PSYCHOGENIC NON-EPILEPTIC SEIZURES (PNES)

LUCIA FUSCO, MD, PhD
NEUROPHYSIOLOGY UNIT
NEUROSCIENCE DEPARTMENT
BAMBINO GESU' CHILDREN HOSPITAL
ROME, ITALY

LUMSA
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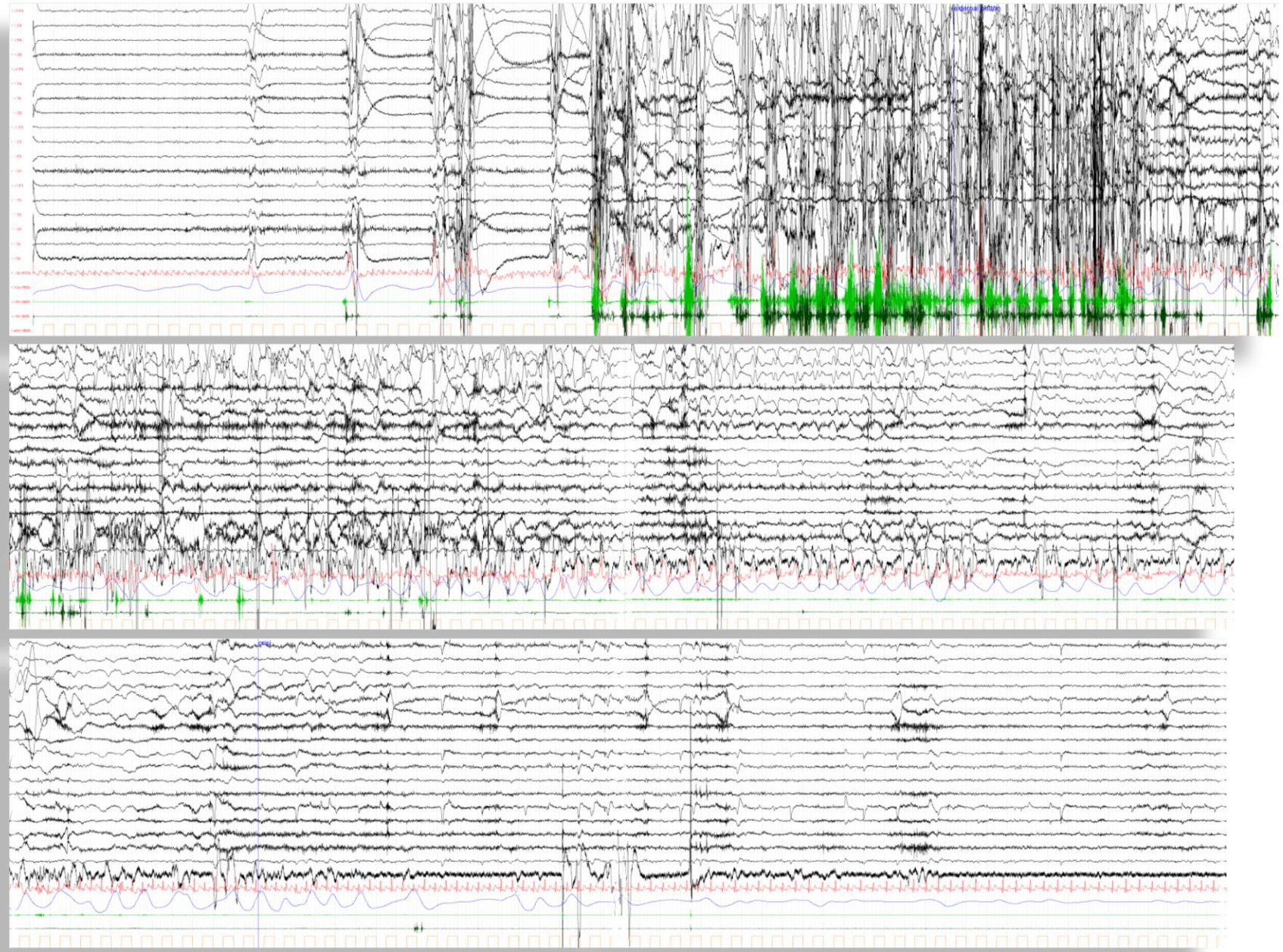
CLASSIFICAZIONE PNES

- PNES (Psychogenic non epileptic seizures)
  - PNES motorie generalizzate
    - convulsive (da lievi a severe)
    - propriospinali
  - PNES motorie focali
    - distali unilaterali o bilaterali
  - PNES solo perdita di coscienza (compreso il mancato risveglio)
  - PNES con fenomeni oculari

DIAGNOSI DIFFERENZIALE

- **Diagnosi differenziale tra**
  - **PNES**
  - **EPILESSIA**
- Tra le **PNES diagnosi differenziale** tra
  - DISTURBO DISSOCIATIVO
  - DISTURBO FITTIZIO
  - SIMULAZIONE

Crisi convulsiva psicogena, no modifiche EEG se non artefatti msucolari



Bambino Gesù
OSPEDALE PEDIATRICO

SPECIAL REPORT

Minimum requirements for the diagnosis of psychogenic nonepileptic seizures: A staged approach

A report from the International League Against Epilepsy Nonepileptic Seizures Task Force

*†W. Curt LaFrance Jr., ‡Gus A. Baker, §Rod Duncan, ¶Laura H. Goldstein, and #Markus Reuber

Epilepsia, 54(11):2005–2018, 2013
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Table 1. Summary of evidence that supports the signs used to distinguish between psychogenic nonepileptic seizures (PNES) and epileptic seizures (ES)*

Signs that favor PNES	Evidence from primary studies	Sensitivity (%) for PNES	Specificity (%) for PNES
Long duration	Good	–	–
Fluctuating course	Good	69 (events)	96
Asynchronous movements	Good (frontal lobe partial seizures excluded)	47–88 (patients)	96–100
		44–96 (events)	93–96
		9–56 (patients)	93–100
Pelvic thrusting	Good (frontal lobe partial seizures excluded)	1–31 (events)	96–100
		7.4–44 (patients)	92–100
Side to side head or body movement	Good (convulsive events only)	25–63 (events)	96–100
		15–36 (patients)	92–100
Closed eyes	Good	34–88 (events)	74–100
		52–96 (patients)	97
Ictal crying	Good	13–14 (events)	100
		3.7–37 (patients)	100
Memory recall	Good	63 (events)	96
		77–88 (patients)	90
Signs that favor ES	**Evidence from primary studies**	**Sensitivity for ES**	**Specificity for ES**
Occurrence from EEG-confirmed sleep	Good	31–59 (events)	100
		–	–
Postictal confusion	Good	61–100 (events)	88
		67 (patients)	84
Stertorous breathing	Good (convulsive events only)	61–91 (events)	100
		–	–
Other signs	**Evidence from primary studies**		
Gradual onset	Insufficient		
Nonstereotyped events	Insufficient		
Flailing or thrashing movements	Insufficient		
Opisthotonus "arc en cercle"	Insufficient		
Tongue biting	Insufficient		
Urinary incontinence	Insufficient		

The sensitivity and specificity values were calculated from the frequencies of clinical signs in PNES and ES.
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Table 2. Overview of proposed diagnostic levels of certainty for psychogenic nonepileptic seizures

	History	Witnessed event	EEG
Diagnostic Level			
Possible	+	By witness or self-report/description	No epileptiform activity in routine or sleep-deprived *interictal* EEG
Probable	+	By clinician who reviewed video recording or in person, showing semiology typical of PNES	No epileptiform activity in routine or sleep-deprived *interictal* EEG
Clinically established	+	By clinician experienced in diagnosis of seizure disorders (on video or in person), showing semiology typical of PNES, while not on EEG	No epileptiform activity in routine or ambulatory *ictal* EEG during a typical ictus/event in which the semiology would make ictal epileptiform EEG activity expectable during equivalent epileptic seizures
Documented	+	By clinician experienced in diagnosis of seizure disorders, showing semiology typical of PNES, while on video EEG	No epileptiform activity immediately before, during or after ictus captured on *ictal* video EEG with typical PNES semiology

Key: +, history characteristics consistent with PNES; EEG, electroencephalography (as noted in the text, additional tests may affect the certainty of the diagnosis—for instance, self-protective maneuvers or forced eye closure during unresponsiveness or normal postictal prolactin levels with convulsive seizures).

Psychogenic nonepileptic vs convulsive epileptic sz

"Convulsive" Nonepileptic Seizures Have a Characteristic Pattern of Rhythmic Artifact Distinguishing Them from Convulsive Epileptic Seizures *Epilepsia*, **45**(11):1344–1350, 2004

*†‡Anita Vinton, *John Carino, §Simon Vogrin, ‖Lachlan MacGregor, *†Christine Kilpatrick, *Zelko Matkovic, and *†Terence J. O'Brien

- La diagnosi di PNES in genere richiede una VideoEEEG Monitoring (VEM)
- Elementi in diagnosi differenziale
  - Frequenza cardiaca stabile
  - Occhi chiusi verso occhi aperti
  - Movimenti pelvici
  - Movimenti latero-laterali del capo tipo ''no-no''
  - Movimenti ritmici i cui artefatti possono simulare il punta-onda
  - La evoluzione della frequenza dei movimenti è differente nelle PNES e nelle crisi epilettiche

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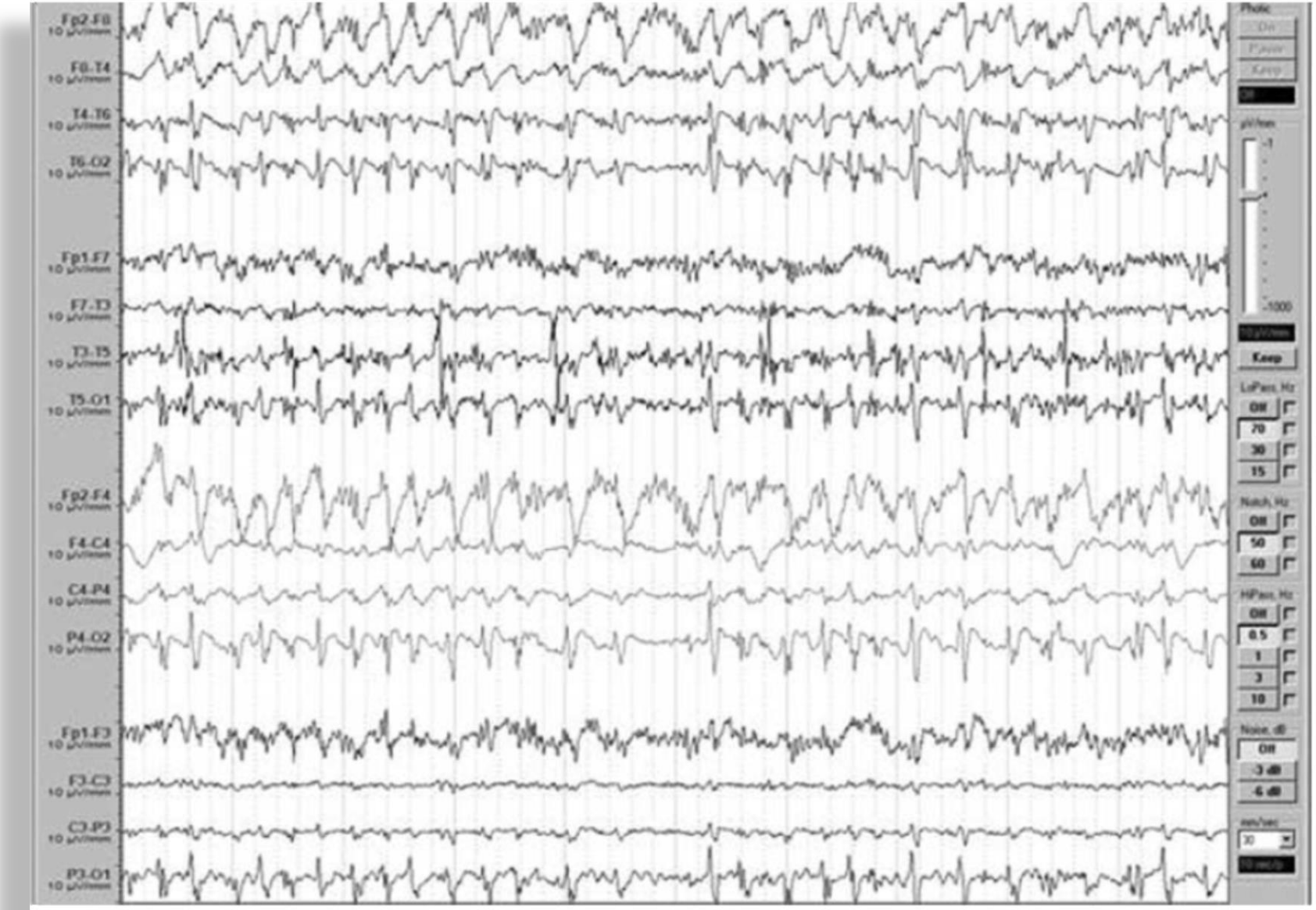

FIG. 1. Segment of an EEG during a psychogenic nonepileptic seizure, with rhythmic movement artifact resembling spike–wave dis-

"Convulsive" Nonepileptic Seizures Have a Characteristic Pattern of Rhythmic Artifact Distinguishing Them from Convulsive Epileptic Seizures

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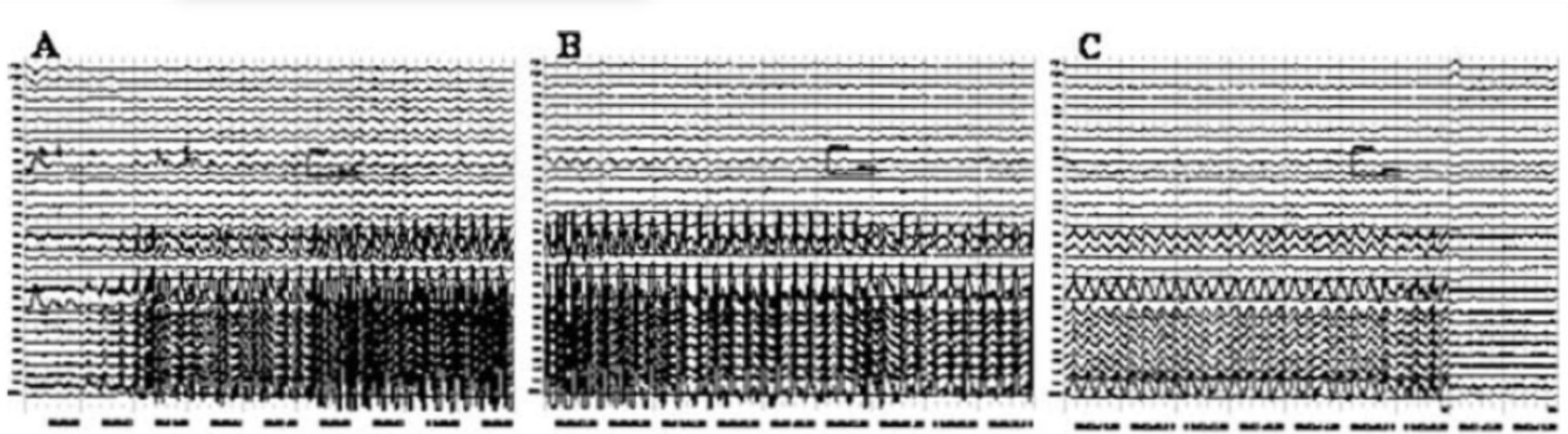
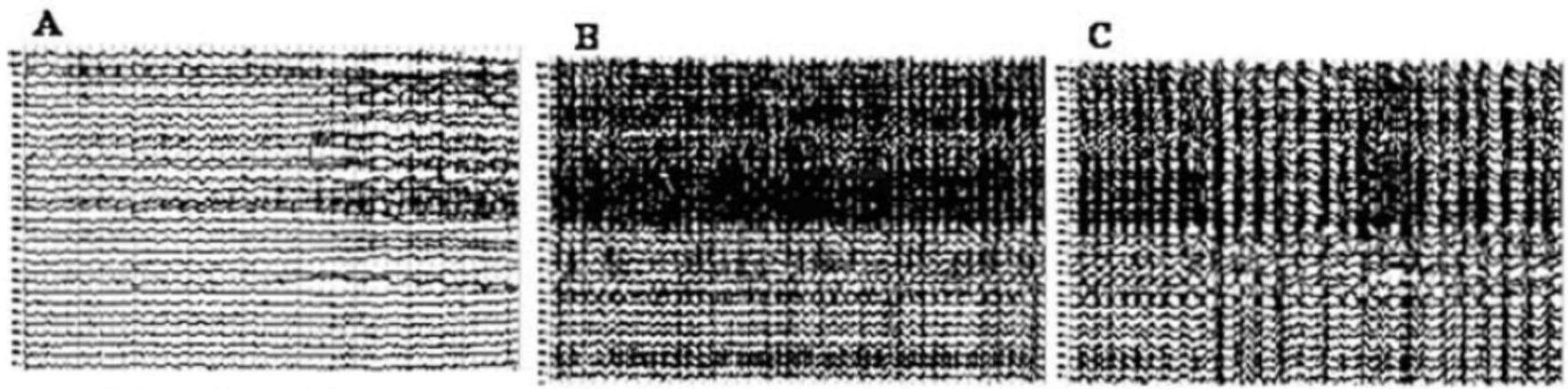


Non Epileptic Seizure



Epileptic Seizure

Time-frequency mapping of the rhythmic limb movements distinguishes convulsive epileptic from psychogenic nonepileptic seizures

*Jade Bayly, *John Carino, †Slavé Petrovski, *Michelle Smit, *†Dilini A. Fernando, *†Anita Vinton, *†Bernard Yan, ‡Jayavardhana R. Gubbi, ‡Marimuthu S. Palaniswami, and *†Terence J. O'Brien

Methods: Time-frequency mapping was performed on accelerometer traces obtained during 56 convulsive seizure-like events from 35 patients recorded during in-patient video-EEG monitoring. Twenty-six patients had PNES, eight had epileptic seizures, and one had both seizure types. The time-frequency maps were derived from fast Fourier transformations to determine the dominant frequency for sequential 2.56-s blocks for the course of each event.

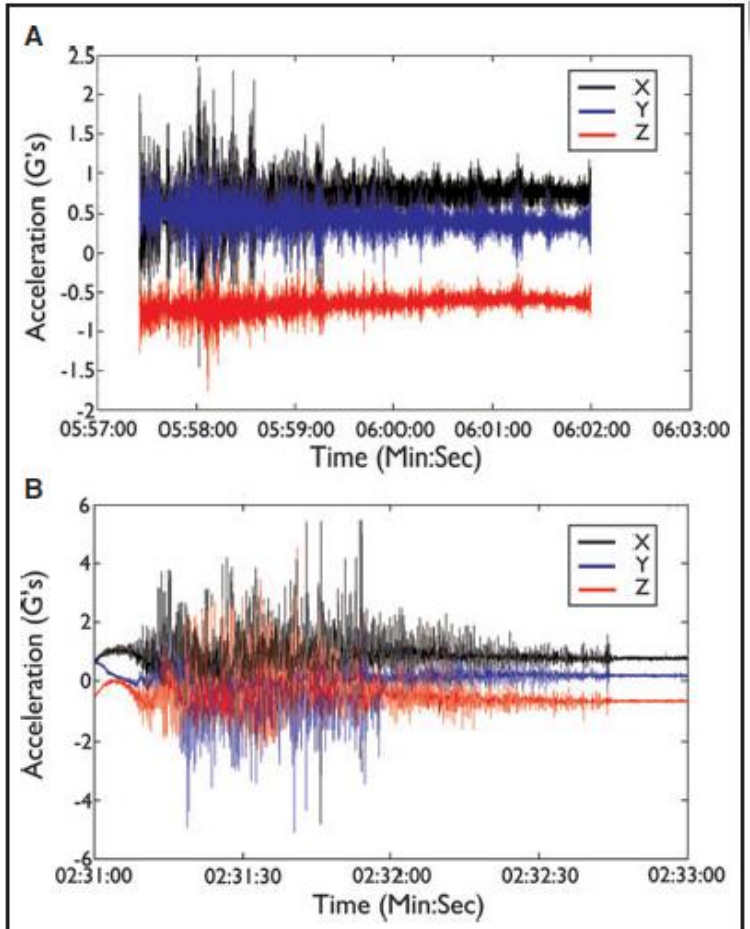
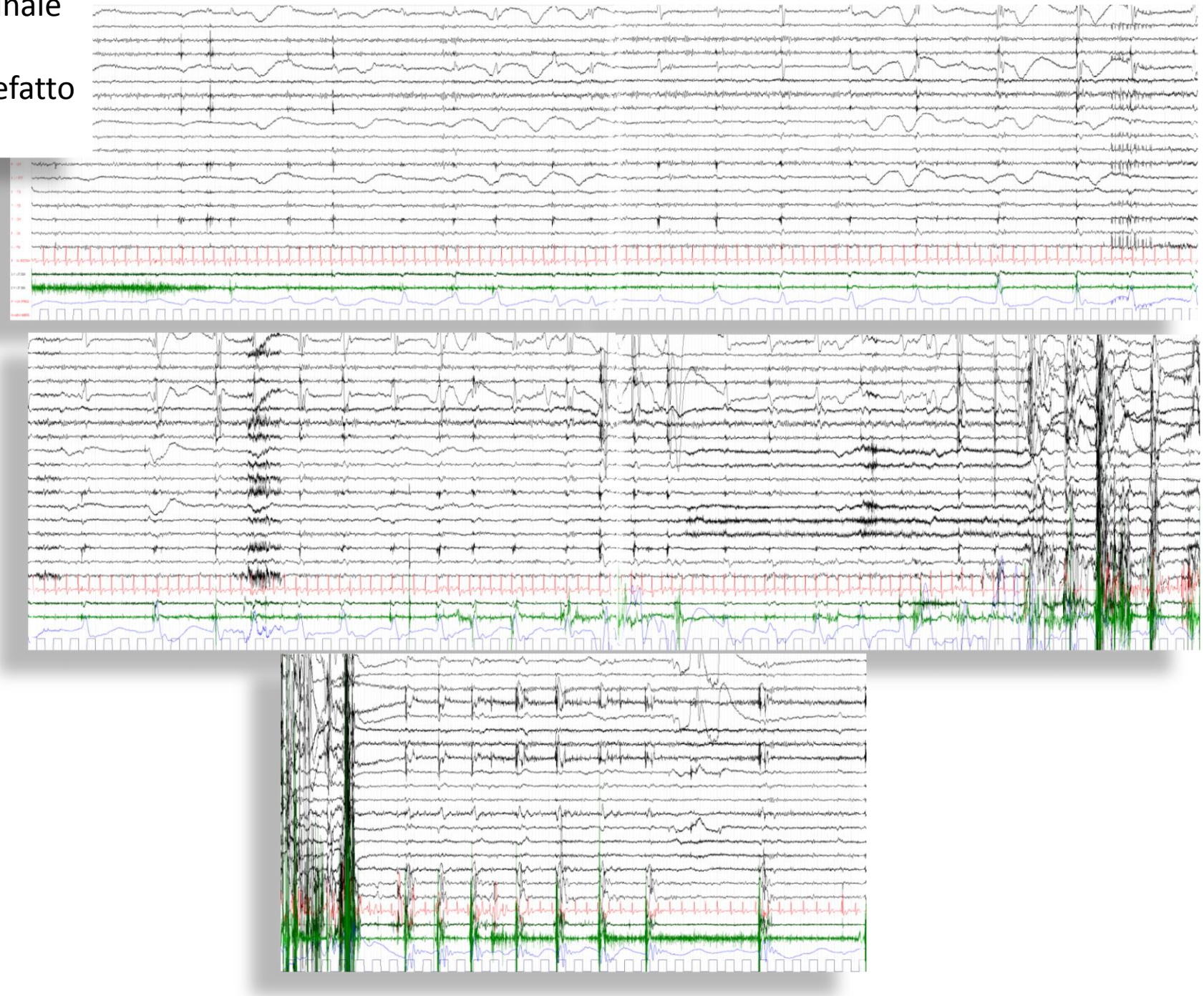


Figure 1.
Raw recordings along X (black), Y (blue), and Z axes (red from accelerometer traces were identified and "blocked"— nonepileptic (A) and epileptic (B)

Key Findings: The coefficient of variation (CoV) of limb movement frequency for the PNES events was less than for the epileptic seizure events (median, 17.18% vs. 52.23%; $p < 0.001$). A blinded review of the time-frequency maps by an epileptologist was accurate in differentiating between the event types, that is, 38 (92.7%) of 41 and 6 (75%) of 8 nonepileptic and epileptic seizures, respectively, were diagnosed correctly, with seven events classified as "nondiagnostic." Using a CoV cutoff score of 32% resulted in similar classification accuracy, with 42 (93%) of 45 PNES and 10 (91%) of 11 epileptic seizure events correctly diagnosed.

Significance: Time-frequency analysis of data from a wristband movement monitor could be utilized as a diagnostic tool to differentiate between epileptic and nonepileptic convulsive seizure-like events.

Mioclono prospinale
No modifiche
EEG se non l'artefatto del movimento



Mioclono propriospinale

- Disturbo del movimento ipercinetico
- Jerks assiali non ritmiche, ripetitive, in genere in flessione, del tronco, delle anche e delle ginocchia
- Descritto nel 1991 da Brown come mioclono da generatore spinale, recentemente considerato funzionale o psicogeno

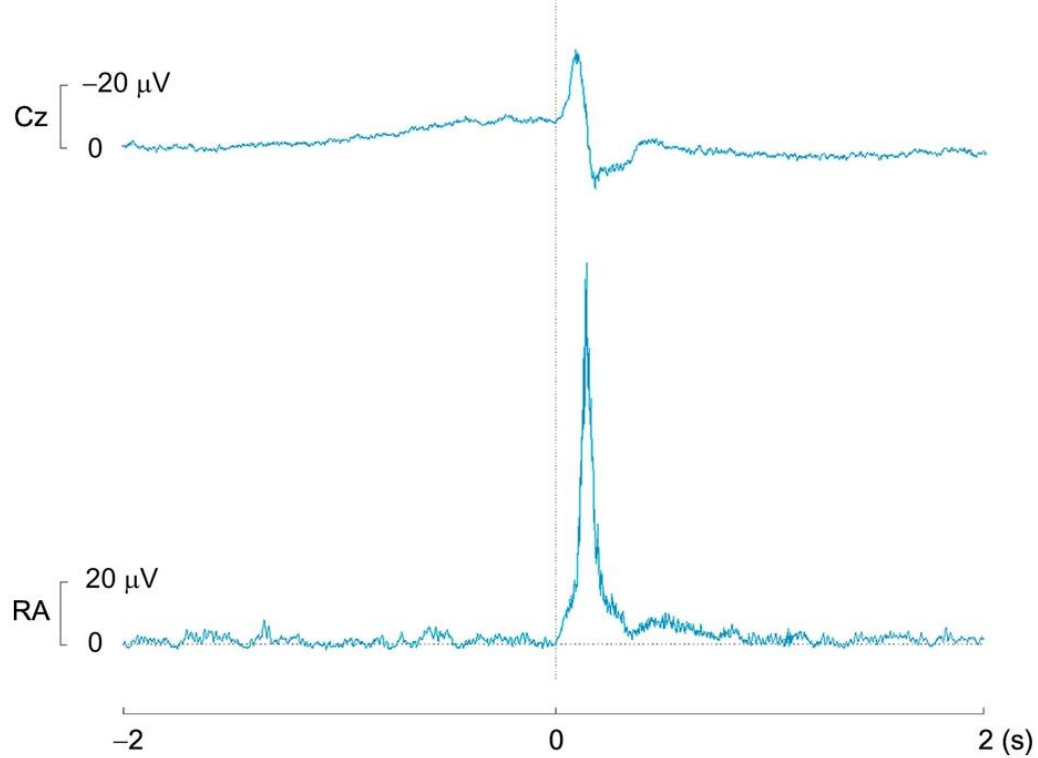
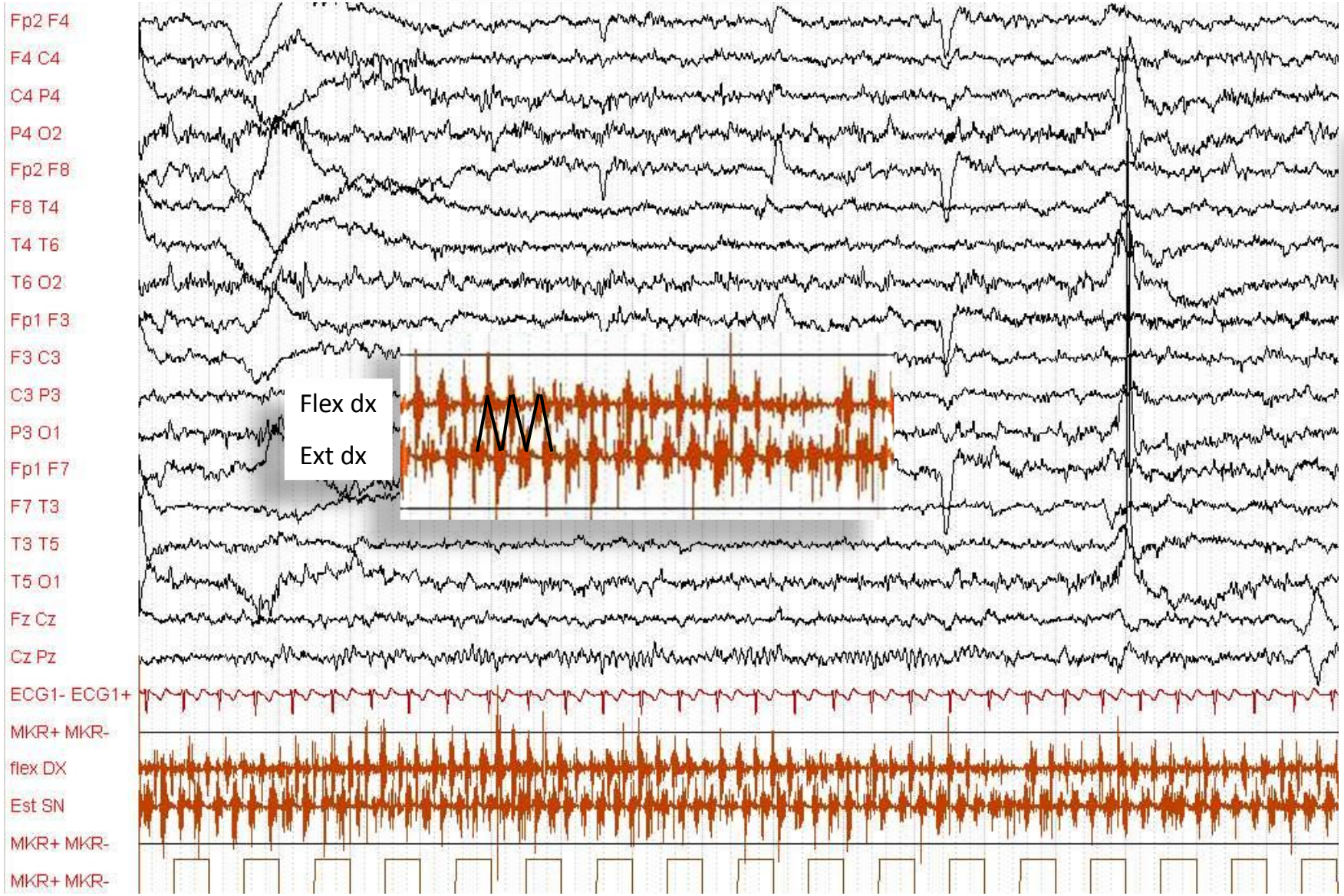


FIG. 21.1 Example of Bereitschaftspotential (BP) recording of a patient with axial jerks. The electromyogram was triggered at the onset of the rectus abdominis (RA) muscle. A premovement potential (BP) is seen starting about 1500 ms prior to the jerk,

Neurophysiologic test	Characteristics	In support of
Surface EMG	Burst duration < 75 ms	Cortical myoclonus
	Burst duration > 75 ms	Tic, subcortical myoclonus, functional jerk
Polymyography	Inconsistent recruitment pattern, entrainment, distractibility	Functional jerk
Startle reflex	Inconsistent recruitment pattern, long-onset latencies (> 100 ms)	Functional jerk
C-reflex	Long-loop reflex with latency of 40–45 ms	Cortical or subcortical reflex myoclonus
EEG-EMG with backaveraging	Cortical spike (latency 10–40 ms)	Cortical myoclonus
	Bereitschaftspotential (latency 1000–2000 ms)	Functional jerk*
EEG-EMG coherence analysis	Significant coherence between EEG and EMG	Cortical myoclonus
SSEP	Giant SSEP	Cortical myoclonus

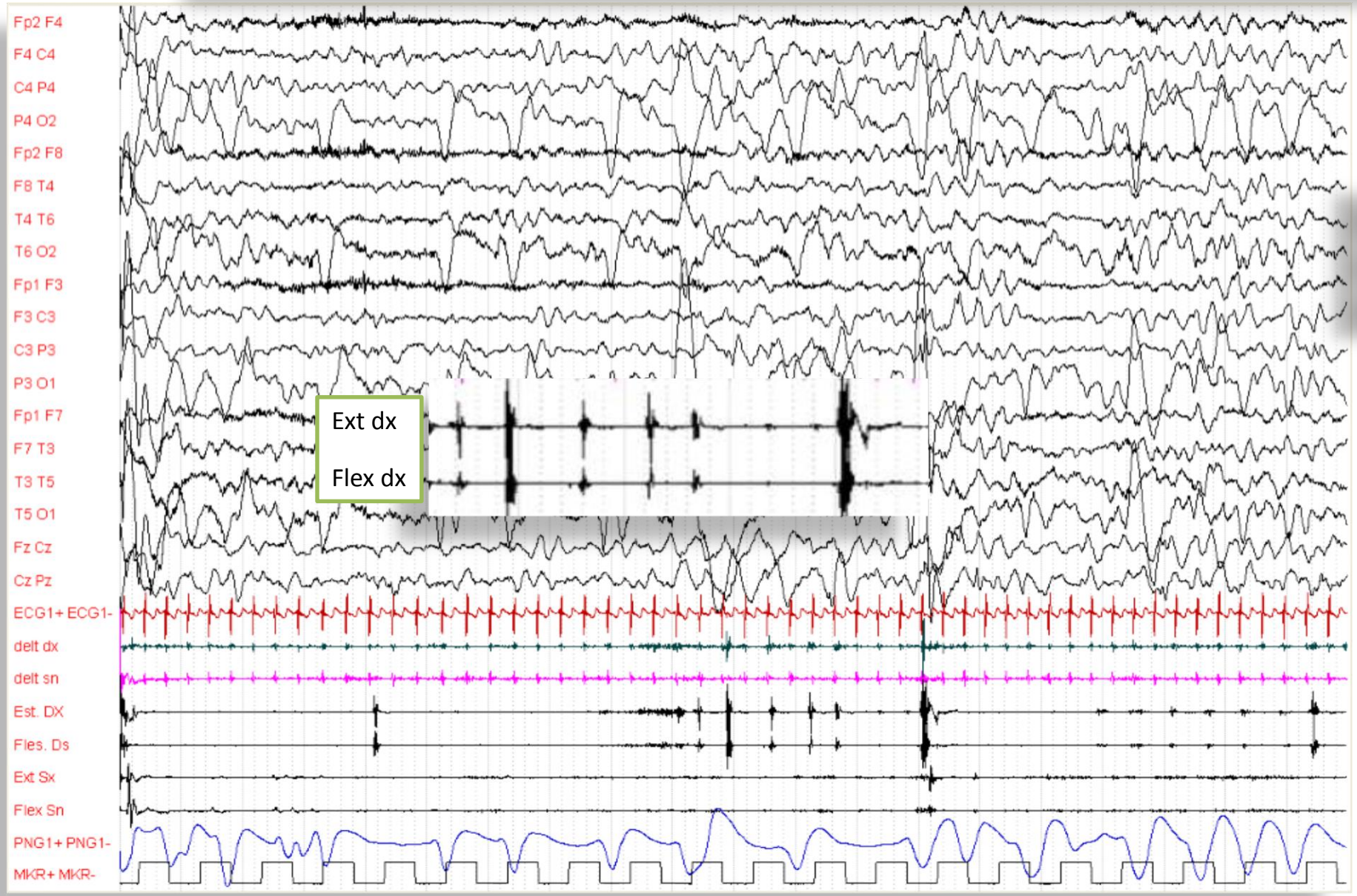
EMG, electromyogram; EEG, electroencephalogram; SSEP, somatosensory evoked potential.

TREMORE QUALE MANIFESTAZIONE PSICOGENA



Tremor:
Triangular contraction of agonist/antagonist muscles

NEUROFISIOLOGIA DEL MIOCLONO CHE PUO' ESSERE MANIFESTAZIONE PSICOGENA



Myoclonus:
co-contraction
agonist/antagonist muscles

TREMORE FUNZIONALE (PSICOGENO)

- Presentazione più comune dei disturbi del movimento funzionali, circa il 50%
  - Esordio improviso
  - Variabilità nel severità del disturbo con remissioni spontanee
  - Variabilità della parte del corpo affetta
  - Molti pazienti hanno un tremore che è presente a riposo, nel mantenimento di posture, e durante l'azione che è inusuale per un tremore organico
  - Tremore funzionale cambia con il livello di attenzione
  - Peggiora durante l'esame neurologico

TREMORE FUNZIONALE (PSICOGENO)

- Tremore funzionale
  - Specifiche manovre durante l'esame possono essere usate per distrarre l'attenzione sul tremore
  - Tapping con l'arto controlaterale a una frequenza differente modifica la frequenza del tremore, questa manovra ha una alta sensitività (73%) e alta specificità (74%)
  - Il tremore si ferma con movimenti ballistici dell'arto controlaterale
  - Paradossalmente peggiora con il carico

MIOCLONO FUNZIONALE (PSICOGENO)

- Il mioclono funzionale rappresenta il 20% dei disturbi funzionali del movimento
  - Manovre di distraibilità (distrattori) utili nell'inibire il mioclono funzionale (tapping arto controlaterale)
  - Burst all'EMG <75 msec non si verificano nel disturbo funzionale
  - Non vero il contrario: burst anche più lunghe possono essere organiche (mioclono spinale circa 200 msec)
  - Potenziale corticale gigante somatosensoriale, punta all'EEG 20 msec prima delle jerks, non si trovano nel mioclono funzionale

MIOCLONO FUNZIONALE (PSICOGENO)

- Mioclono funzionale
  - Il test diagnostico più utile è il EEG/EMG back-averaging che valuta la presenza di un potenziale corticale immediatamente prima del movimento
  - Nelle persone sane, così come nel mioclono funzionale, 1,5 sec prima del movimento si vede sull'EEG un potenziale lento in salita che raggiunge l'acme all'inizio del movimento: questo potenziale pre-movimento è il Bereitschafts-potential

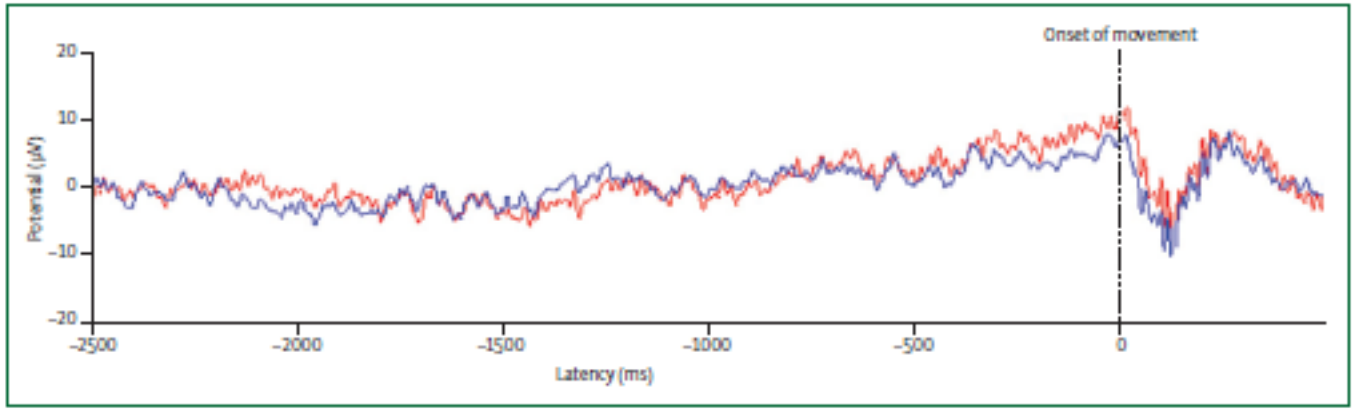
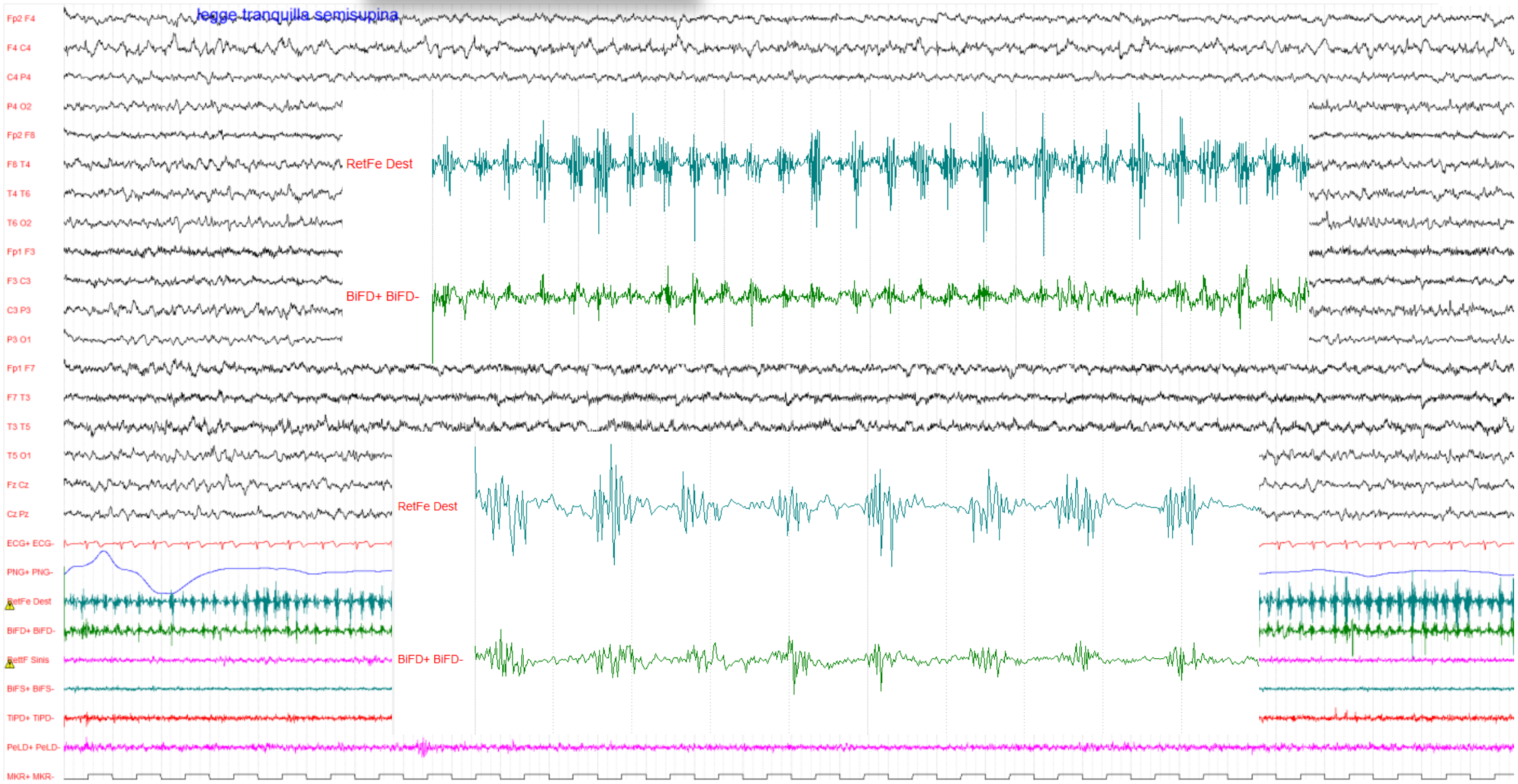
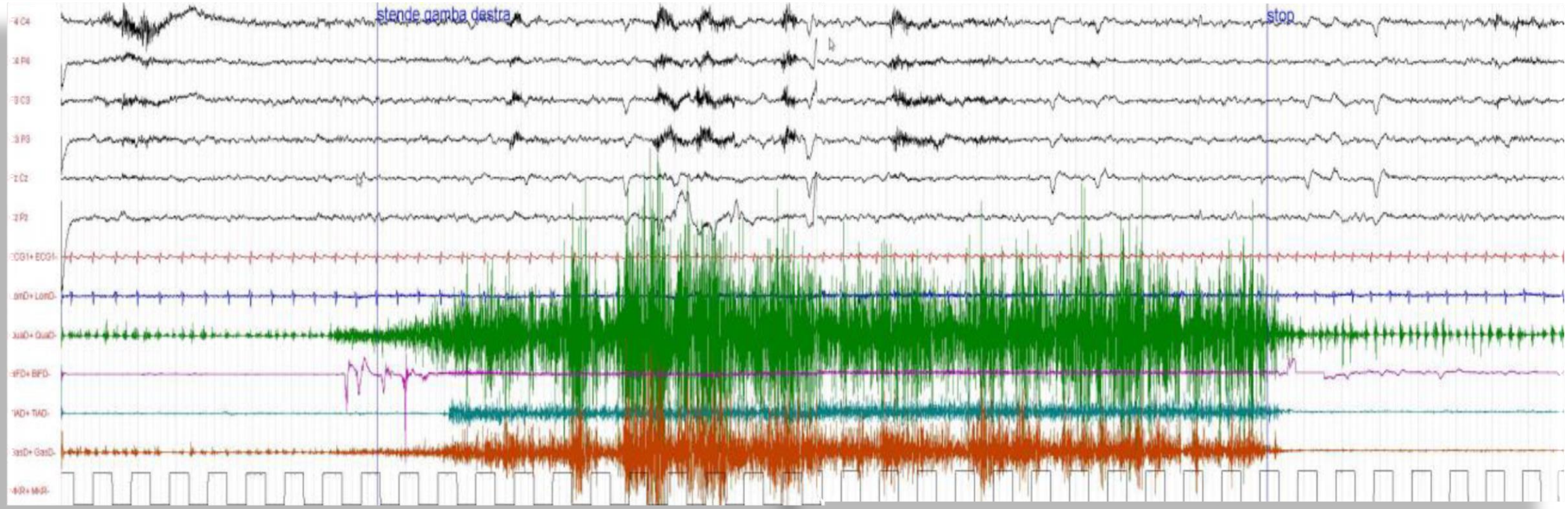


Figure 2: **Electroencephalogram recordings from a patient with functional myoclonus**
A slow rising potential can be seen, which starts around 1 s before movement.

MIOCLONO PSICOGENO

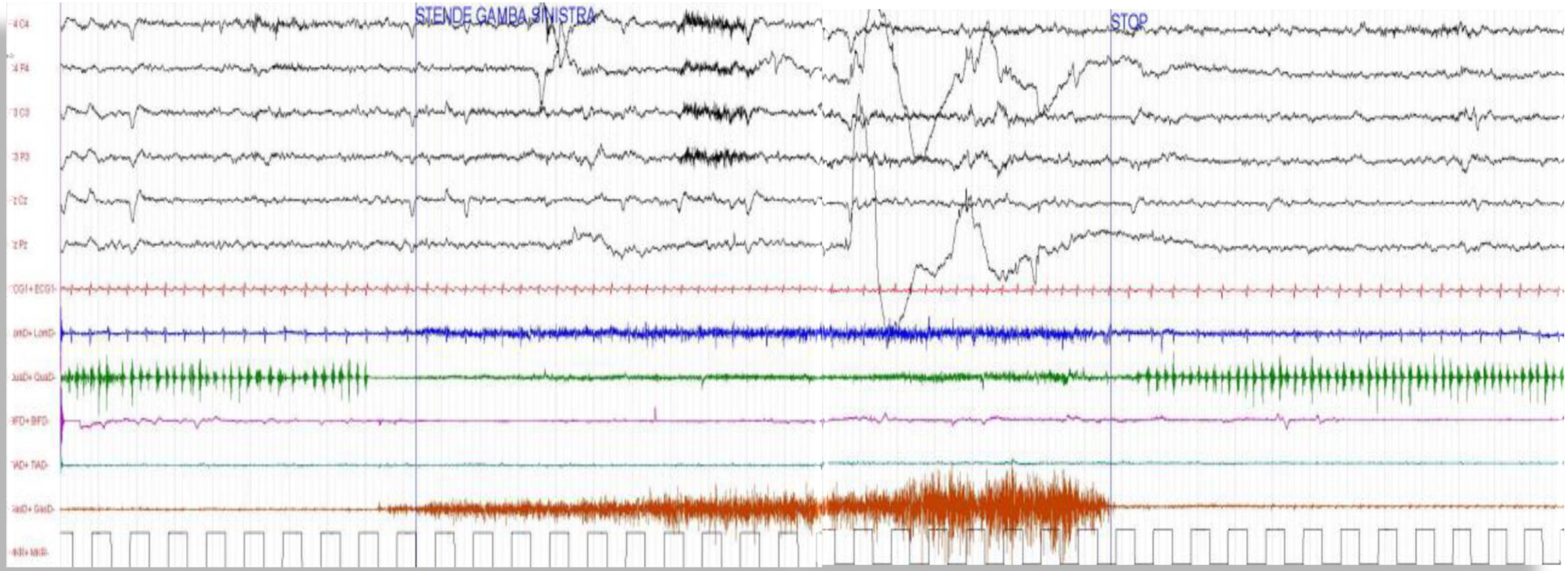


PROVE DI INTERFERENZA SUL MIOLCONO PSICOGENO, CHE ABOLISCONO IL MIOCLONO



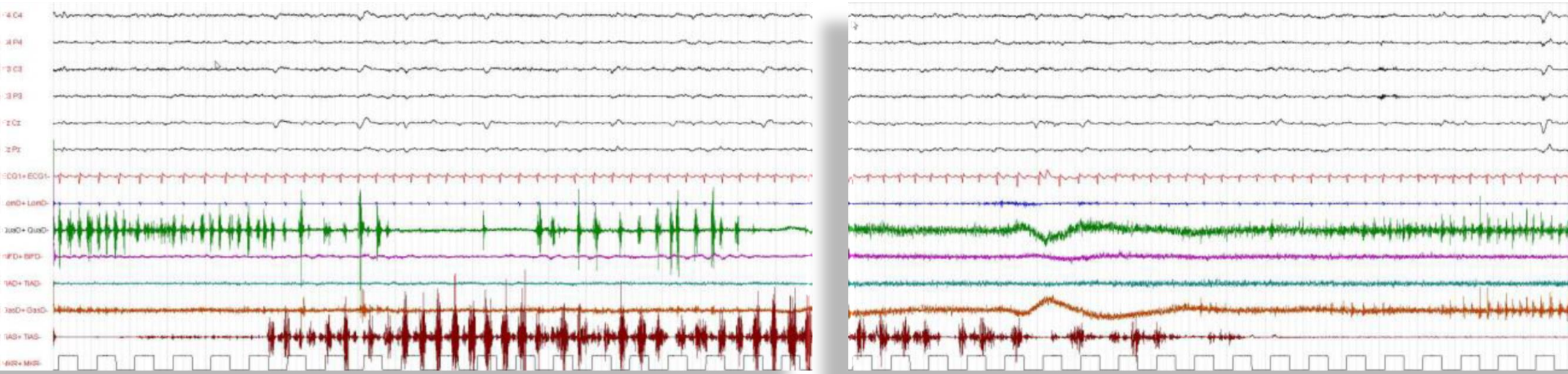
Evidenza del fenomeno mioclonico a riposo a carico dei muscoli quadricipite e gastrocnemio di destra, la contrazione volontaria dell'arto inferiore di destra determina la scomparsa del fenomeno
e la sua rapida ricomparsa alla fine della contrazione.

PROVE DI INTERFERENZA SUL MIOLCONO PSICOGENO, CHE ABOLISCONO IL MIOCLONO



La contrazione volontaria dell'arto inferiore controlaterale
al fenomeno (non documentato in poligrafia) determina la scomparsa
del fenomeno e la rapida ricomparsa alla fine della prova

PROVE DI INTERFERENZA SUL MIOLCONO PSICOGENO, CHE ABOLISCONO IL MIOCLONO

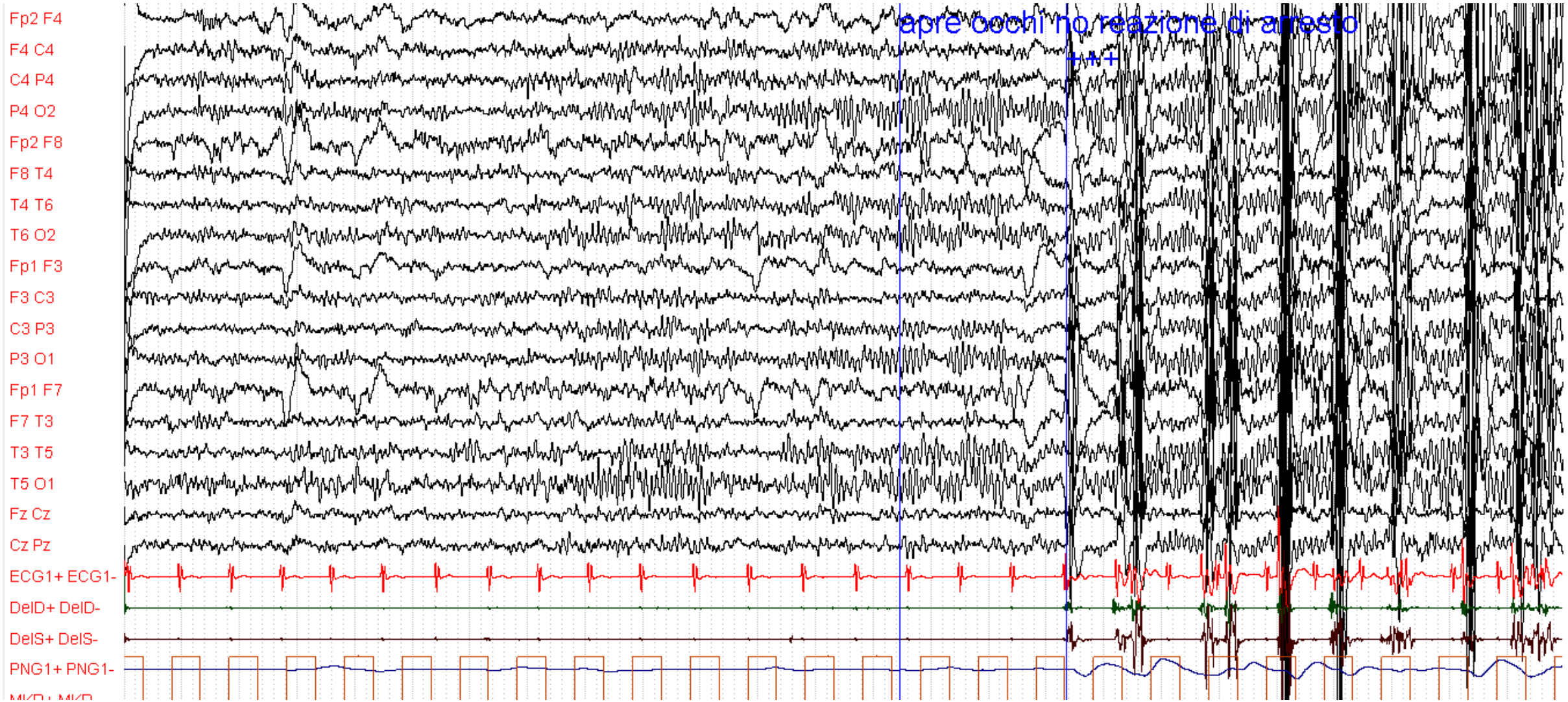


La contrazione volontaria fasica del muscolo tibiale anteriore controlaterale (flette e estende il piede di sinistra) determina dapprima la perdita della ritmicità del movimento a destra e poi la sua completa scomparsa.
Il movimento riappare poi alla fine della prova con la usuale ritmicità e frequenza

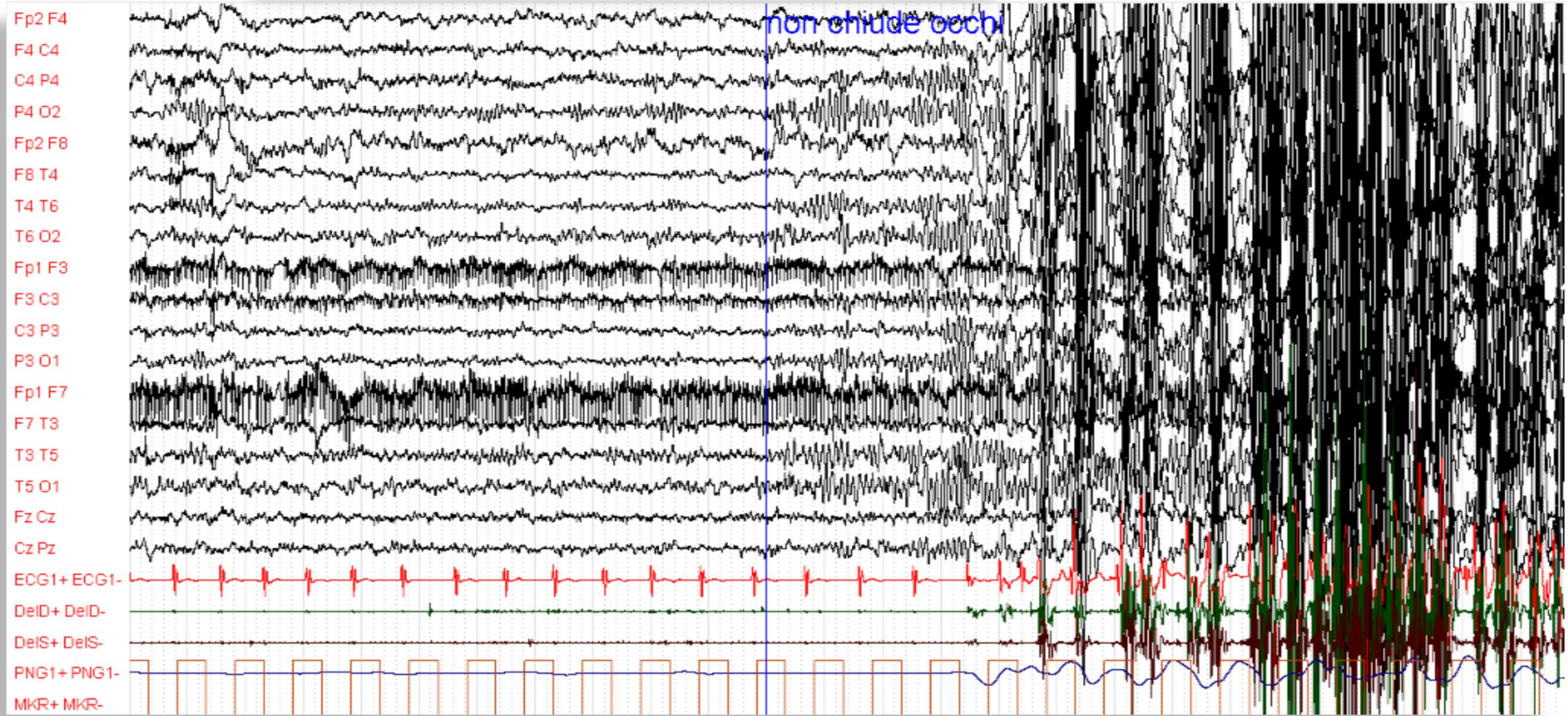
DIAGNOSI DIFFERENZIALE TRA PNES E EPILESSIA

- Diagnosi differenziale tra
  - PNES
  - EPILESSIA
- **Tra le PNES diagnosi differenziale tra**
  - **DISTURBO DISSOCIATIVO**
  - **DISTURBO FITTIZIO**
  - **SIMULAZIONE**

Persistenza dell'alfa posteriore alla chiusura degli occhi
Alfa paradosso in stato dissociativo



Comparsa di attività afa posteriore senza chiudere gli occhi
Stato dissociativo



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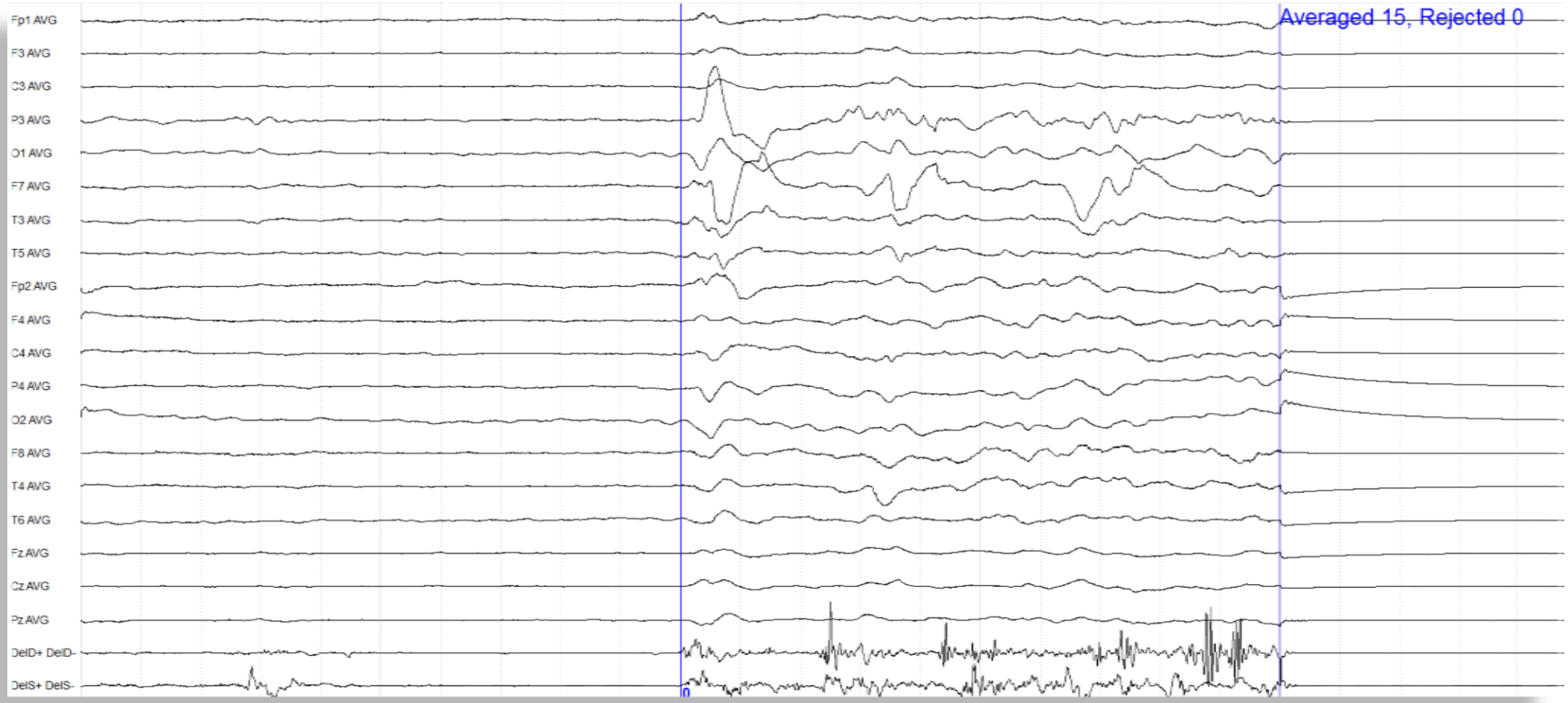
Assenza del Bereishaft potential che indica
Contrazione muscolare volontaria



le contrazioni EMG sui Deltoidi «0» NON sono anticipate da una ampia deflessione sulle regioni del vertice

La ILAE ha identificato le **Psychogenic Non Epileptic Seizures** (**PNES**) come una delle dieci condizioni neuropsichiatriche chiave, associate a epilessia

Epilepsia, 52(11):2133–2138, 2011
doi: 10.1111/j.1528-1167.2011.03276.x

SPECIAL REPORT

International consensus clinical practice statements for the treatment of neuropsychiatric conditions associated with epilepsy

*Mike P. Kerr, †Seth Mensah, ‡Frank Besag, §Bertrand de Toffol, ¶Alan Ettinger, #Kousuke Kanemoto, **Andres Kanner, ††Steven Kemp, ‡‡Ennapadum Krishnamoorthy, §§W. Curt LaFrance Jr, ¶¶Marco Mula, ##Bettina Schmitz, ***Ludgers Tebartz van Elst, †††Julian Trollor, and ‡‡‡Sarah J. Wilson

10 key neuropsychiatric issues associated with epilepsy

- Depressive disorders in Epilepsy
- Anxiety disorders in Epilepsy
- Psychoses in Epilepsy
- Non-epileptic seizures (NES) and imitators of epilepsy in Epilepsy
- Cognitive dysfunction in Epilepsy
- AED-related neurobehavioral disturbance in Epilepsy
- Suicidality in Epilepsy
- Psychiatric disorders in children and adolescents in Epilepsy
- Psychiatric disorders in children with intellectual disabilities and Epilepsy
- Epilepsy surgery-related psychiatric issues

Importanza della diagnosi di crisi psicogene

- Il trattamento di un paziente con PNES inizia con una accurata diagnosi
- La mancata diagnosi di PNES e la presunta diagnosi di epilessia porta a un inappropriato trattamento, con un rischio significativo di danno iatrogeno, morbilità, e costi per il paziente per il sistema sanitario nazionale.
- Studi hanno dimostrato che la mancata diagnosi si verifica per una non corretta interpetrazione della storia o per una non corretta interpetrazione dell'EEG

CRISI PSICOGENE E DISTURBO DEL MOVIMENTO

- Confini a volte difficili da definire
- Importanza della diagnosi differenziale tra crisi psicogena, disturbo del movimento e epilessia
- Epilessia (raramente anche crisi psicogene) e disturbo del movimento possono coesistere come effetto di una stessa causa rendendo la diagnosi delle tre manifestazioni molto complessa

Glossario dei disturbi del movimento (1)

- **Tremore:** movimento involontario ritmico oscillatorio intorno a un asse articolare
  - Tremore di azione: ogni tremore prodotto da contrazione volontaria di un muscolo, posturale, isometrico, o cinetico (intenzionale)
  - Tremore distonico: oscillazione spontanea, ritmica (sebbene non costante), prodotta da contrazione di muscoli distonici esacerbata nel tentativo di mantenere una postura
  - Tremore a riposo: definito come un tremore in una parte del corpo che non è attivata volontariamente
- **Atetosi**:
  - è un movimento involontario, lento, continuo, di contorsione, che impedisce il mantenimento di una postura stabile

Glossario dei disturbi del movimento (2)

- **Ballismo:**
  - movimento involontario di grande ampiezza, ripetitivo ma di di entità variabile, della parte prossimale degli arti
- **Corea:**
  - stato di movimenti involontari, non ripetitivi, irregolari, casualmente distribuiti e improvvisi.
- **Distonia:**
  - disturbo del movimento caratterizzato da contrazione muscolare sostenuta o intermittente che causa posture anomale o movimenti anomali spesso ripetitivi
- **Mioclono:**
  - è una sequenza di scosse, ripetute, non ritmiche, brevi, shock like, dovute a una contrazione involontaria positiva (mioclono positivo) o a un perdita di tono rilassamento (mioclono negativo) di uno o più muscoli

Glossario dei disturbi del movimento (3)

- **Tics:**
  - movimenti ripetuti ma intermittenti o frammenti di movimenti che possono essere sempre soppressi dalla volontà sono usualmente associati a una «urgenza» a fare il detto movimento (compulsione)
- **Stereotipie:**
  - movimenti non finalistici , ripetuti continuamente per un certo periodo di tempo nella stessa forma in multiple occasioni e in genere a risoluzione con la distraibilità
- **Miorritmie:**
  - Movimenti «jerky» ripetitivi, ritmici, frequenti a lenta frequenza (1-4 Hz) primariamente coinvolgenti i muscoli assiali e gli arti. Si manifestano a riposo o nel mantenimento di una postura, scompaiono con il sonno.
- **Acatisia:**
  - si riferisce a una sensazione soggettiva di incapacità a stare fermi, e quindi a movimenti che sono fatti appositamente per ridurre questa sensazione.
- **Miokimia:**
  - contrazioni muscolari non ritmiche, di burts di unità motorie irregolari, che si verificano in diplette o triplette largo range di frequenza (da 5 a 150 Hz) (palpebre, muscoli facciali)

Glossario dei disturbi del movimento (4)

- **Opsoclono:** definito come la intrusione nella fissazione di saccadi coniugati oculari ripetitivi, rapidi, involontari, che sono coniugati irregolari per ampiezza e frequenza e in tutte le direzioni di sguardo
- **Bradikinesia akinesia:** lentezza nei movimenti diminuzione dell'ampiezza del movimento
- **Catatonia:**
  - mantenimento di una postura contro gravità, passivamente indotta
  - No attività psicomotoria
  - Agitazione non influenzabile dall'esterno
  - Mutismo
  - Posturing: assunzione volontaria di alcune posture contro gravità
  - Stereotipie motorie

Glucose 1 transporter deficiency

- Autosomal dominant condition due to mutation in the glucose transporter
- Low CSF glucose content and low CSF glucose to serum glucose ratio (<0.5)
- Seizures onset in the first year of life
  - atypical absences
  - infantile spasms
  - in older children convulsive seizures
- Absences persist in childhood
- Other neurological phenotype
  - ataxia
  - Excercise-induced diskynesia
  - Intellectual disability

Movement Disorders
CLINICAL PRACTICE
CASE SERIES

Paroxysmal Nonepileptic Events in Glut1 Deficiency

Joerg Klepper, Dr med,[1,] Baerbel Leiendecker,[2] Christin Eltze, MD,[3] Nicole Heussinger, Dr med[1]*

Abstract: Movement disorders are a major feature of Glut1 deficiency. As recently identified in adults with paroxysmal exercise-induced dystonia, similar events were reported in pediatric Glut1 deficiency. In a case series, parent videos of regular motor state and paroxysmal events were requested from children with Glut1 deficiency on clinical follow-up. A questionnaire was sent out to 60 families. Videos of nonparoxysmal/paroxysmal states in 3 children illustrated the ataxic-dystonic, choreatiform, and dyskinetic-dystonic nature of paroxysmal events. Fifty-six evaluated questionnaires confirmed this observation in 73% of patients. Events appeared to increase with age, were triggered by low ketosis, sleep deprivation, and physical exercise, and unrelated to sex, hypoglycorrhachia, SLC2A1 mutations, or type of ketogenic diet. We conclude that paroxysmal events are a major clinical feature in Glut1 deficieny, linking the pediatric disease to adult Glut1D-associated exercise-induced paroxysmal dyskinesias.

Paroxysmal eye–head movements in Glut1 deficiency syndrome

OPEN

Toni S. Pearson, MD*
Roser Pons, MD*
Kristin Engelstad, MS
Steven A. Kane, MD, PhD
Michael E. Goldberg, MD
Darryl C. De Vivo, MD

Bambino Gesù
OSPEDALE PEDIATRICO

Table 1 Clinical characteristics of 18 patients with paroxysmal eye-head movements

Patient	Sex	First symptom	Onset of eye movements, age, mo	Onset of seizures, age, mo	Age at diagnosis, mo	CSF glucose, mg/dL	CSF:serum glucose ratio	RBC 3-OMG uptake, %	*SLC2A1* mutation type	Clinical severity[a]
1	M	Eye movements	1	3	86	24	0.30	70	Missense	Moderate
2	F	Eye movements	3	15	27	28	0.35	66	Missense	Mild
3	M	Eye movements	4	—	78	34	0.39	43	Missense	Mild
4	F	Eye movements	3	7	8	27	0.34	45	Frameshift	Mild
5	F	Eye movements	2	3.5	3.5	27	0.33	43	Missense	Severe
6	F	Eye movements + seizures	3	3	26	32	0.43	59	Insertion	Moderate
7	M	Eye movements	2	—	90	35	0.40	45	Insertion	Moderate
8	M	Eye movements	6	9	45	36	0.49	59	Missense	Mild
9	F	Seizure	1.5	0.5	77	37	—	—	Frameshift	Moderate
10	M	Eye movements	<1	8	120	—	—	52	Missense	Moderate
11	M	Eye movements	6	13	19	—	—	38	Splice site	—
12	M	Eye movements	3	24	96	30	0.37	50	Missense	Severe
13	F	Eye movements	2	18	95	32	—	—	—	—
14	F	Eye movements + seizures	5	5	16	26	0.30	40	Frameshift	Moderate
15	M	Seizure	1.5	1	94	37	0.38	51	Missense	Moderate
16	M	Seizure	8	4	30	31	—	—	Deletion	Moderate
17	F	Eye movements + seizures	<1	<1	30	29	0.36	56	Frameshift	Moderate
18	F	Eye movements	3	18	41	33	0.38	59	Splice site	Severe

Abbreviation: RBC 3-OMG = red blood cell 3-O-methyl-glucose.
[a] Clinical severity rating based on Columbia Neurologic Score.[9]

Epilepsy and outcome in *FOXG1*-related disorders

Laurie E. Seltzer, Mandy Ma, Sohnee Ahmed, Mary Bertrand, William B. Dobyns, James Wheless, Alex R. Paciorkowski

Objective: *FOXG1*-related disorders are associated with severe intellectual disability, absent speech with autistic features, and epilepsy. Children with deletions or intragenic mutations of *FOXG1* also have postnatal microcephaly, morphologic abnormalities of the corpus callosum, and choreiform movements. Duplications of 14q12 often present with infantile spasms, and have subsequent intellectual disability with autistic features. Long term epilepsy outcome and response to treatment has not been studied systematically in a well-described cohort of subjects with *FOXG1*-related disorders. We report on the epilepsy features and developmental outcome of 23 new subjects with deletions or intragenic mutations of *FOXG1*, and 7 subjects with duplications.

Methods: Subjects had either chromosomal microarray or *FOXG1* gene sequencing performed as part of routine clinical care. Development and epilepsy follow-up data were collected from medical records from treating neurologists and through telephone parental interviews using standardized questionnaires.

Results: Epilepsy was diagnosed in 87% of the subjects with FOXG1-related disorders. The mean age of epilepsy diagnosis in *FOXG1* duplications was significantly younger than those with deletions/intragenic mutations (p=0.0002). All of the duplication *FOXG1* children with infantile spasms responded to hormonal therapy and only one required long-term anti-epileptic therapy. In contrast, more children with deletions/intragenic mutations required anti-epileptic drugs on follow-up (p<0.0005). All subjects with *FOXG1*-related disorders had neurodevelopmental disabilities after 3 years of age, regardless of the epilepsy type or intractability of seizures. All had impaired verbal language and social contact, and three duplication subjects were formally diagnosed with autism. Subjects with deletion/intragenic mutations however had significantly worse ambulation (p=0.04) and functional hand use (p<0.0005).

Significance: Epilepsy and developmental outcome characteristics allow clinicians to distinguish among the *FOXG1*-related disorders. Further genotype-phenotype studies of *FOXG1* may help to elucidate why children develop different forms of developmental epilepsy.

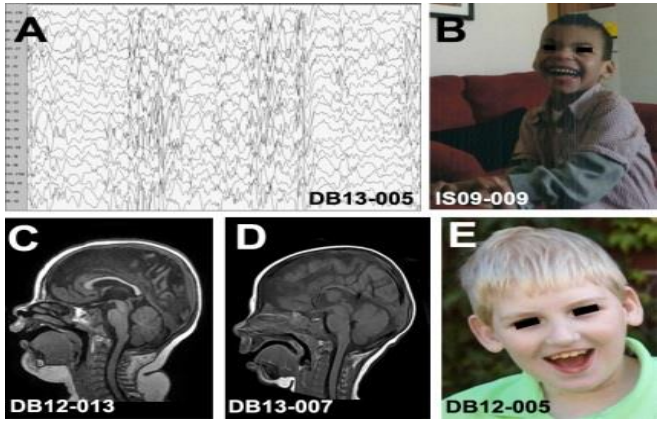


Figure 1: Differential characteristics of subjects with duplications or deletions/intragenic mutations of *FOXG1* on 14q12. Infantile spasms with hypsarrhythmia (A) has been commonly described with duplications. Children with smaller 14q12 duplications are non-dysmorphic, and have autistic features (B). MRI in duplications of 14q12 show a normal gyral pattern and intact corpus callosum (C), while children with deletions/intragenic mutations of *FOXG1* have hypoplasia of the corpus callosum (D), foreshortened frontal lobes with gyral simplification, postnatal microcephaly, and multiple neurodevelopmental disabilities (E).

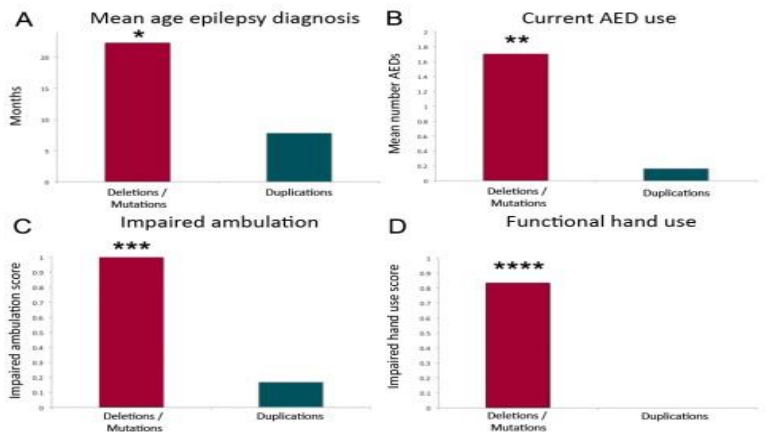


Figure 2: Significant differences were found between subjects with *FOXG1* deletions/intragenic mutations compared to those with duplications in the areas of mean age of epilepsy diagnosis (A; *p=0.0002), current numbers of anti-epileptic drugs (AED) used (B; **p<0.0005), impaired ambulation (C;***p=0.04), and impaired functional hand use (D; ****p<0.0005).

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The hyperkinetic movement disorder of *FOXG1*-related epileptic–dyskinetic encephalopathy

ELENA CELLINI[1] | AGLAIA VIGNOLI[2] | TIZIANA PISANO[1] | MELANIA FALCHI[1] | ANNA MOLINARO[3] | PATRIZIA ACCORSI[4] | ALESSIA BONTACCHIO[4] | LORENZO PINELLI[5] | LUCIO GIORDANO[4] | RENZO GUERRINI[1] | ON BEHALF OF THE FOXG1 SYNDROME STUDY GROUP*

AIM Forkhead Box G1 (*FOXG1*) syndrome is a developmental encephalopathy characterized by postnatal microcephaly, structural brain abnormalities, facial dysmorphisms, severe delay with absent language, defective social interactions, and epilepsy. Abnormal movements in *FOXG1* syndrome have often been mentioned but not characterized.

METHOD We clinically assessed and analysed video recordings of eight patients with different mutations or copy number variations affecting the *FOXG1* gene and describe the peculiar pattern of the associated movement disorder.

RESULTS The age of the patients in the study ranged from 2 to 17 years old (six females, two males). They had severe epilepsy and exhibited a complex motor disorder including various combinations of dyskinetic and hyperkinetic movements featuring dystonia, chorea, and athetosis. The onset of the movement disorder was apparent within the first year of life, reached its maximum expression within months, and then remained stable.

INTERPRETATION A hyperkinetic–dyskinetic movement disorder emerges as a distinctive feature of the *FOXG1*-related phenotype. *FOXG1* syndrome is as an epileptic–dyskinetic encephalopathy whose clinical presentation bears similarities with *ARX*- and *STXBP1*-gene related encephalopathies.

Apostolos Papandreou, MBBS*
Ruth B. Schneider, MD*
Erika F. Augustine, MD
Joanne Ng, MBChB
Kshitij Mankad, MD
Esther Meyer, PhD
Amy McTague, MBChB
Adeline Ngoh, MBBS
Cheryl Hemingway, PhD
Robert Robinson, PhD
Sophia M. Varadkar, MPCPI
Maria Kinali, MD
Vincenzo Salpietro, MD
Margaret C. O'Driscoll, MD
S. Nigel Basheer, FRCPI
Richard I. Webster, FRACP
Shekeeb S. Mohammad, FRACP
Shpresa Pula, MD
Marian McGowan, MD
Natalie Trump, PhD
Lucy Jenkins, BSc
Frances Elmslie, FRCP
Richard H. Scott, PhD
Jane A. Hurst, FRCP
Belen Perez-Duenas, PhD
Alexander R. Paciorkowski, MD‡
Manju A. Kurian, PhD‡

Delineation of the movement disorders associated with *FOXG1* mutations

OPEN

ABSTRACT

Objective: The primary objective of this research was to characterize the movement disorders associated with *FOXG1* mutations.

Methods: We identified patients with *FOXG1* mutations who were referred to either a tertiary movement disorder clinic or tertiary epilepsy service and retrospectively reviewed medical records, clinical investigations, neuroimaging, and available video footage. We administered a telephone-based questionnaire regarding the functional impact of the movement disorders and perceived efficacy of treatment to the caregivers of one cohort of participants.

Results: We identified 28 patients with *FOXG1* mutations, of whom 6 had previously unreported mutations. A wide variety of movement disorders were identified, with dystonia, choreoathetosis, and orolingual/facial dyskinesias most commonly present. Ninety-three percent of patients had a mixed movement disorder phenotype. In contrast to the phenotype classically described with *FOXG1* mutations, 4 patients with missense mutations had a milder phenotype, with independent ambulation, spoken language, and normocephaly. Hyperkinetic involuntary movements were a major clinical feature in these patients. Of the symptomatic treatments targeted to control abnormal involuntary movements, most did not emerge as clearly beneficial, although 4 patients had a caregiver-reported response to levodopa.

Conclusions: Abnormal involuntary movements are a major feature of *FOXG1* mutations. Our study delineates the spectrum of movement disorders and confirms an expanding clinical phenotype. Symptomatic treatment may be considered for severe or disabling cases, although further research regarding potential treatment strategies is necessary. ***Neurology*® 2016;86:1794–1800**

Children'Hospital
Bambino Gesù
Rome

lucia.fusco@opbg.net