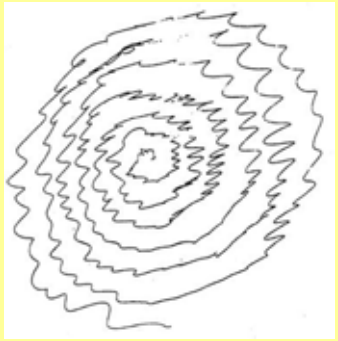
Grad 5

Grad 6



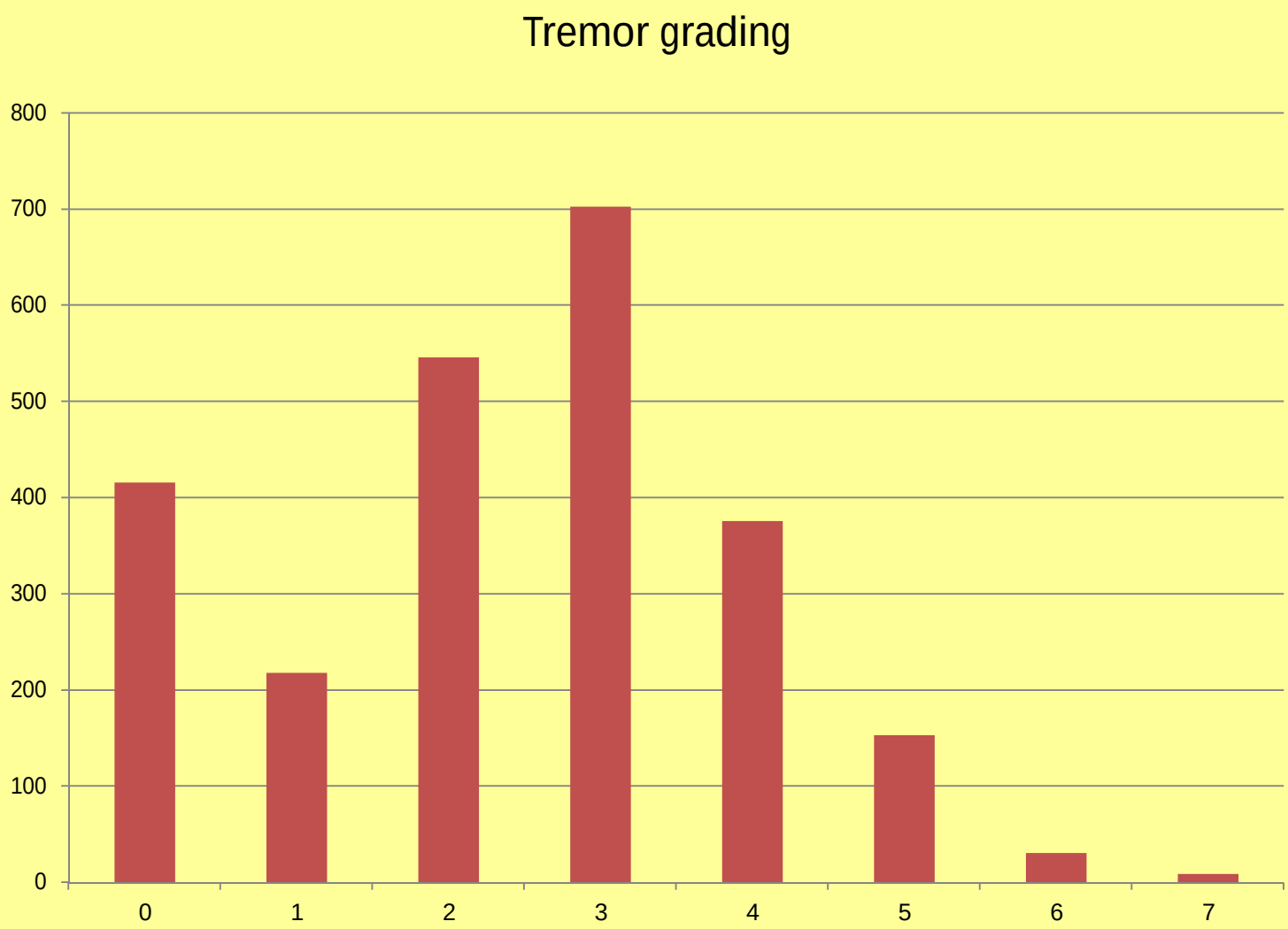
Grad 7

Grad 8

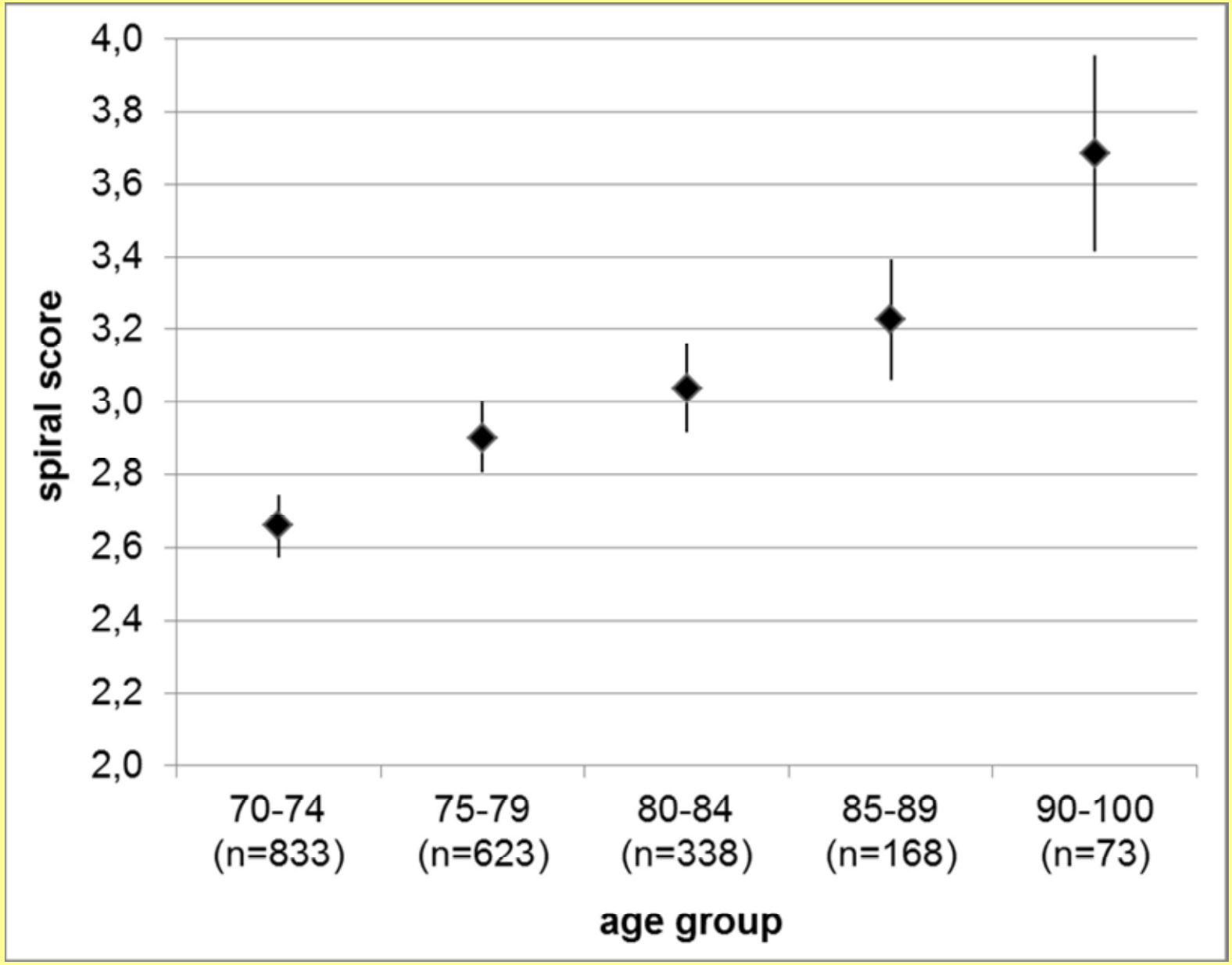


Grad 9

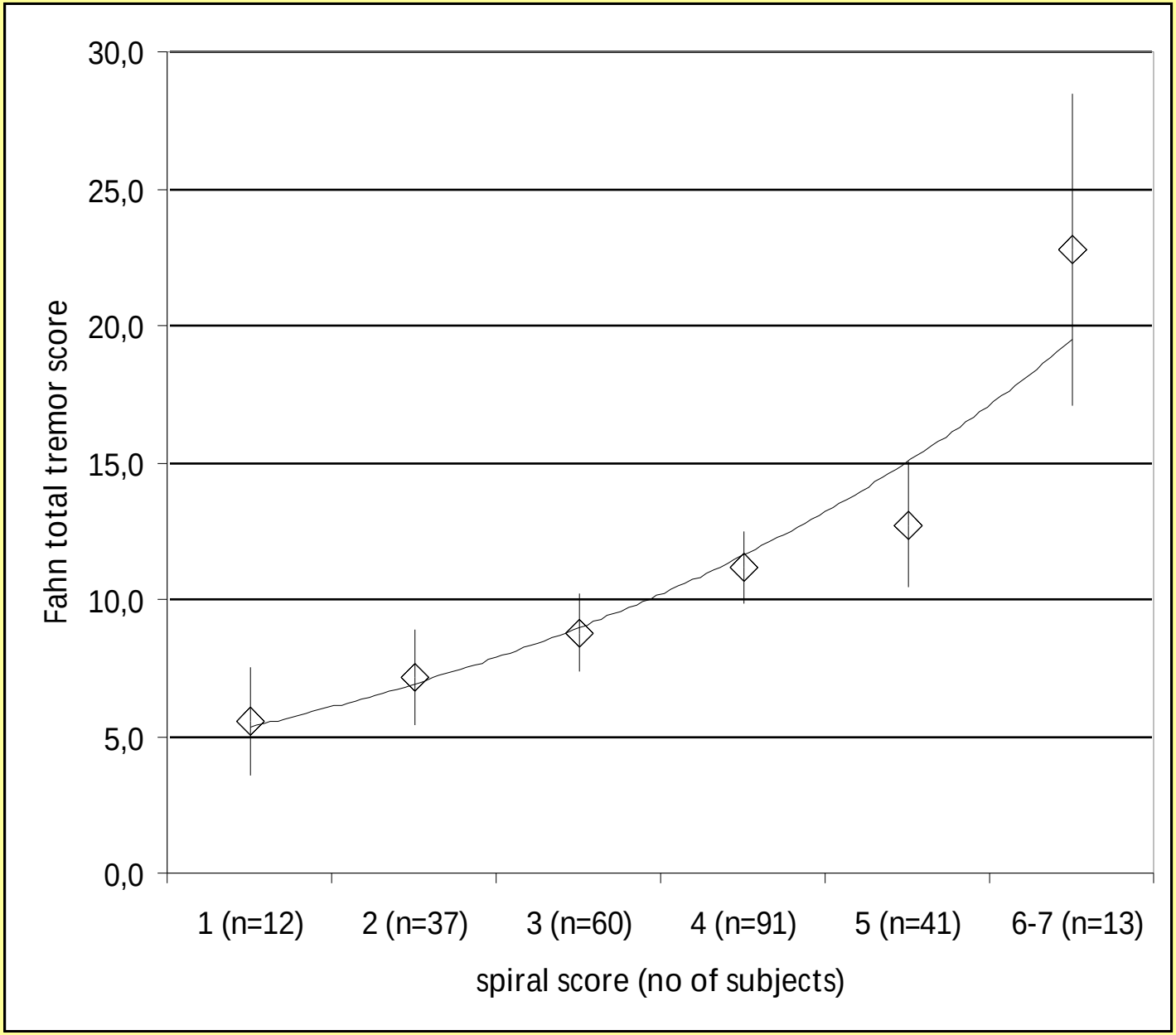
Spiral-grading of 2403 persons with an age >70 years



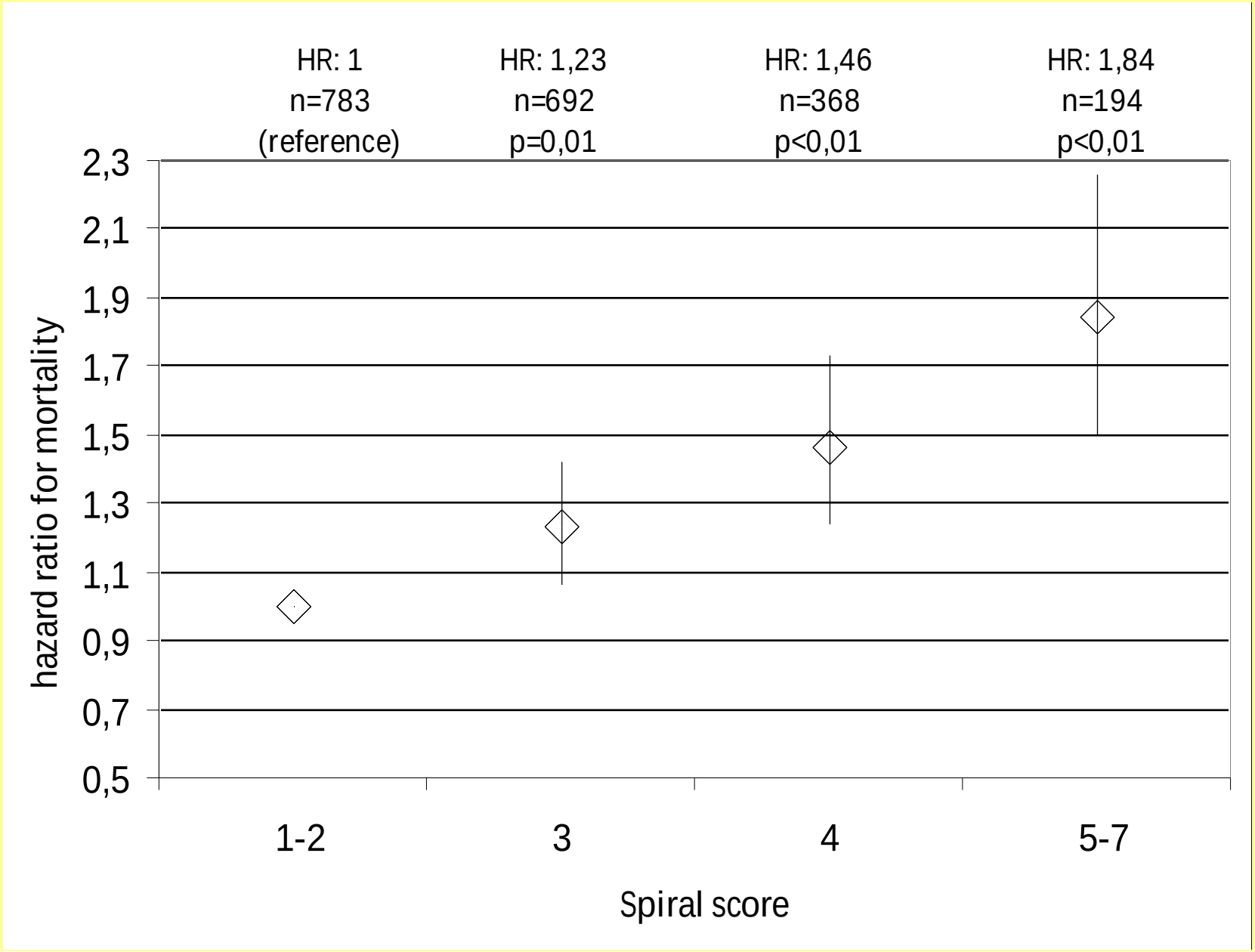
Tremor Score is increasing with age

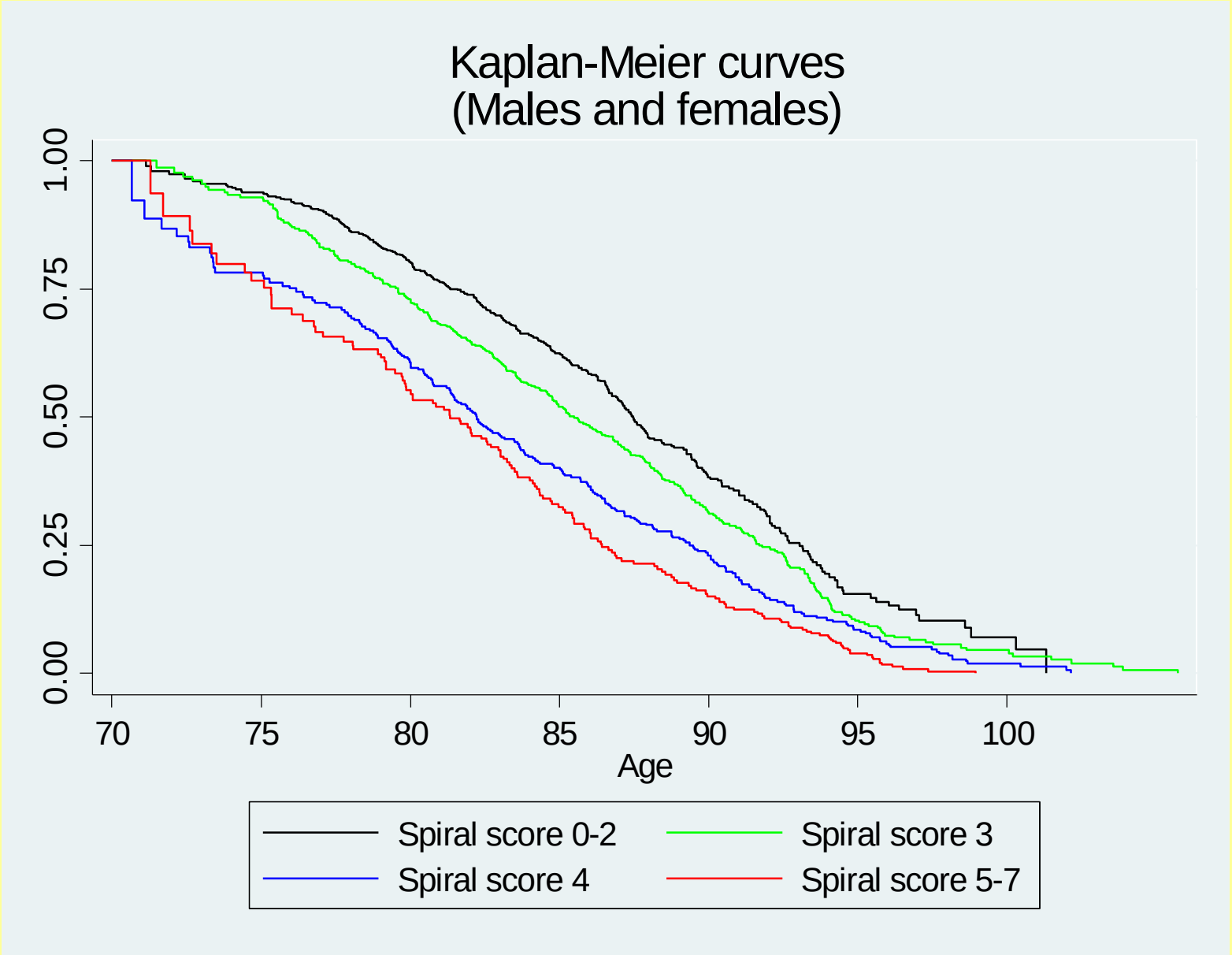


The spiral score is logarithmically related to the Fahn tremor scale



The hazard ratio for mortality is increasing with higher spiral scores




Kaplan-Meier curves
(Males and females)
1.00
0.75
0.50
0.25
0.00
70
75
80
85
90
95
100
Age
Spiral score 0-2
Spiral score 3
Spiral score 4
Spiral score 5-7

Classical aging parameters are worsening with higher spiral scores

Spiral score	N[a]	Grip strength (kg) (95%CI)	Cognitive composite (95%CI)	ADL Strength score (95%CI)
0-2	783	Ref		
3	692	-0.75 (-1.35;-0.15)	-1.12 (-1.46;-0.77)	-0.10 (-0.16;-0.04)
4	368	-0.90 (-1.66;-0.14)	-1.58 (-2.00;-1.15)	-0.13 (-0.20;-0.05)
5-7	194	-2.99 (-4.13;-1.85)	-2.57 (-3.11;-2.03)	-0.36 (-0.47;-0.24)

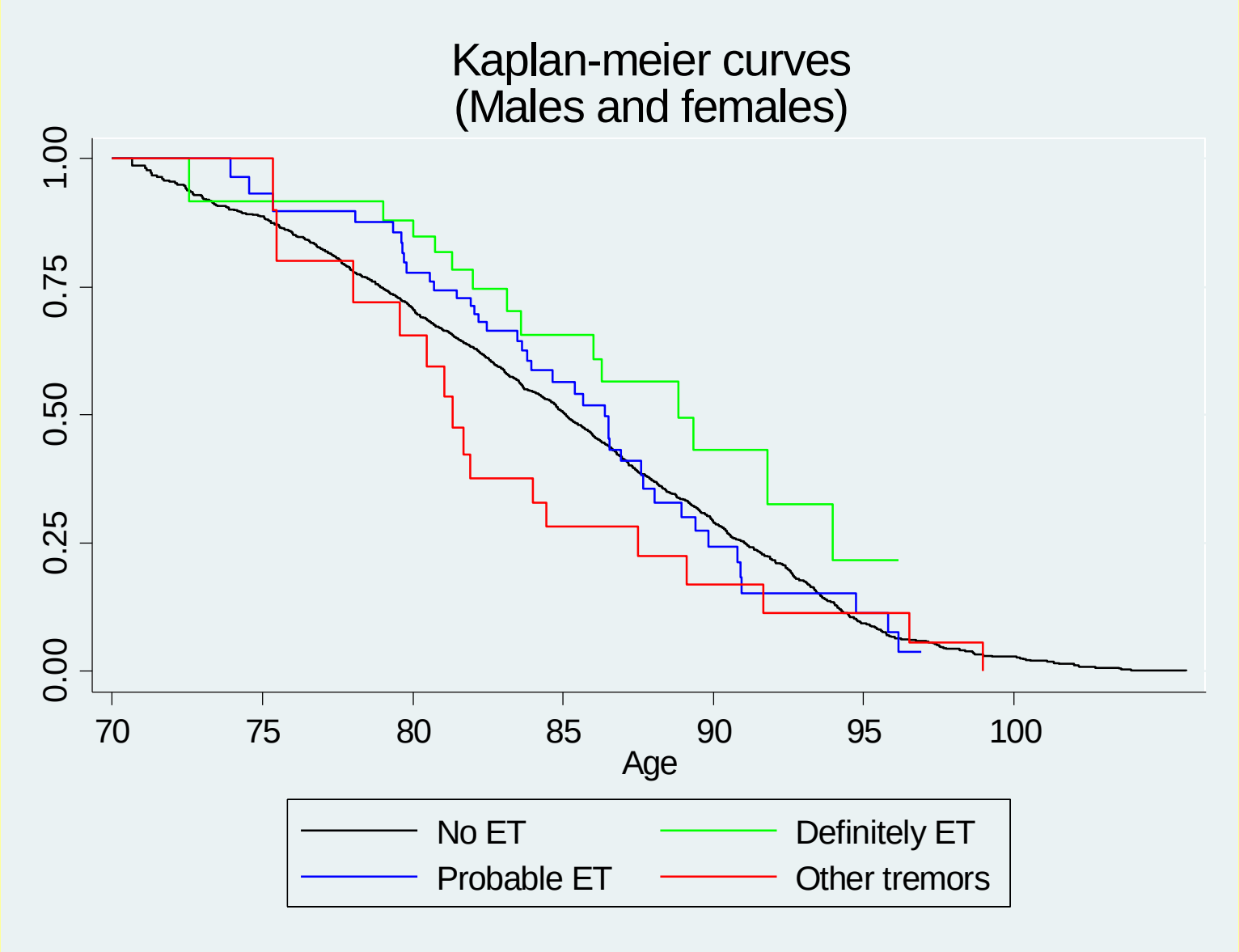
The spiral score is an independent predictor for mortality

tremor cases (spiral s. > 3) vs. non-tremor cases (spiral s. ?3)

Adjusted for	Age, sex	Age, sex, and medication	Age, sex, grip strength, ADL strength score, and cognitive and functioning	Age, sex, grip strength, ADL strength score, and cognitive functioning, and all medications
N	2,037	2,037	1,952	1,952
HR (95% CI)	1.45 (1.27;1.66)	1.43 (1.26;1.63)	1.21 (1.05;1.40)	1.21 (1.05;1.40)
P	<0.01	<0.01	<0.01	<0.01

What about essential tremor patients?

The hazard ratio is lower for essential tremor



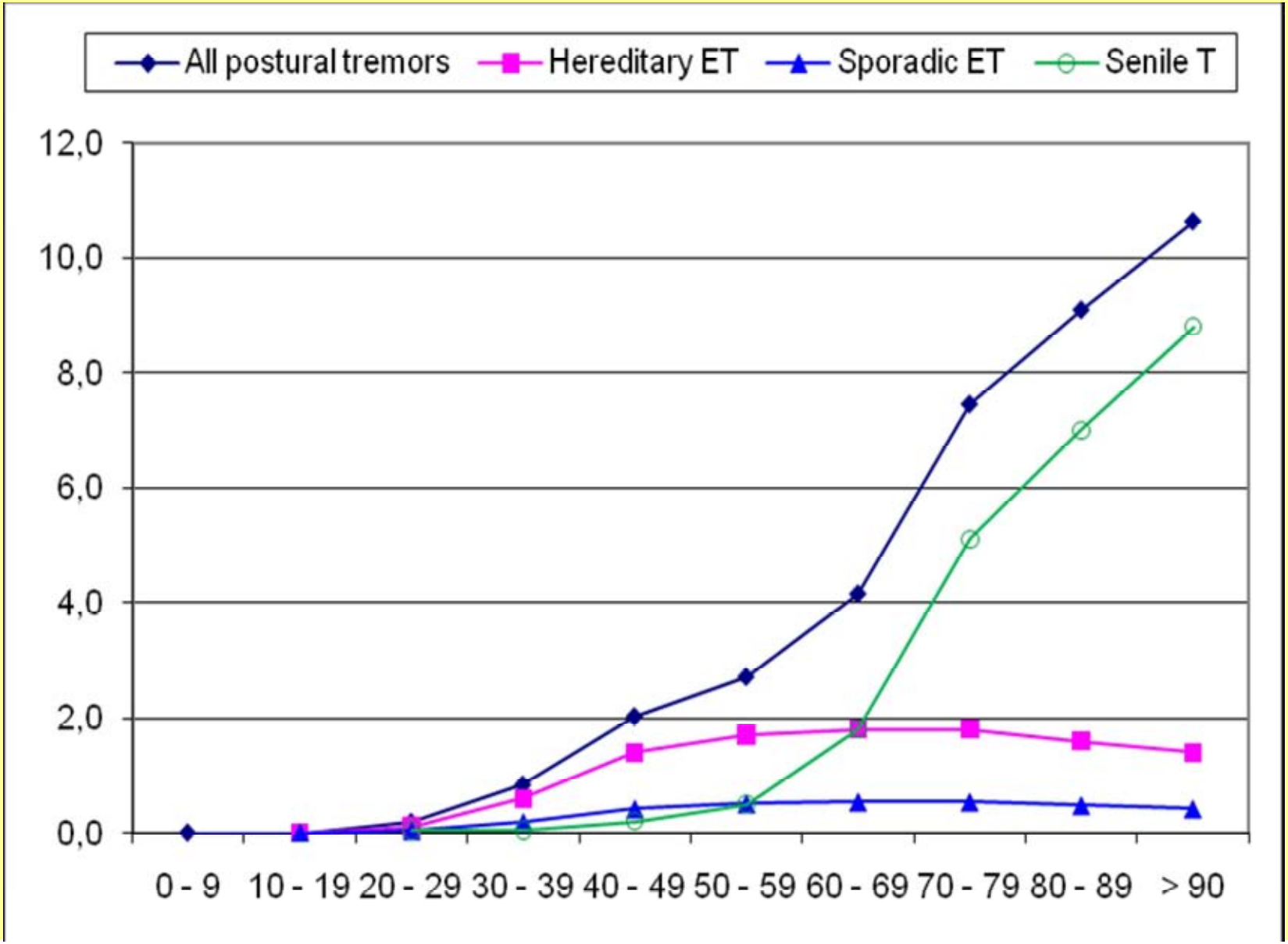
ET-patients have a significantly longer life expectancy than all subjects of the aging population

Tremor groups vs other participants	Reference group (n)	HR (95% CI)	p-value
Definite ET (n=34)	2,035	0.52 (0.31-0.90)	0.02
Probable ET (n=67)		0.83 (0.61-1.13)	0.25
Other tremors (n=17)		1.06 (0.58-1.93)	0.86
Intact pairs only			
Definitely ET (n=29)	923	0.45 (0.23-0.858)	0.02
Probable ET (n=58)		0.77 (0.53-1.13)	0.18
Other tremors (n=13)		1.37 (0.64-2.97)	0.42

Aging parameters are better for ET patients

				Grip strength (95%CI)	Cognitive composite (95%CI)	ADL strength score (95%CI)
Tremor group		N *	N * (ref. group)	Ref.		
a	Definite ET	31	2,298	0.10 (-2.16;2.36)	0.73 (-0.25;1.70)	0.14 (-0.02;0.28)
	Probable and possible ET	61		-0.23 (-2.09;1.63)	-0.23 (-0.11;0.66)	0.09 (-0.05;0.22)
	Other tremors	22		*-3.90 (-6.17;-1.62)*	-0.87 (-2.50;0.75)	*-0.60 (-0.94;-0.25)*

Tremor and aging: A hypothesis on tremor in the elderly



Conclusion

Essential tremor

- Full penetrance is reached in families with ET at age 65
- Evidence for longevity in ET

Senile (age-related) tremor

- Epidemiologic evidence for an age-related tremor
- If tremor starts after the 6th decade (65?):
  - More frequent dementia
  - Shorter life span after tremor onset

ET is not a unique disease

- Senile tremor is probably the largest subgroup of „ET“
- Classical hereditary ET the 2nd largest
- Sporadic ET in children and adults < 65years the 3rd largest

Coworkers elsewhere:
Kaare Christensen (Odense)
Rodger Elble (Springfield)
Alfonso Fasano (Roma)
Mark Hallett (Bethesda)
Paul Krack (Grenoble)
Jens Volkmann (Würzburg)

Coworkers in Kiel:

Delia Lorenz
M. Muthuraman
Christine Daniels
Jan Raethjen
Frank Papengut
Kirsten Zeuner
Helge Hellriegel
Thilo v. Eimeren
Karina Knudsen
Stefan Klebe
Jens Volkmann
Caroline Poremba
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