Malattie infiammatorie

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CENTRO REGIONALE EPILESSIE RC

Malattie infiammatorie del SNC e declino cognitivo

Caratteristiche spesso presenti:

rapidità di insorgenza

pattern di deficit cognitivi atipico

possibile reversibilità

Curr Treat Options Neurol (2017) 19: 40
DOI 10.1007/s11940-017-0474-1

Dementia (J Pillai, Section Editor)

Comprehensive and Methodical: Diagnostic and Management Approaches to Rapidly Progressive Dementia

Supriya Mahajan, MD[1]
Brian S. Appleby, MD[1,2,3,*]

Table 1. Differential diagnosis for rapidly progressive dementia

Infectious:
- Streptococcal meningitis
- *Listeria monocytogenes* meningitis
- *Neisseria* meningitis
- Tuberculosis meningitis/tubercular encephalitis
- Neurosyphilis
- Neuroborreliosis
- Whipple's disease
- Herpes simplex virus 1 or 2 encephalitis
- West Nile encephalitis
- Rabies encephalitis
- Progressive multifocal leukoencephalopathy
- Mucor fungal encephalitis
- CNS toxoplasmosis
- Balamuthia amoebic encephalitis
- AIDS dementia complex
- Variant Creutzfeldt-Jakob disease
- Iatrogenic Creutzfeldt-Jakob disease

Vascular:
- Stroke
- Mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes (MELAS)
- Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL)
- Dural arteriovenous fistula
- Posterior reversible encephalopathy syndrome

Metabolic:
- Electrolyte abnormalities
- Wernike-Korsakoff syndrome
- Uremia
- Hepatic encephalopathy
- Porphyria
- Vitamin B12 deficiency
- Niacin deficiency
- Leukodystrophies

Endocrine:
- Hypo/hyperthyroidism
- Hypo/hyperparathyroidism
- Adrenal insufficiency

Oncologic:
- Primary CNS tumor
- CNS lymphoma
- Metastatic solid tumor
- Meningeal carcinomatosis
- Paraneoplastic syndrome

Toxic:
- Serotonin syndrome
- Neuroleptic malignant syndrome
- Bismuth toxicity
- Lithium toxicity
- Mercury toxicity
- Arsenic toxicity
- Alcoholic dementia
- Lead toxicity

Autoimmune:
- Steroid-responsive encephalopathy with autoimmune thyroiditis
- Lupus cerebritis
- Neurosarcoidosis
- Multiple sclerosis
- CNS vasculitis
- Amyloid beta related angiitis (ABRA)
- Acute disseminated encephalomyelitis (ADEM)
- NMDA receptor encephalitis
- LGI1 limbic encephalitis
- CASPR limbic encephalitis
- $GABA_a$ or $GABA_b$ limbic encephalitis
- AMPA receptor limbic encephalitis
- Hu antibody limbic encephalitis
- GAD antibody limbic encephalitis
- DPPX encephalitis
- Bickerstaff encephalitis
- Behcet's disease
- Hypereosinophilic disease

Psychiatric (primary):
- Psychotic disorders
- Depression
- Bipolar disorder
- Factitious disorders
- Conversion disorder

Neurodegenerative:
- Previously diagnosed dementia syndrome with superimposed delirium
- Rapidly progressive Alzheimer's disease
- Prion disease
- Frontotemporal degeneration
- Progressive supranuclear palsy
- Dementia with Lewy bodies
- Corticobasal degeneration
- Multiple system atrophy

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Sclerosi multipla e declino cognitivo

Cognition in multiple sclerosis

State of the field and priorities for the future

James F. Sumowski, PhD, Ralph Benedict, PhD, Christian Enzinger, MD, Massimo Filippi, MD, Jeroen J. Geurts, PhD, Paivi Hamalainen, PhD, Hanneke Hulst, PhD, Matilde Inglese, MD, PhD, Victoria M. Leavitt, PhD, Maria A. Rocca, MD, Eija M. Rosti-Otajarvi, PhD, and Stephen Rao, PhD

Neurology® 2018;90:1-11. doi:10.1212/WNL.0000000000004977

- Charcot, 1877: marcato indebolimento della memoria e lentezza nella formazione dei pensieri nelle persone con SM
- Per quasi tutto il XX secolo: aspetto trascurato (accento su disabilità motoria)

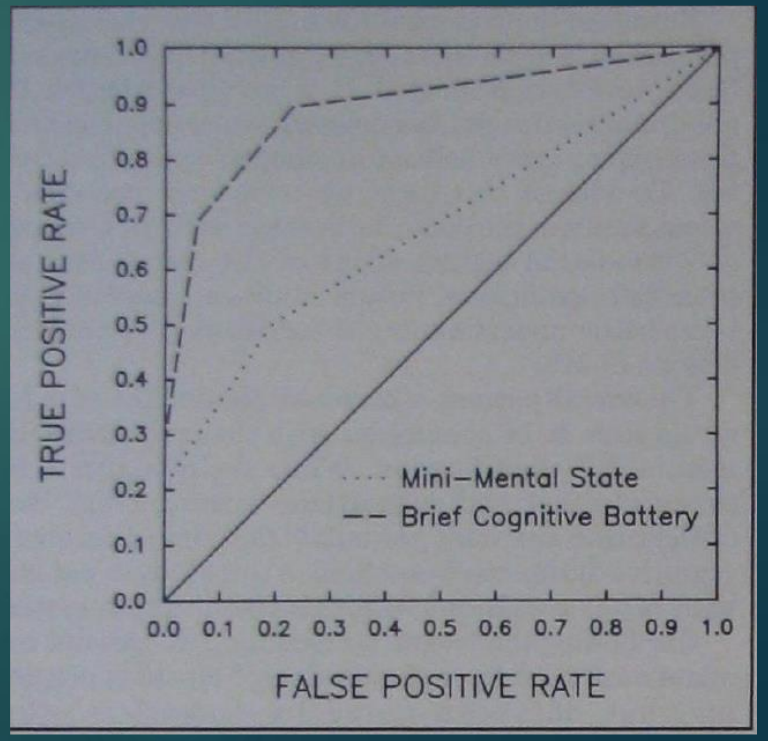
Cognitive dysfunction in multiple sclerosis.

I. Frequency, patterns, and prediction

Neurology 1991;41:685–691

Stephen M. Rao, PhD; Gary J. Leo, DO; Linda Bernardin, MS; and Frederick Unverzagt, MS

- 100 pazienti con SM (meno di metà RR) e 100 controlli sani
- Solo 43% trattati
- Assenza di relazione con la durata di malattia, ma relazione con severità (EDSS)
- La forma clinica non predice disabilità
- Domini più compromessi: memoria episodica, attenzione, ragionamento astratto



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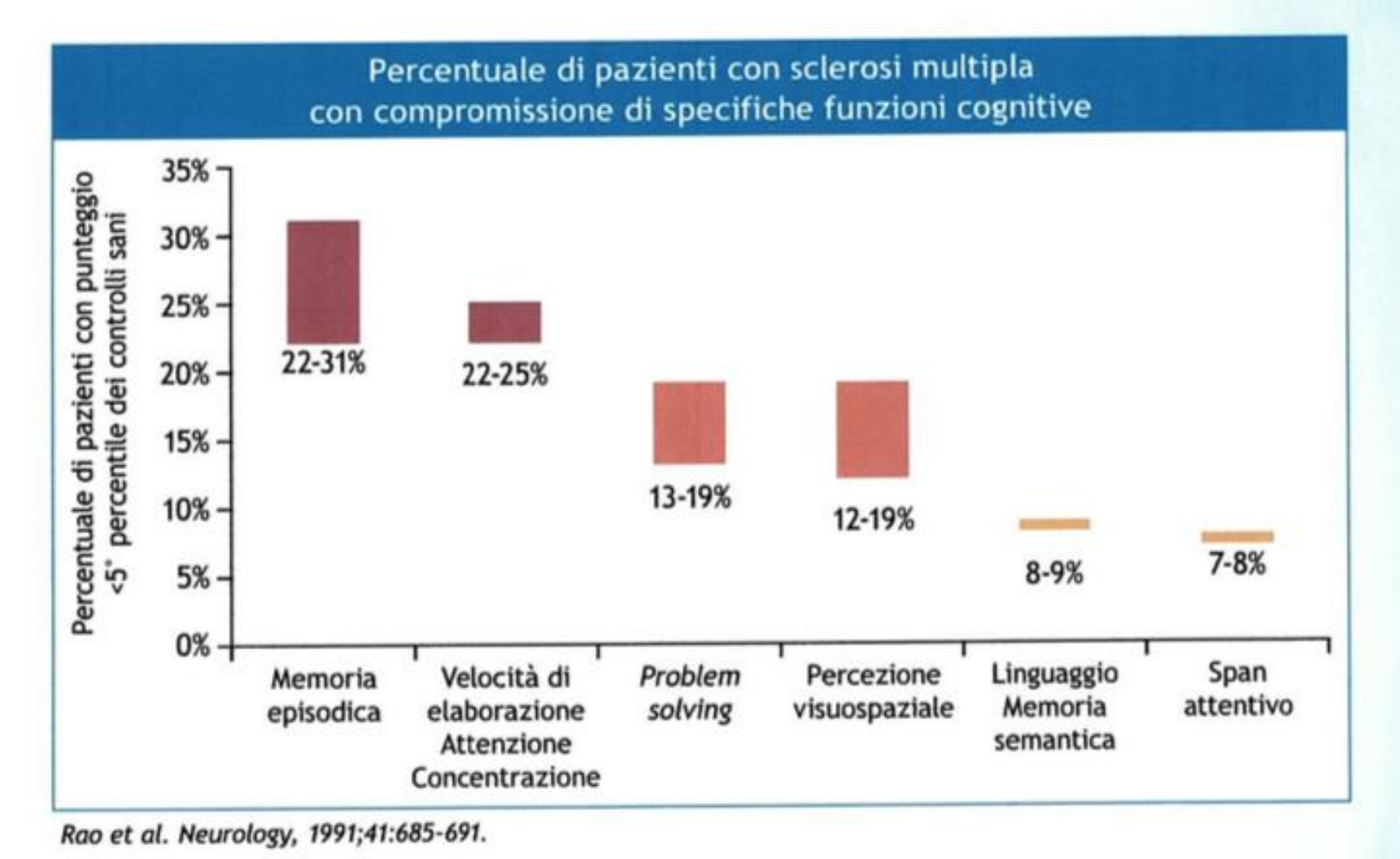
1. EPIDEMIOLOGIA

- Frequenza complessiva: 45-70% (Chiaravallotti et al., 2008)
- Può essere presente anche in fase precoce
- Descrizione di deficit in singoli domini cognitivi anche dopo il primo episodio demielinizzante
- Probabilmente più frequente nelle forme PP piuttosto che RR (Connick *et al.*, 2013; Denney *et al.*, 2005; Jønsson *et al.*, 2006)
- Andamento progressivo

2. PROFILO COGNITIVO



Rao et al. Neurology, 1991;41:685-691.

Problemi: il deficit può essere discreto e può coinvolgere funzioni difficili da misurare (multitasking)

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3. VALUTAZIONE NEUROPSICOLOGICA

- Sviluppati molti tests e batterie con varia sensibilità e specificità
- Richiedono tempo → difficile uso routinario
- Batterie specifiche a differenti steps

Table 2 Review of cognitive tests and guidelines for cognitive assessment

Test; cognitive domain	Batteries; validated outcomes	Advantages	Disadvantages	Recommendations
SDMT Cognitive processing speed	**MACFIMS** **BRB** **MS-COG** **BICAMS** **MSFC** Total correct (in 90 s)	Very high sensitivity (mean d = 1.11)[13]: most sensitive task in MS Good to excellent reliability Fast and easy to administer Well-tolerated by patients Uniform across languages No floor or ceiling effects Multiple alternate forms available Preliminary evidence for 3–4 point clinically meaningful change[13]	Other functions affected by MS may contribute to performance (incidental learning of symbol-digit pairings,[e14] visual scanning)	1. Highly recommended as a cognitive monitoring tool in clinical practice 2. Highly recommended as a cognitive assessment tool in research, including cross-sectional and longitudinal designs, and as an outcome in clinical trials 3. SDMT should not be considered a pure measure of latent processing speed (due to concomitant learning and visual scanning requirements) 4. Incorporation of cognitive assessment into clinical practice with tablet- or Internet-based processing speed tasks is a goal for the future
PASAT Cognitive processing speed, working memory	**MACFIMS** **BRB** **MS-COG** 1. PASAT-3 total correct 2. PASAT-2 total correct	Moderate sensitivity (mean d = 0.63),[13] but less sensitive than the SDMT as a task of cognitive processing speed/efficiency Previously the most widely used cognitive test in MS research, including clinical trials; there is therefore a large amount of research PASAT data to compare across prior studies PASAT stimuli are auditory; most cognitive efficiency tasks require visual processing; PASAT may be useful for patients with poor vision	Reliability limited by practice effects Susceptible to ceiling effects Poorly tolerated by patients Specificity limited by multiple factors, including math ability and test-taking anxiety	1. Not recommended for cognitive monitoring in clinical practice (The SDMT is more sensitive to cognitive deficits,[e15] and has replaced PASAT as the MSFC cognitive task[13]) 2. Not recommended for clinical trials or designs with multiple administrations (due to practice effects) 3. The PASAT is a putative cognitive processing task, which allows results to be compared across previous studies 4. There is a need for new cognitive efficiency tasks using nonvisual stimuli for patients with visual impairment
SRT Verbal memory	**BRB** **MS-COG** 1. TL 2. LTS 3. CLTR 4. Delayed recall	High sensitivity (mean d = 0.86)[13] Several alternate forms (although reliability across alternate forms needs further validation in MS) The selective reminding paradigm emphasizes retrieval of words from long-term store (secondary memory) rather than repetition from working (primary) memory	There is no single authoritative set of normative data, although there are different sets of published norms SRT (like other verbal memory assessments) is a poor candidate for future unsupervised assessment because tablet-based tasks assess verbal recognition, which is less sensitive than verbal recall in MS	1. Recommended as a verbal memory test for clinical and research use, especially when more than 2 administrations are planned 2. The SRT has 3 validated initial learning outcomes (TL, LTS, CLTR) that are highly intercorrelated; researchers are advised to identify which of these 3 measures of initial learning will be used
CVLT-II Verbal memory	**MACFIMS** **BICAMS** 1. TL 2. LDFR	High sensitivity (mean d = 0.89)[13] Good age- and sex-adjusted normative data from a large standardization sample in the United States One standard and one alternate form well-validated	There is only one alternate form For the standard administration, additional trials between TL and LDFR (List B, Short Delay Free Recall, Short Delay Cued Recall) add time, and are required to use published normative data for LDFR CVLT-II (like other verbal memory tests) is a poor candidate for future unsupervised assessment, as stated above for the SRT	1. Recommended as a verbal memory test for clinical and research use, especially when robust normative data are needed (but not when more than 2 administrations are required) 2. Unlike processing speed and visuospatial memory, it will be more challenging to develop table- or Internet-based verbal memory tests appropriate for persons with MS 3. Researchers should report whether all trials of the CVLT-II (e.g., List B, SDFR, SDCR) were administered or omitted 4. Recently published CVLT-III uses the same stimuli and administration as the CVLT-II, but adds a new scoring option to sum delayed recall trials (SDFR, SDCR, LDFR, LDCR) into one composite, which is more reliable than LDFR alone; this requires validation in MS
BVMT-R Visuospatial memory	**MACFIMS** **BICAMS** 1. TL 2. Delayed recall	Very high sensitivity (mean d = 1.03)[13] Good reliability and validity Time-efficient for a memory test (much briefer than SRT and CVLT-II) Well-tolerated by patients Six well-validated alternate forms Good age- and sex-adjusted normative data published in a large standardization sample in the United States	Severe motor impairment in patients with advanced disease may complicate assessment	1. Recommended as a good test for memory monitoring: BVMT-R is the most sensitive memory test within batteries designed for persons with MS 2. Recommended for research, including observational cross-sectional and longitudinal designs, and as an outcome in clinical trials 3. The drawing/construction requirement (although modest) may preclude assessment in patients with severe motor impairment; a tablet-based (or completely motor-free) visuospatial task would be ideal; however, no such task is currently validated for persons with MS
10/36 SPART Visuospatial memory	**BRB** 1. TL 2. Delayed recall	Construction/drawing is not required, which may be helpful in persons with severe motor impairment; however, upper extremity function is still needed (patients place markers on a grid)	Lower sensitivity (mean d = 0.48)[e16–e18] than other memory tests for MS (BVMT-R, SRT, CVLT-II) Reliability and good normative data are lacking	1. Due to low sensitivity, unknown reliability, and poor normative data, the SPART is not recommended as a clinical test for memory monitoring 2. SPART is a reasonable measure of spatial memory for research; however, BVMT-R is a more sensitive choice with established reliability and robust norms 3. SPART may be a useful test of spatial memory for patients with severe drawing impairment, although SPART still requires placement of markers
COWAT Verbal fluency	**BRB** MACFIMS 1. Total score (3 trials with different letters)	Moderate sensitivity (mean d = 0.54),[13] but lower than other tasks in used in MS Validated alternate form Time-efficient and easy to administer	Much more related to education and vocabulary than MS disease burden Unclear whether task's sensitivity is only explained by processing speed	1. Not recommended for screening or brief monitoring in clinical practice 2. Not recommended as an outcome for clinical trials, unless verbal fluency is the specific target of the intervention 3. Reasonable component of a comprehensive neuropsychological assessment for research or practice
D-KEFS sorting test Executive function	**MACFIMS** 1. Total correct sorts 2. Description score	Alternate form is available (unlike most executive function tasks) Sensitivity is moderate (d = 0.67) based on one large study[3] (incidence of higher-level executive dysfunction may be lower than processing speed and memory deficits in MS, at least as currently measured in the clinic)	Reliability is low (which is typical for tests of higher-level executive function) Administration time is long and procedures are cumbersome	1. Not recommended for brief monitoring in clinical practice 2. Not recommended for clinical trials, unless executive function is the specific target of the intervention 3. May be useful in the context of a comprehensive clinical evaluation, especially when patient performance can be closely monitored for qualitative problem-solving approach
JOLO Visuospatial processing	**MACFIMS** 1. Total correct	Good reliability and established validity as a visuospatial task Alternate form is available Easy for patients to understand	Lower sensitivity (d = 0.49)[1] than other tasks used in MS (not necessarily a criticism of JOLO; visuospatial ability is less impaired than speed and memory)	1. Not recommended for brief monitoring in clinical practice 2. Recommended as a valid task of visuospatial function for comprehensive cognitive evaluations in research or practice 3. Not recommended as an outcome in clinical trials unless visuospatial function is the target of intervention

Abbreviations: BICAMS = Brief International Cognitive Assessment for MS; BRB = Brief Repeatable Battery; BVMT-R = Brief Visuospatial Memory Test, Revised; CLTR = Consistent Long-Term Retrieval; COWAT = Controlled Oral Word Association Test; CVLT-II = California Verbal Learning Test, second edition; D-KEFS = Delis-Kaplan Executive Function System; JOLO = Judgment of Line Orientation; LDFR = Long Delay Free Recall; LTS = Long-Term Storage; MACFIMS = Minimal Assessment of Cognitive Function in MS; MS = multiple sclerosis; MSFC = Multiple Sclerosis Functional Composite; PASAT = Paced Auditory Serial Addition Test; SDCR = Short-Delay Cued Recall; SDFR = Short-Delay Free Recall; SDMT = Symbol Digit Modalities Test; SPART = Spatial Recall Test; SRT = Selective Reminding Test; TL = Total Learning.

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Batterie di test neuropsicologici usati nella sclerosi multipla			
Funzioni	Batterie		
	BICAMS	BRB	MACFIMS
Attenzione *Working memory*	SDMT	SDMT PASAT	SDMT PASAT
Funzioni esecutive			D-KEFS sorting test
Memoria episodica verbale	CVLT-II	SRT	CVLT-II
Memoria episodica visuospaziale	BVMT-R	SPART (10/36)	BVMT-R
Linguaggio		WLG	COWA
Percezione visuospaziale			JOL

BRB-N: Brief Repeatable Battery for Neuropsychological evaluation; MACFIMS: Minimal Assessment of Cognitive Function in MS; SDMT: Symbol Digit Modalities Test; PASAT: Paced Auditory Serial Addition Test (3- and 2-second versions); D-KEFS sorting test: Delis Kaplan Executive Function System sorting test; SRT: Selective Reminding Test; CVLT-II: California Verbal Learning Test, second version; SPART: Spatial Recall test; BVMT-R: Brief Visuospatial Memory Test, revised version; WLG: Word List Generation; COWA: Controlled Oral Word Association Test; JOL: Judgement of line orientation test.

Brochet. Diagnosing cognitive problems. Cognition and MS. MS in focus 2013. Multiple Sclerosis International Federation.

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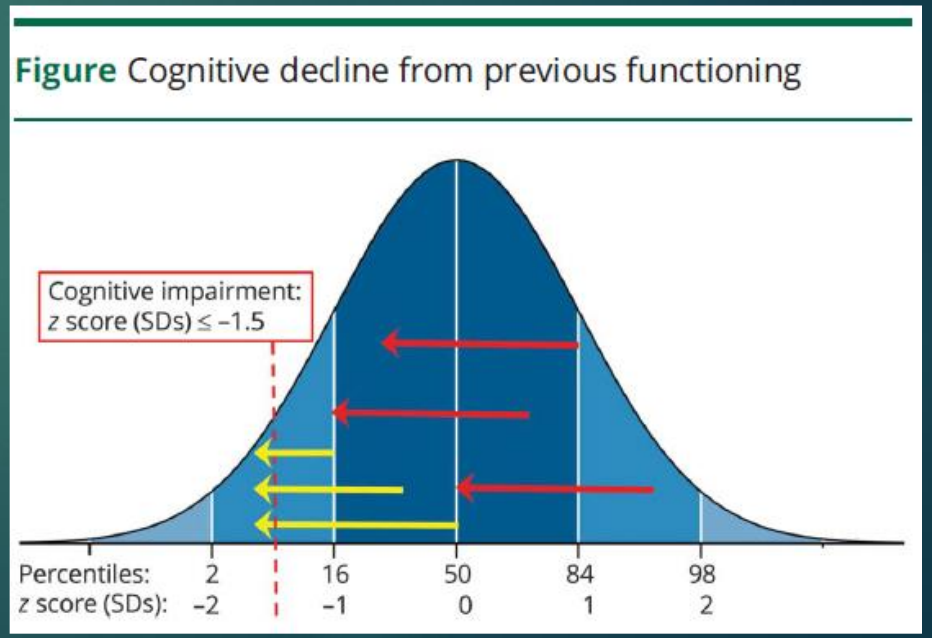
Neurology® 2018;90:1-11. doi:10.1212/WNL.0000000000004977

4. SIGNIFICATO CLINICO Problemi aperti

- Cosa si intende per «impairment cognitivo»?
- Declino vs. deficit cognitivo (valutaz. trasversali)
- Cambiamento clinicamente significativo



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5. PREDIZIONE

- La maggior parte degli studi è trasversale o retrospettiva: impossibile tracciare rapporto di causa/effetto
- Rapporto con disabilità motoria: incerto
- Relazione tra forma di malattia (RR vs. PP) e disabilità cognitiva

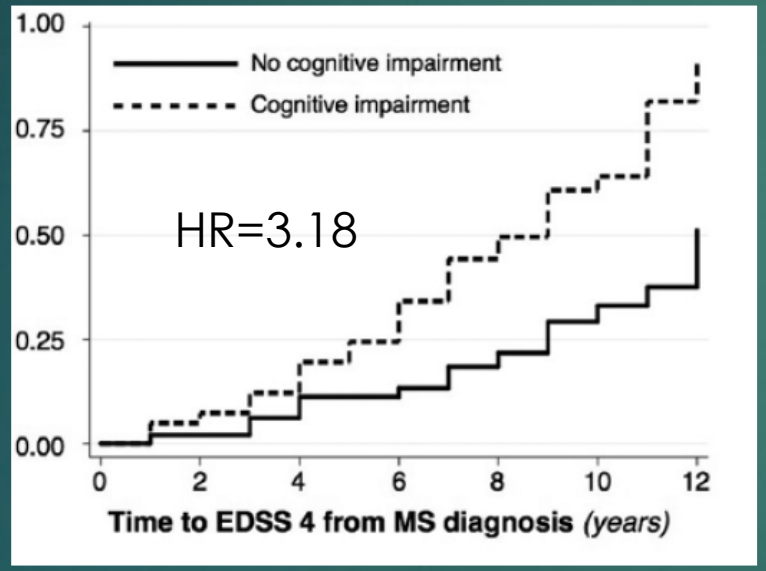
Cognitive impairment at diagnosis predicts 10-year multiple sclerosis progression

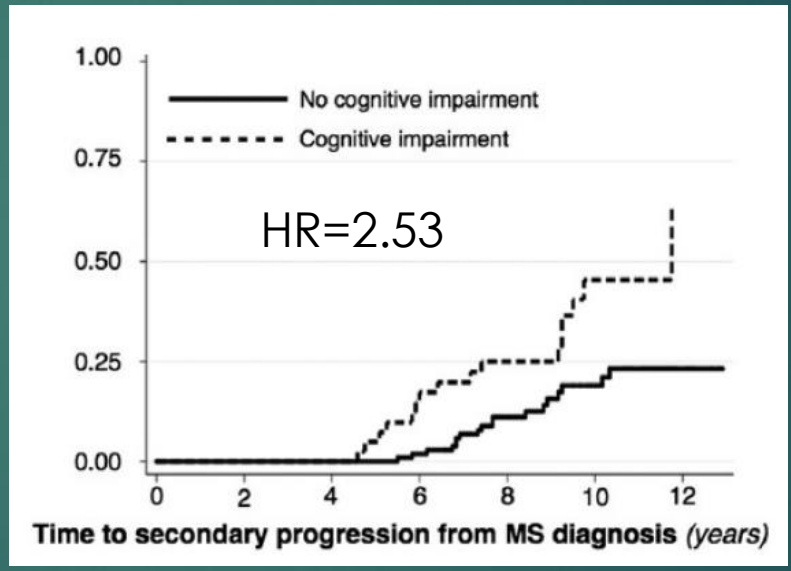
Marcello Moccia, Roberta Lanzillo, Raffaele Palladino, Kiara Chu-Mei Chang, Teresa Costabile, Cinzia Russo, Anna De Rosa, Antonio Carotenuto, Francesco Saccà, Giorgia Teresa Maniscalco and Vincenzo Brescia Morra

Multiple Sclerosis Journal
1–9
DOI: 10.1177/1352458515599075

5. PREDIZIONE

- 155 pazienti con SM-RR seguiti per 10 anni
- Outcomes: tempo alla ricaduta, raggiungimento di EDSS=4, tempo alla SP





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M. Ron, MD
G. Comi, MD

The contribution of MRI in assessing cognitive impairment in multiple sclerosis

Neurology® 2010;75:2121-2128

6. NEUROIMAGING

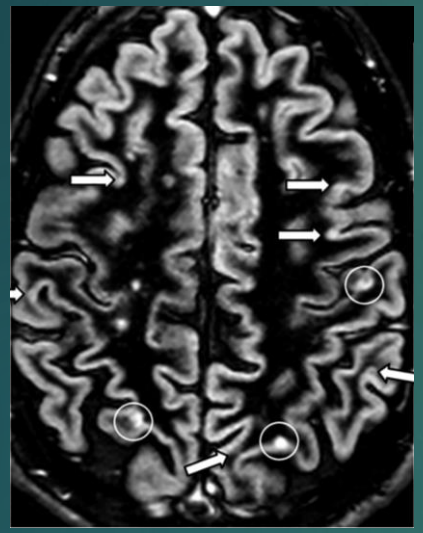
- Studi antichi: relazione modesta tra carico lesionale in T2 e performance ai tests neuropsicologici
- Non associazioni con lesioni in specifiche regioni della SB
- Alterazioni in T1: scarsa correlazione
- Atrofia globale e regionale: conseguenza di distruzione del parenchima e strettamente associata a danno cognitivo (Zivadinov 2001, Rovaris 2006, Houtchens 2007)
- Sedi maggiormente correlate a danno cognitivo: talami (Rovaris 2006), corteccia cerebrale (Fisniku 2008, Amato 2007, Morgen 2006)

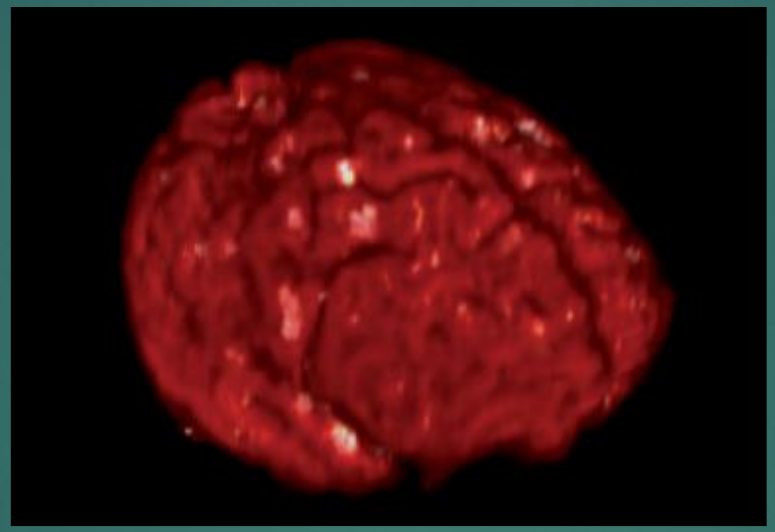
EXPERT REVIEWS

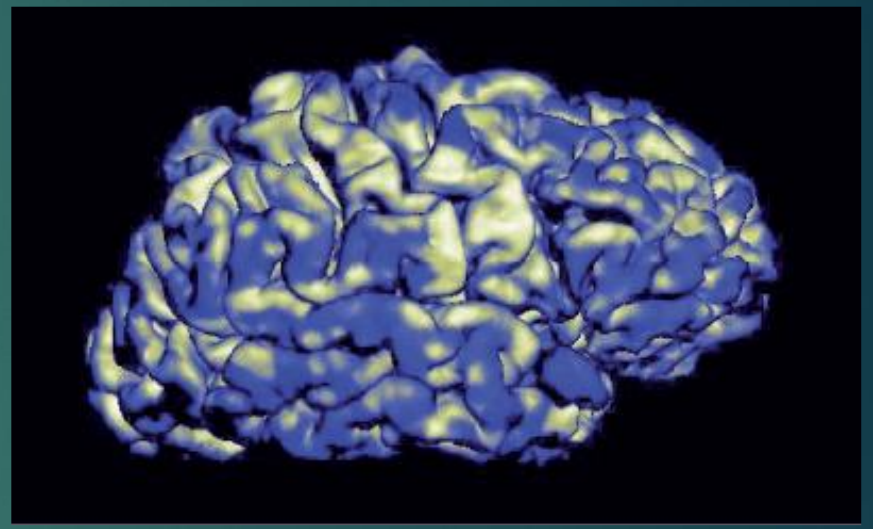
Cortical pathology and cognitive impairment in multiple sclerosis

Massimiliano Calabrese[†1], Francesca Rinaldi[1], Paola Grossi[1] and Paolo Gallo[1]

Expert Rev. Neurother. 11(3), 425–432 (2011)







- Deficit cognitivi specifici (es. memoria, attenzione, velocità di processazione informazioni) potrebbero essere meglio spiegati da anomalie corticali che da lesioni della sostanza Bianca
- Danno corticale diffuso o discreto legato a declino cognitivo

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The contribution of MRI in assessing cognitive impairment in multiple sclerosis

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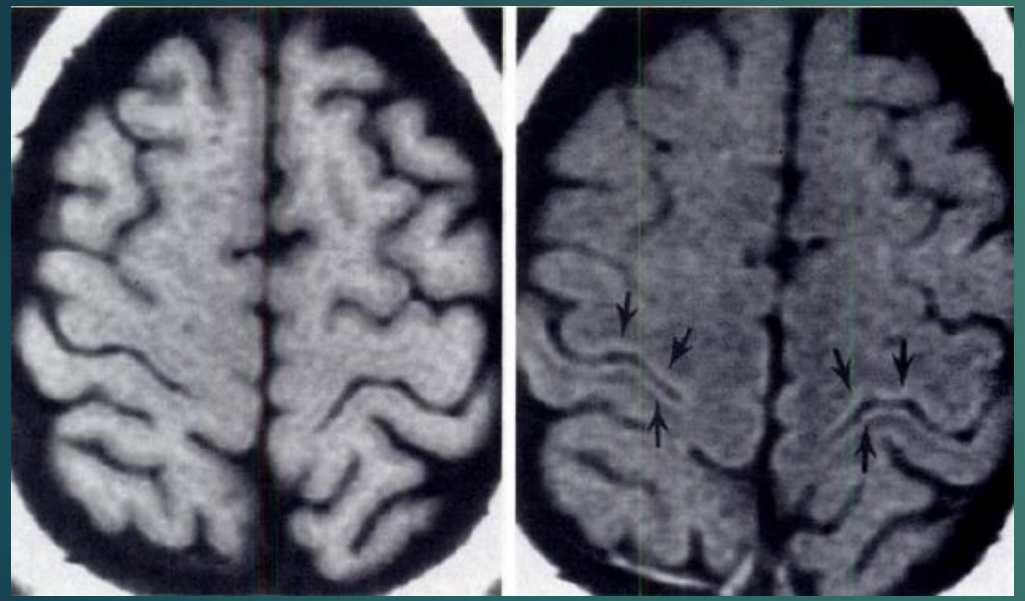
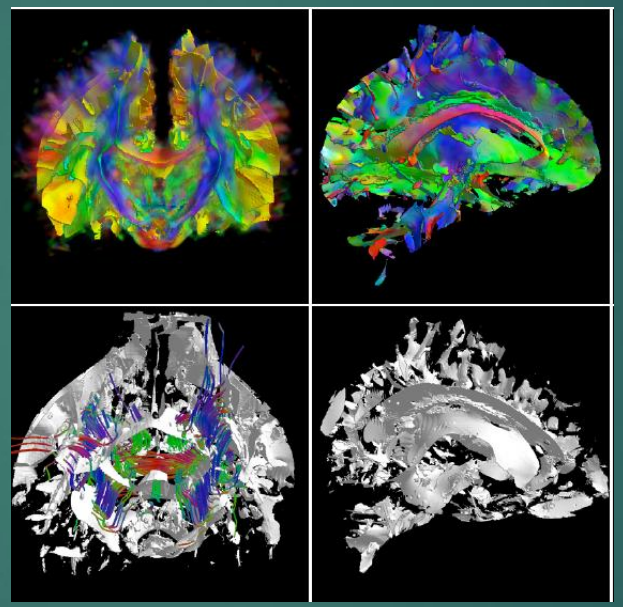
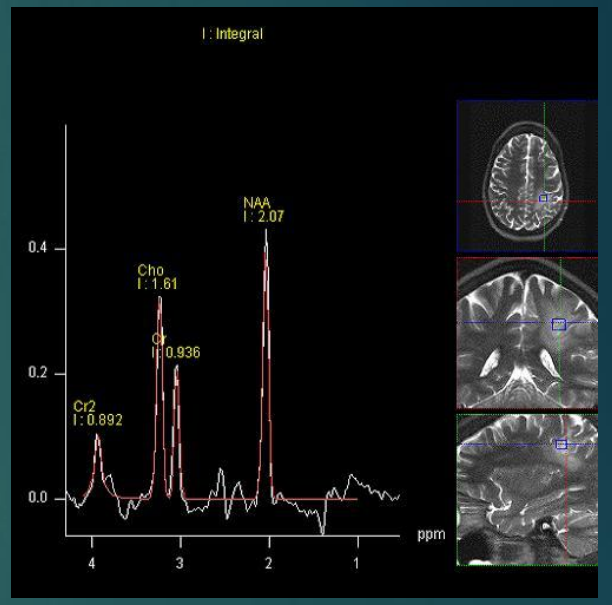
Tecniche non convenzionali



Magnetization transfer



Diffusion tensor imaging



Spettroscopia

Encefaliti autoimmuni e declino cognitivo

Chapter 14

Autoimmune dementia and encephalopathy

Handbook of Clinical Neurology, Vol. 133 (3rd series)
Autoimmune Neurology

EOIN P. FLANAGAN, DANIEL A. DRUBACH, AND BRADLEY F. BOEVE*
Department of Neurology, Mayo Clinic, Rochester, MN, USA

Summary of clinical, laboratory, and neuroimaging/ electrophysiologic "red flags" for autoimmune dementia and encephalopathy

Clinical
- Subacute onset with fluctuations
- Personal/family history (first-degree relative) of autoimmunity
- Rapid progression
- Tremor/myoclonus
- Occurring in association with new-onset seizures (e.g., faciobrachial dystonic seizures)
- History of recent or past neoplasia or risk factors for cancer (e.g., long history of smoking)

Laboratory
- Serologic evidence of systemic autoimmunity
- Detection of a neural-specific autoantibody (Table 14.4)
- Inflammatory spinal fluid (increased white cell count, elevated protein > 100 mg/dL, elevated oligoclonal bands or IgG index/synthesis rate)

Neuroimaging/electrophysiology
- Magnetic resonance imaging showing mesial temporal T2 signal abnormalities
- Epileptiform activity on electroencephalogram in the setting of dementia/encephalopathy (spikes, sharp waves, seizure captured, other specific pattern, e.g., delta-brush pattern)

- Rapida progressione
- Segni associati («encephalopathy and dementia»)
- Neoplasia
- Tests paraclinici

Epidemiologia

- Prevalenza di encefalite autoimmune: sconosciuta (probabilmente sottostimata)
- 20–25% dei pazienti con demenza ad esordio <45 anni (Kelley et al., 2008)
- Età: molto variabile, picco di incidenza 50-60 anni, ma descritti casi in bambini ed in età molto avanzata (Flanagan et al., 2010)
- Prevalenza nel sesso femminile (tranne LGI1)

Encefaliti (limbiche) autoimmuni ed autoanticorpi

Categorie di anticorpi

Contro Ag intracellulari

(nucleo, citoplasma)

Anti-Hu, anti-Ri, anti-Cv2, anti-amfifisina

- Spesso associati a neoplasia
- Risposta ad immunoterapia meno brillante
- Spesso esiti

Anti-GAD65

Contro Ag di superficie

Anti-LGI1, anti-NMDAR, anti-GABAR, anti-AMPA

- Raramente paraneoplastici
- Prognosi migliore

Indizi per la diagnosi di forme specifiche

Antibodies with specificity for neural antigens, oncologic associations and specific clinical clues to the diagnosis in patients with autoimmune dementia and encephalopathy

Antibody*	Oncologic associations†	Clinical clues beyond dementia/encephalopathy
VGKC–complex LGI1	Uncommon (small-cell lung carcinoma; thymoma; thyroid; renal cell)	Faciobrachial dystonic seizures, hyponatremia
CASPR2	Uncommon (thymoma)	Peripheral nerve hyperexcitability/neuromyotonia/Isaac's syndrome, Morvan's syndrome (encephalopathy, hyperhidrosis, insomnia)
NMDA IgG NMDA IgA/IgM	Teratoma, usually ovarian	Young females, psychosis, oral dyskinesias, hypoventilation, may follow HSV encephalitis, delta brush pattern on EEG Atypical features (subacute onset, fluctuating course, abnormal CSF)
AMPA	Thymic tumors, lung carcinomas, breast carcinoma	Limbic encephalitis
$GABA_A$	Uncommon (hematologic malignancy)	Limbic encephalitis, status epilepticus, stiff-person syndrome
$GABA_B$	Small-cell lung carcinoma, other neuroendocrine neoplasia	Limbic encephalitis, coexisting calcium channel N-type autoantibody
DPPX	Uncommon (hematologic malignancies)	Severe weight loss and diarrhea, brainstem involvement, exaggerated startle
mGluR5	Uncommon. Hodgkin's lymphoma	Limbic encephalitis (Ophélia syndrome)
LgLON5	None as yet	Sleep disorder (OSA, RBD, poor sleep architecture), gait ataxia
ANNA-1 (anti-Hu)	Small-cell carcinoma	Limbic encephalitis, autoimmune gastrointestinal dysmotility, sensory neuronopathy
ANNA-2 (anti-Ri)	Small-cell carcinoma or breast adenocarcinoma	Opsoclonus-myoclonus, jaw dystonia, laryngospasm
ANNA-3	Small-cell carcinoma	Limbic encephalitis
AGNA (SOX-1 antibodies)	Small-cell carcinoma	Lambert–Eaton syndrome
PCA-2	Small-cell carcinoma	Limbic encephalitis, ataxia
CRMP-5 IgG (anti-CV2)	Small-cell carcinoma, thymoma	Chorea, optic neuropathy/retinopathy, myelopathy
Amphiphysin	Breast adenocarcinoma, small-cell carcinoma	Stiff-person syndrome, myelopathy
Anti-Ma proteins (usually Ma2, sometimes Ma1)	Testis, small-cell carcinoma, other solid organ cancers	Hypothalamic/diencephalic disorder (narcolepsy/cataplexy), brainstem encephalitis, limbic encephalitis

Profilo neuropsicologico

- Deficit di memoria recente: più frequente e grave
- Possibile presentazione tipo FTD con cambiamento di personalità, ritiro sociale, anomalie del comportamento, danno funzioni esecutive e memoria integra

A clinical approach to diagnosis of autoimmune encephalitis

Francesc Graus, Maarten J Titulaer, Ramani Balu, Susanne Benseler, Christian G Bien, Tania Cellucci, Irene Cortese, Russell C Dale, Jeffrey M Gelfand, Michael Geschwind, Carol A Glaser, Jerome Honnorat, Romana Höftberger, Takahiro Iizuka, Sarosh R Irani, Eric Lancaster, Frank Leypoldt, Harald Prüss, Alexander Rae-Grant, Markus Reindl, Myrna R Rosenfeld, Kevin Rostásy, Albert Saiz. Arun Venkatesan. Angela Vincent, Klaus-Peter Wandinger, Patrick Waters, Josep Dalmau

Lancet Neurol **2016; 15: 391–404**

- Criteri precedenti: basati su autoanticorpi e su risposta ad immunoterapia → impossibile diagnosi precoce!
- Esistono molte sovrapposizioni della sintomatologia, esistono forme non responsive all'immunoterapia
- Definizione di encefalite autoimmune «possibile» che giustifica immunoterapia precoce

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Panel 1: Diagnostic criteria for possible autoimmune encephalitis

Diagnosis can be made when all three of the following criteria have been met:

1 Subacute onset (rapid progression of less than 3 months) of working memory deficits (short-term memory loss), altered mental status*, or psychiatric symptoms

2 At least one of the following:
- New focal CNS findings
- Seizures not explained by a previously known seizure disorder
- CSF pleocytosis (white blood cell count of more than five cells per mm^3)
- MRI features suggestive of encephalitis†

3 Reasonable exclusion of alternative causes (appendix)

*Altered mental status defined as decreased or altered level of consciousness, lethargy, or personality change. †Brain MRI hyperintense signal on T2-weighted fluid-attenuated inversion recovery sequences highly restricted to one or both medial temporal lobes (limbic encephalitis), or in multifocal areas involving grey matter, white matter, or both compatible with demyelination or inflammation.

- Deficit di memoria: incapacità di formare nuove memorie (danno ippocampale) o deficit di working memory
- Alterato stato mentale: livello di coscienza o cambiamento di personalità

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Lancet Neurol **2016; 15: 391–404**

Panel 2: Diagnostic criteria for definite autoimmune limbic encephalitis

Diagnosis can be made when all four* of the following criteria have been met:

1. Subacute onset (rapid progression of less than 3 months) of working memory deficits, seizures, or psychiatric symptoms suggesting involvement of the limbic system
2. Bilateral brain abnormalities on T2-weighted fluid-attenuated inversion recovery MRI highly restricted to the medial temporal lobes†
3. At least one of the following:
   - CSF pleocytosis (white blood cell count of more than five cells per mm^3)
   - EEG with epileptic or slow-wave activity involving the temporal lobes
4. Reasonable exclusion of alternative causes (appendix)

*If one of the first three criteria is not met, a diagnosis of definite limbic encephalitis can be made only with the detection of antibodies against cell-surface, synaptic, or onconeural proteins. †^{18}Fluorodeoxyglucose (^{18}F-FDG) PET can be used to fulfil this criterion. Results from studies from the past 5 years suggest that ^{18}F-FDG-PET imaging might be more sensitive than MRI to show an increase in FDG uptake in normal-appearing medial temporal lobes.[44,45]

Imaging

A clinical approach to diagnosis of autoimmune encephalitis

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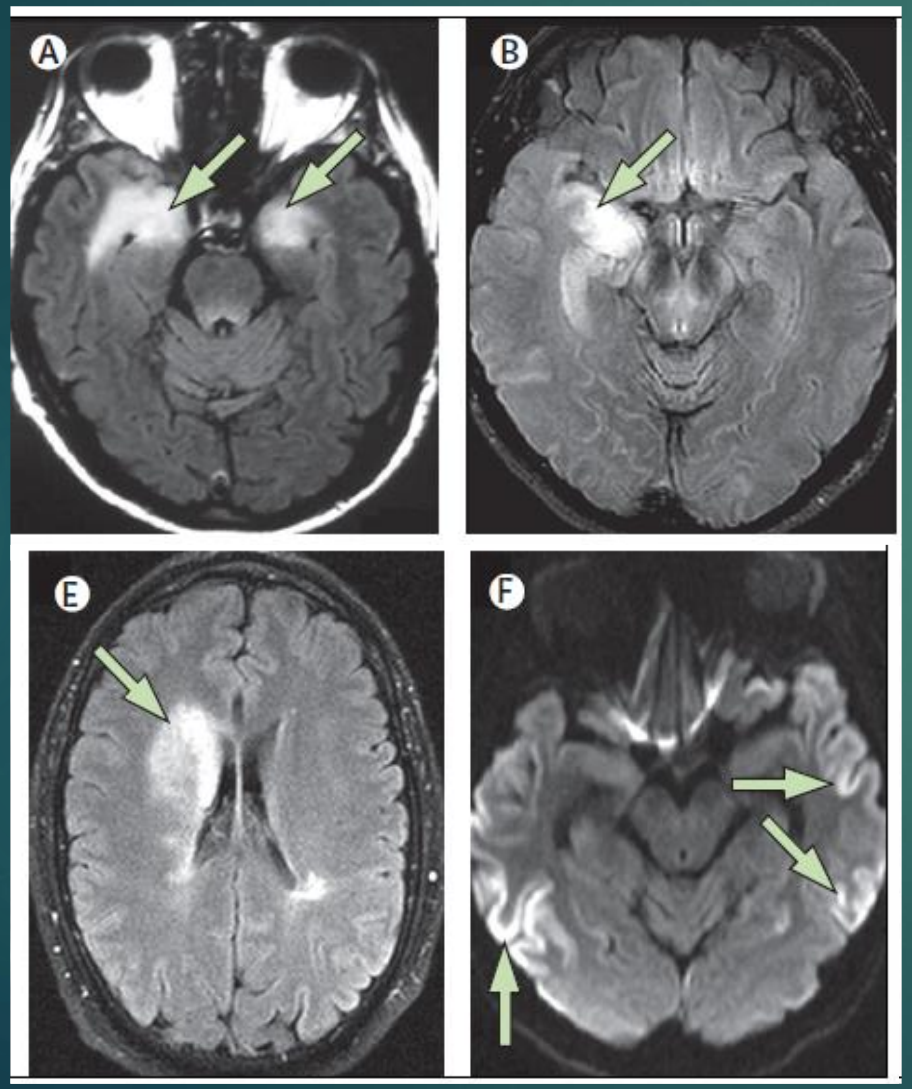


A. Encefalite limbica, no anticorpi

B. Glioma

E. Anti-NMDA e anti-MOG

F. AMPAR

Electroencephalography of Autoimmune Limbic Encephalopathy

Peter W. Kaplan and Raoul Sutter*†*

(*J Clin Neurophysiol* 2013;30: 490–504)

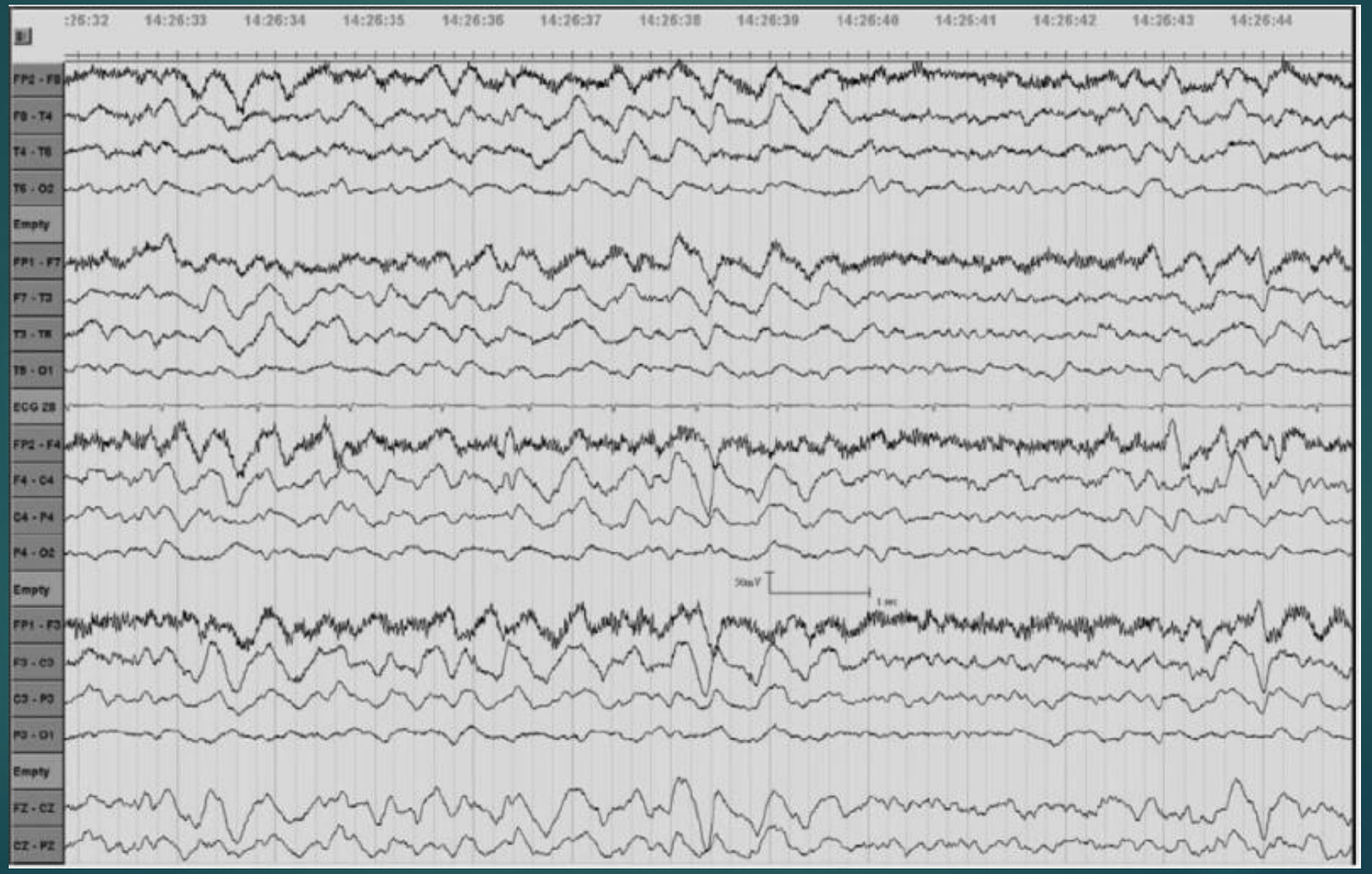
- EEG: da normale a stato epilettico
- Anomalie descritte: alterazione attività di fondo

  rallentamenti focali o diffusi

  anomalie epilettiformi isolate o periodiche

  soppressione dell'attività
- «Extreme delta brush»

Anti-LGI1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14:26:34
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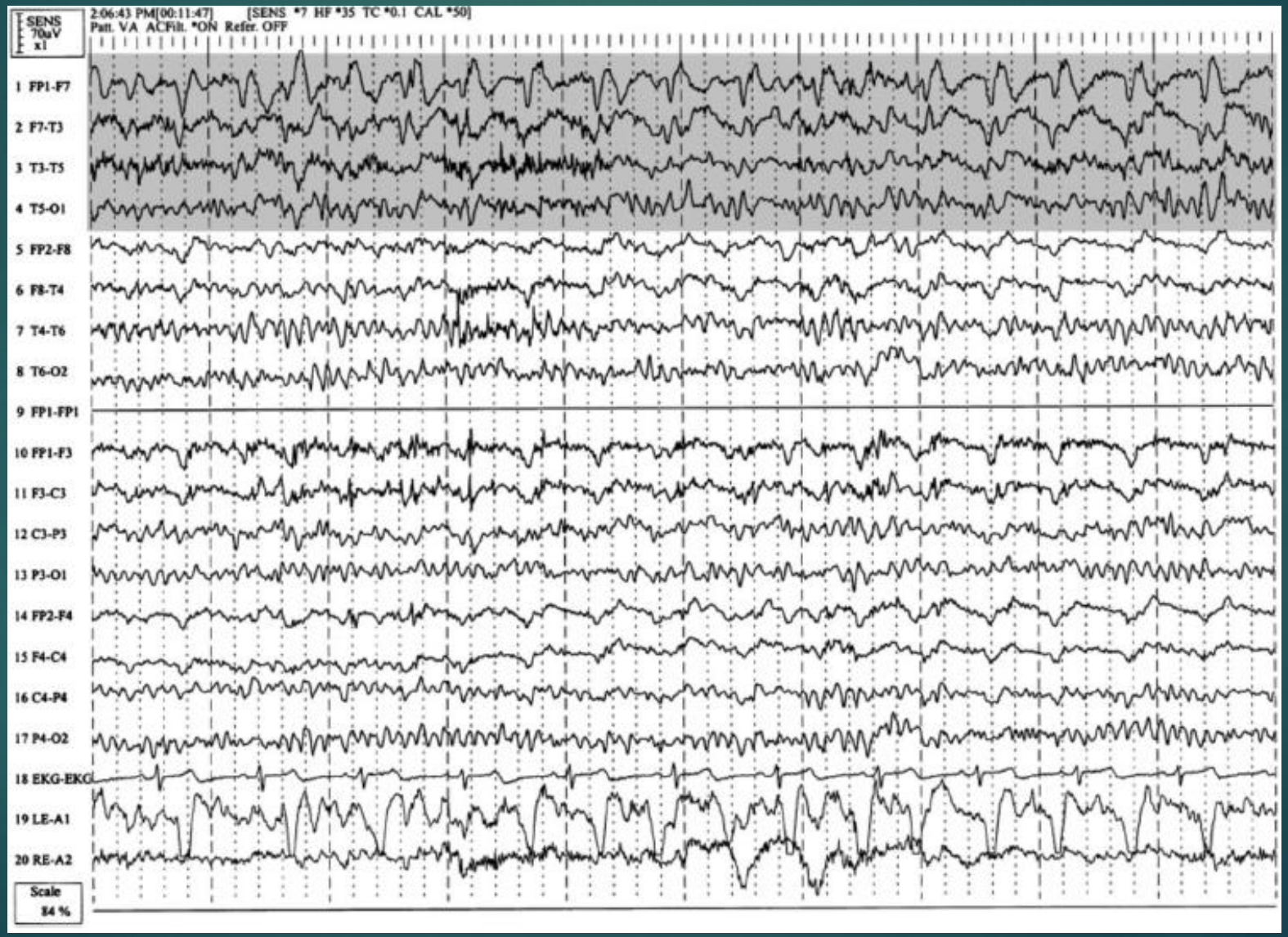
14:26:41
14:26:42
14:26:43
14:26:44
FP2 - F8
F8 - T4
T4 - T6
T6 - O2
Empty
FP1 - F7
F7 - T3
T3 - T5
T5 - O1
ECG 28
FP2 - F4
F4 - C4
C4 - P4
P4 - O2
Empty
FP1 - F3
F3 - C3
C3 - P3
P3 - O1
Empty
FZ - CZ
CZ - PZ

Anti-LGI1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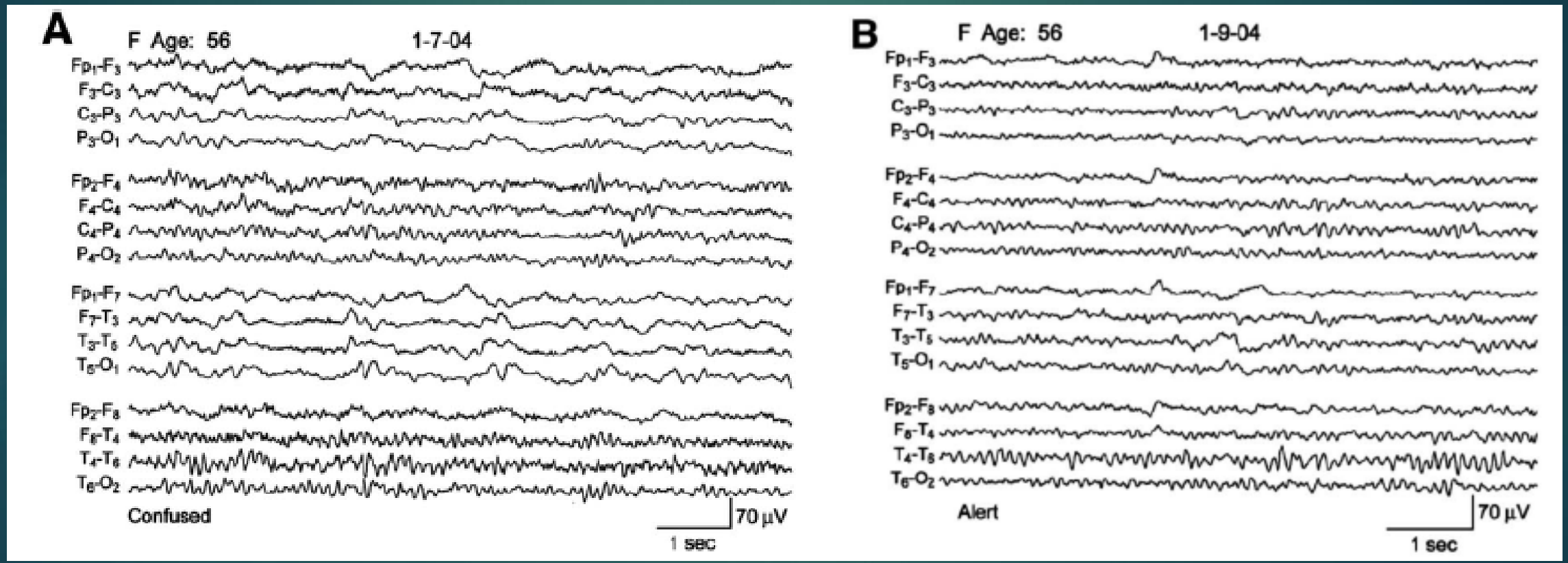
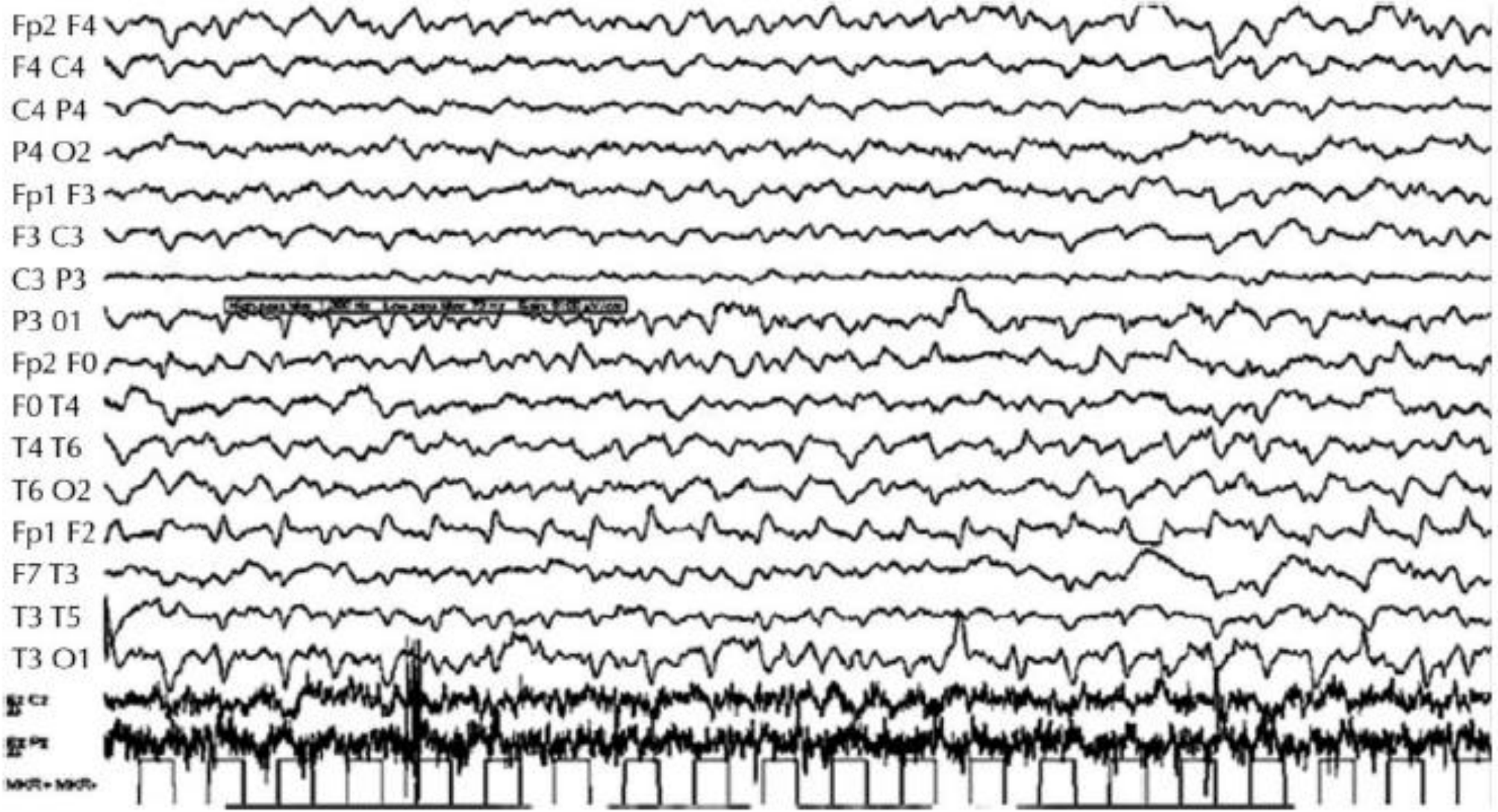
2:06:43 PM[00:11:47] [SENS *7 HF *35 TC *0.1 CAL *50]
Patt. VA ACFilt. *ON Refer. OFF
1 FP1-F7
2 F7-T3
3 T3-T5
4 T5-O1
5 FP2-F8
6 F8-T4
7 T4-T6
8 T6-O2
9 FP1-FP1
10 FP1-F3
11 F3-C3
12 C3-P3
13 P3-O1
14 FP2-F4
15 F4-C4
16 C4-P4
17 P4-O2
18 EKG-EKG
19 LE-A1
20 RE-A2
Scale 84 %

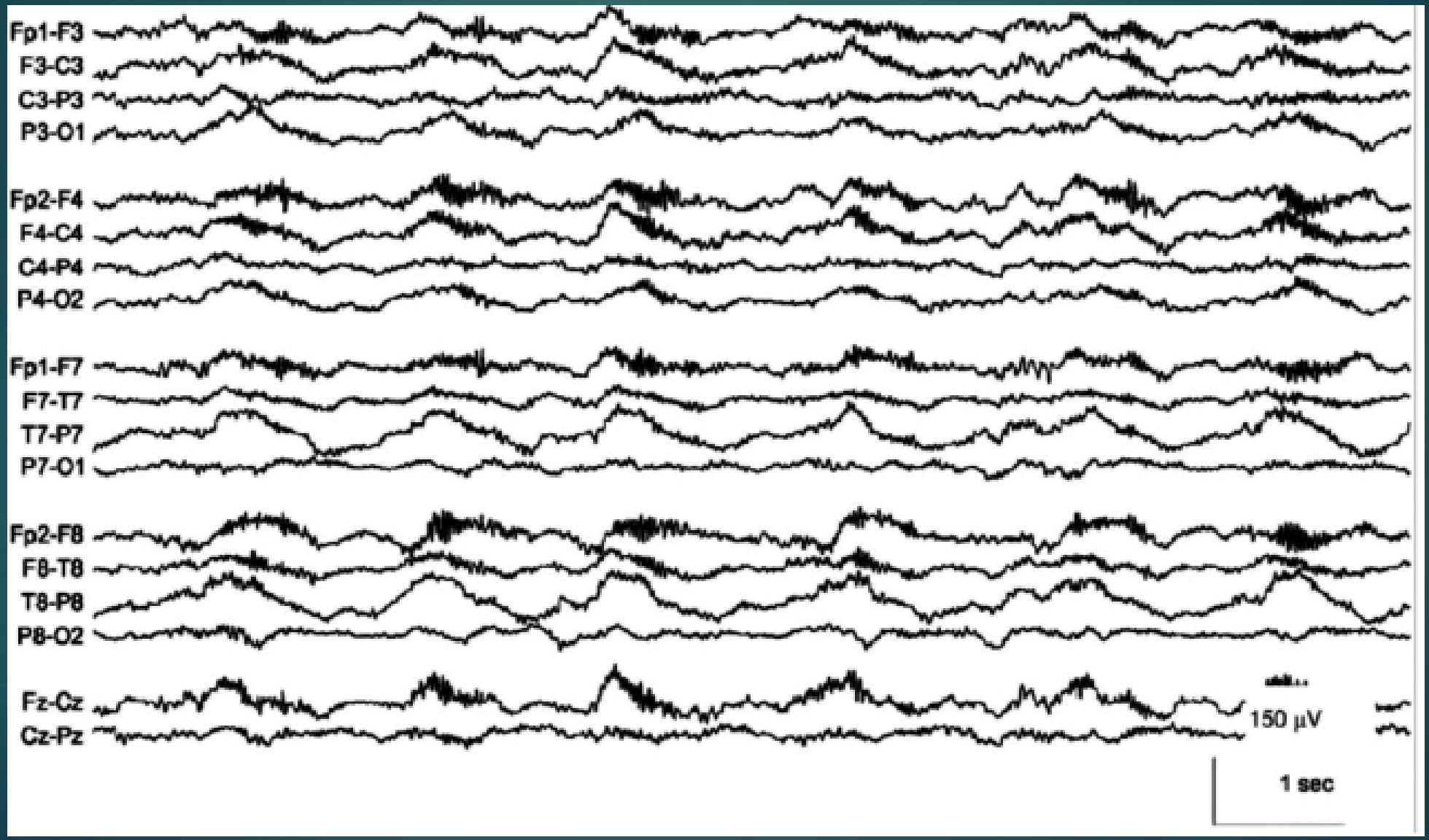
Hashimoto


A
F Age: 56
1-7-04
Fp1-F3
F3-C3
C3-P3
P3-O1
Fp2-F4
F4-C4
C4-P4
P4-O2
Fp1-F7
F7-T3
T3-T5
T5-O1
Fp2-F8
F8-T4
T4-T6
T6-O2
Confused
70 µV
1 sec
B
F Age: 56
1-9-04
Fp1-F3
F3-C3
C3-P3
P3-O1
Fp2-F4
F4-C4
C4-P4
P4-O2
Fp1-F7
F7-T3
T3-T5
T5-O1
Fp2-F8
F8-T4
T4-T6
T6-O2
Alert
70 µV
1 sec

Anti-NMDAR


Fp2 F4
F4 C4
C4 P4
P4 O2
Fp1 F3
F3 C3
C3 P3
P3 01
Fp2 F0
F0 T4
T4 T6
T6 O2
Fp1 F2
F7 T3
T3 T5
T3 O1

Anti-NMDAR


Fp1-F3
F3-C3
C3-P3
P3-O1
Fp2-F4
F4-C4
C4-P4
P4-O2
Fp1-F7
F7-T7
T7-P7
P7-O1
Fp2-F8
F8-T8
T8-P8
P8-O2
Fz-Cz
Cz-Pz
150 µV
1 sec

Trattamento e prognosi

- Prima linea: steroidi o IgEV o plasmaferesi
- Seconda linea: rituximab, ciclofosfamide, altro
- Se paraneo: chirurgia neoplasia
- La prognosi è influenzata dalla rapidità del trattamento
- Le recidive non sono rare (10-20%)