La stadiazione della SLA: ingravescenza di malattia

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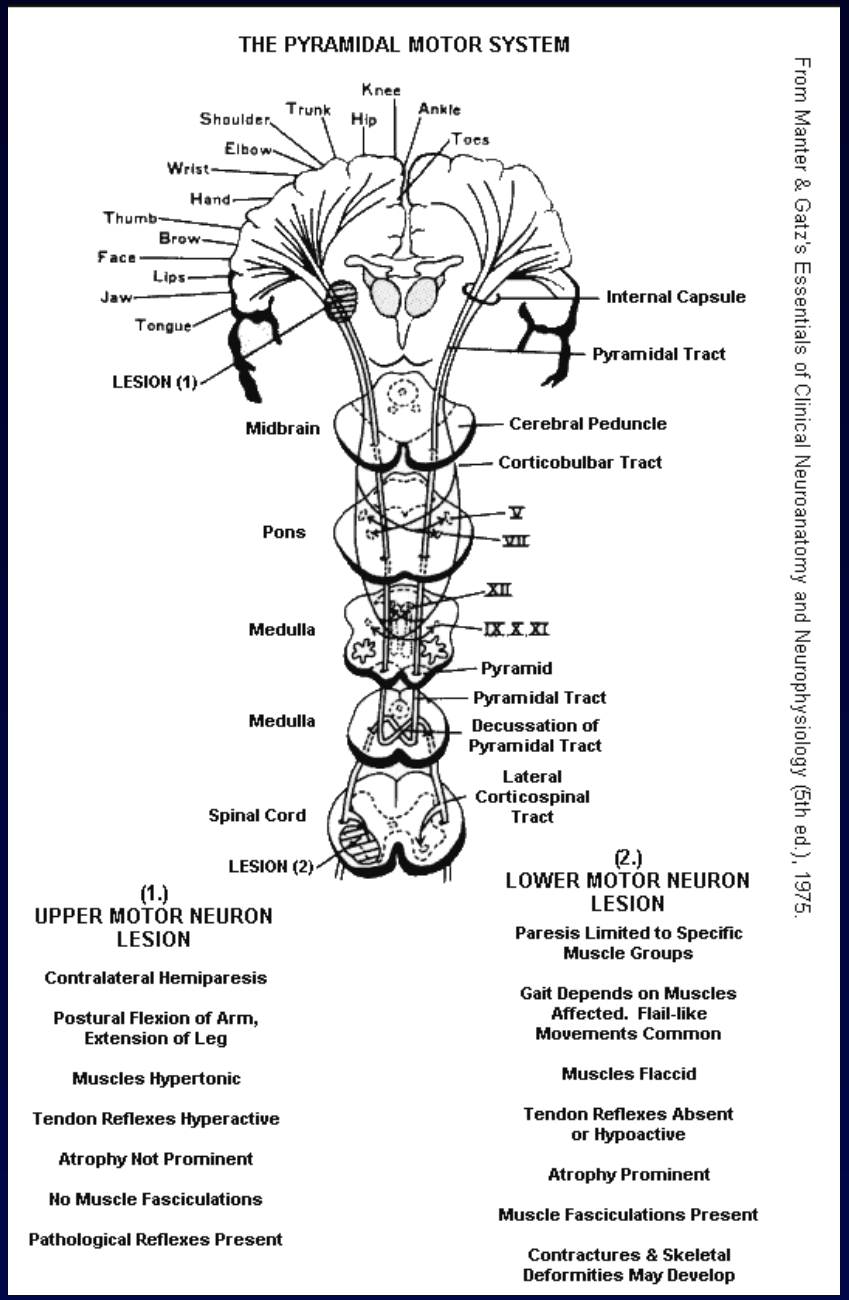
Diagnosi di SLA: una lotta contro il tempo!

- Tempo medio alla diagnosi: > 12 mesi !
- SLA: in un ampio spettro di Malattie del Motoneurone che causano degenerazione del I° e/o II° MN
- La SLA “classica” colpisce sia il I° che II° MN
- Nelle fasi precosi: l’ interessamento del I° o del II° MN può creare problemi
- Diagnosi corretta nel 95% dei casi, diagnosi precoce errata in 27% dei pazienti (Belsh and Shiffman, 1996)
- “L’ ultimo medico è sempre il più bravo” !

Diagnosi di SLA: una lotta contro il tempo

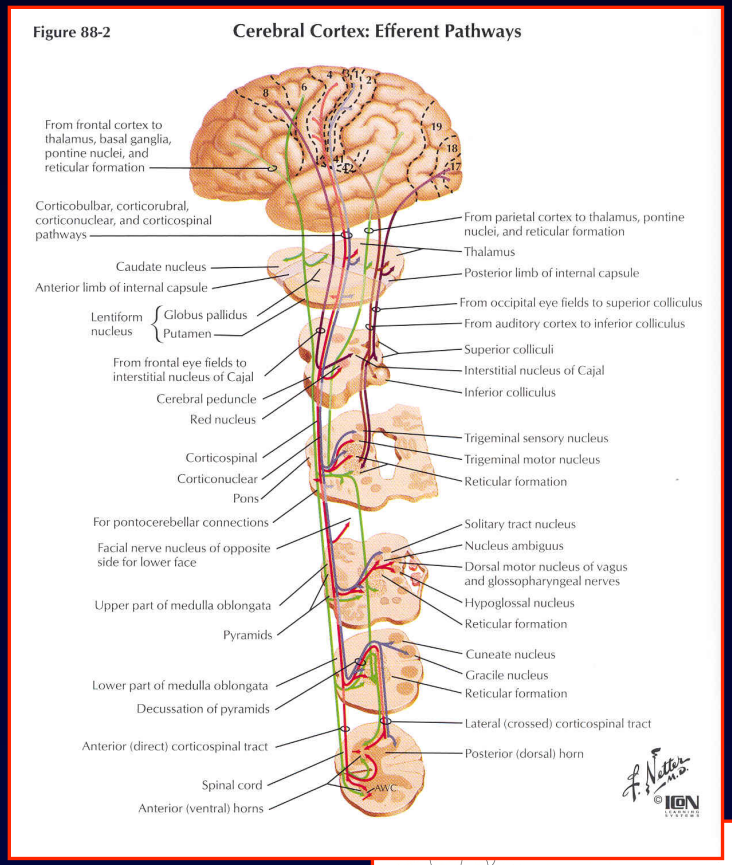
- WFN El Escorial Criteria 1994, 2000: nelle fasi precosi limitano la certezza diagnostica
- Diagnosi: falsi+ e falsi– importanti
- Non esiste un singolo test specifico per la SLA: la diagnosi si basa su un' anamnesi attenta ed una valutazione clinica accurata
- Sindromi SLA-Plus: malattia multisistemica (disfunzioni cognitive, per esempio)

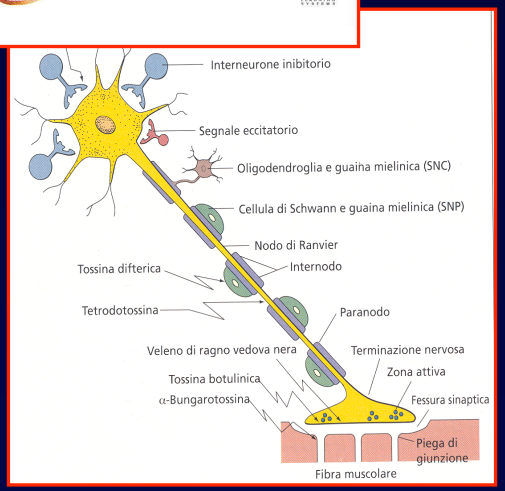
Il sistema

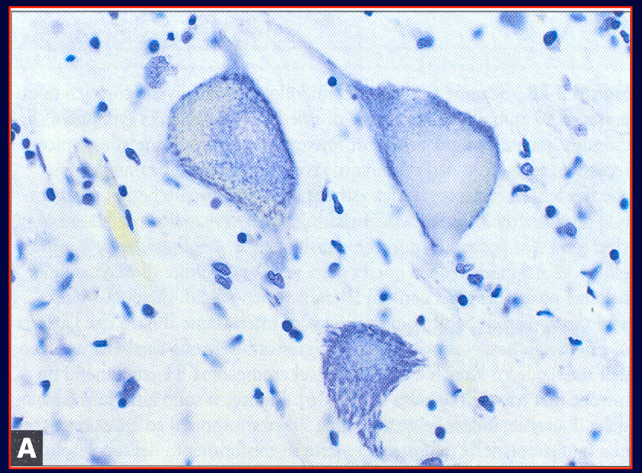

THE PYRAMIDAL MOTOR SYSTEM
Knee
Shoulder
Trunk
Hip
Ankle
Elbow
Toes
Wrist
Hand
Thumb
Brow
Face
Lips
Jaw
Tongue
LESION (1)
Internal Capsule
Pyramidal Tract
Midbrain
Cerebral Peduncle
Corticobulbar Tract
Pons
V
VIII
XII
Medulla
IX, X, XI
Pyramid
Pyramidal Tract
Medulla
Decussation of Pyramidal Tract
Lateral Corticospinal Tract
Spinal Cord
LESION (2)
(1.)
UPPER MOTOR NEURON LESION
Contralateral Hemiparesis
Postural Flexion of Arm, Extension of Leg
Muscles Hypertonic
Tendon Reflexes Hyperactive
Atrophy Not Prominent
No Muscle Fasciculations
Pathological Reflexes Present
(2.)
LOWER MOTOR NEURON LESION
Paresis Limited to Specific Muscle Groups
Gait Depends on Muscles Affected. Flail-like Movements Common
Muscles Flaccid
Tendon Reflexes Absent or Hypoactive
Atrophy Prominent
Muscle Fasciculations Present
Contractures & Skeletal Deformities May Develop
From Manter & Gatz's Essentials of Clinical Neuroanatomy and Neurophysiology (5th ed.), 1975.

SLA e Malattie del Motoneurone

Una malattia da vulnerabilità selettiva di un sistema







Motoneuroni SLA

Passi richiesti per la diagnosi di SLA (WFN guidelines)

Momenti	Razionale
1. Anamnesi, esame fisico	Rilievo di segni/sintomi evocativi per il livello di certezza diagnostica
2. EMG	Degenerazione di II° MN nelle regioni clinicamente interessate Degenerazione del II° MN in regioni clinicamente non ineteressate Esclusione di altri disordini

Criteri d' esclusione!

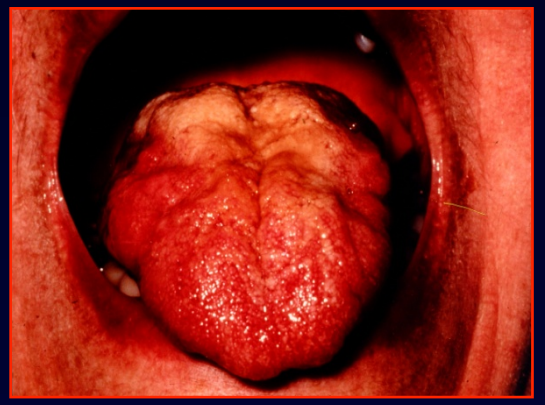
Mitsumoto et al, 1998, 2006

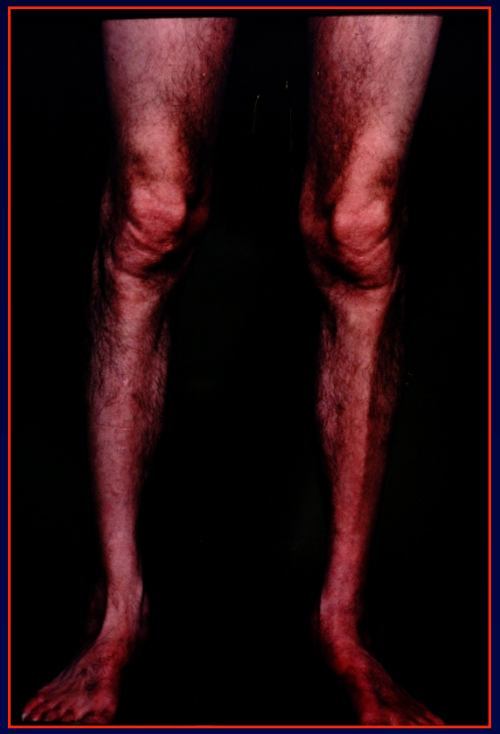
El Escorial ha imposto rigore:

sine qua non: segni/sintomi di I° e II° MN

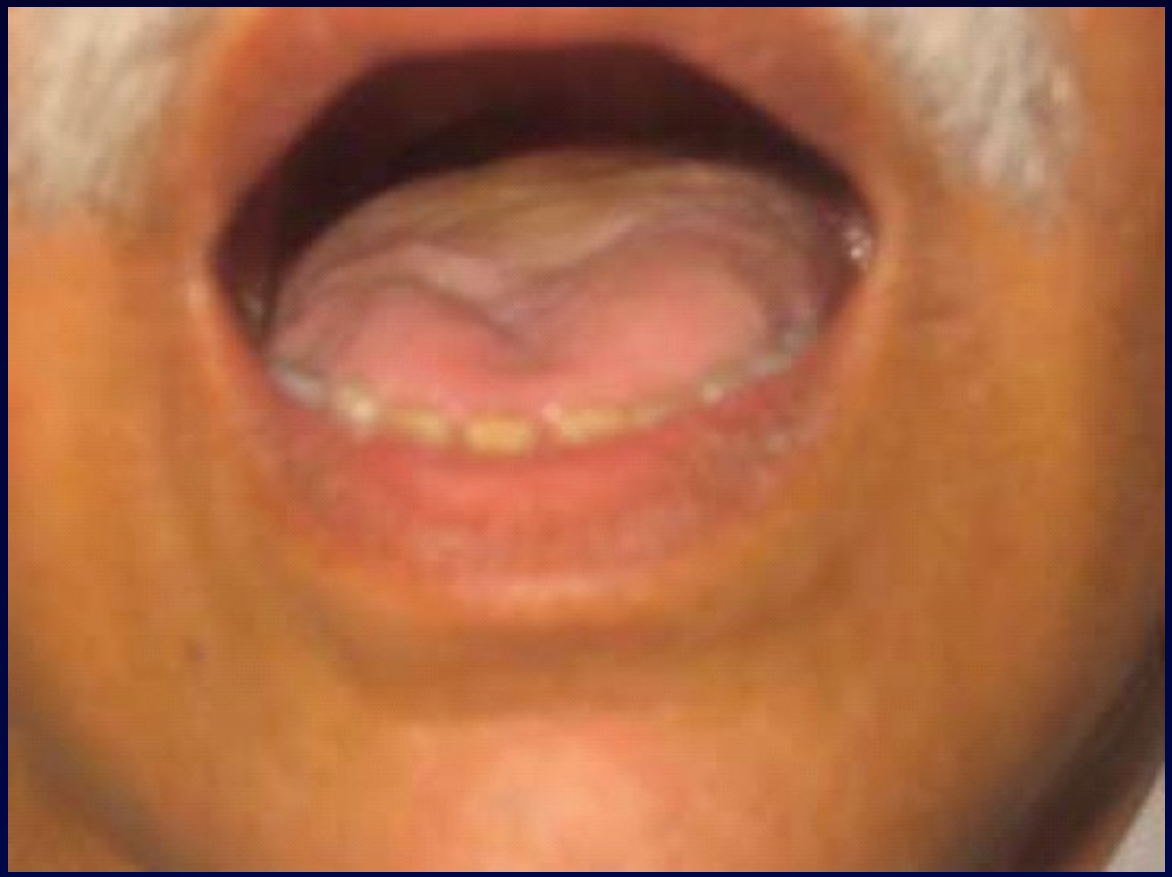
	Bulbare	Cervicale	Toracico Abdominale	Lombare
I° MN	+	+	+/-	+
II° MN	+	+	+	+

SLA clinicamente definita





In patients with ALS bulbar onset, the muscles of speech are typically involved before those of swallowing



Wasting of the tongue with fasciculations

sine qua non: segni di I° e II° MN

UMN and LMN findings in bulbar and limb muscles in ALS

Bulbar	
UMN symptoms	*LMN symptoms*
Dsyphagia	Difficulty chewing
Spastic dysarthria	Sialorrhea
Laryngosapasm	Dysphagia
Pseudobulbar affect	Slurred speech
Cheek biting	Hoarseness
UMN signs	*LMN signs*
Poor palate movement	Facial weakness
Slow tongue movement	Tongue weakness
Jaw jerk	Tongue atrophy
Palmomental sign	Facial/tongue fasciculations
Active facial reflex	
Limb	
UMN symptoms	*LMN symptoms*
Stiff, slow movement	Weakness
Clonus triggered by movement	Cramps
UMN signs	*LMN signs*
Spasticity	Weakness
Hyperreflexia	Muscle atrophy
Spastic gait	Fasciculations
Pathologic reflexes (Babinski, Hoffman's)	Hyporeflexia

sine qua non: segni di I° e II° MN

UMN and LMN findings in axial and respiratory muscles in ALS

Axial

UMN symptoms
- Unsteadiness

UMN signs
- Absent abdominal reflexes

LMN symptoms
- Head drop/difficulty holding head up
- Trouble standing erect

LMN signs
- Neck extensor weakness
- Bent spine
- Abdominal protuberance

Respiratory

LMN symptoms
- Dyspnea
- Orthopnea
- Morning headache
- Daytime sleepiness
- Confusion

LMN signs
- Tachypnea
- Reduced volume of speech
- Use of accessory muscles
- Abdominal paradox

SLA: esordio clinico

- "Fatigue", perdita di tolleranza all' esercizio, fasciculazioni, crampi, atrofia muscolare, ed ipostenia

- Presentazione clinica in 1535 pazienti (Eisen, 1999)
  disartria (33%),
  disfunzione nondolorosa della mano (20%),
  ipostenia atrofica della spalla (14%),
  caduta del piede (12%),
  fascicolazioni/crampi (11%),
  intolleranza all' esercizio (4%),
  insufficenza respiratoria (4%),
  alterazioni cognitive (2%).

- Ipostenia senza dolore in territori di varie radici nervose in un arto (Ravits et al., 2007).

- Ipostenia della musculatura bulbare all' esordio: meno frequente (15–40%), più spesso nella donna di > 55 anni.

- Nell' esordio bulbare la disartria viene prima della disfagia

- Raramente esordio respiratorio

Presentazione Atipica

Progressione Rapida

- durata media 30 – 36 mesi

- la progressione rapida può essere generalizzata all' inizio

- comune nella FSLA (SOD1A4V)

- con esordio acuto: DD sindrome vascolare acuta

- RMN per l' esordio acuto per una DD di mielopatia compressiva, infettiva, infiltrativa

- sempre necessaria RMN encefalo/midollo (DD: SM)

EMG: modified Lambert's criteria for ALS diagnosis

- NERVE CONDUCTION STUDIES
  - normal sensory nerve conduction studies
    - amplitude may be reduced in entrapment sites and with age
  - normal motor nerve conduction studies
    - in the presence of < amplitude of CMAP, conduction velocity may be <
    - exclusion of persistent conduction block along several peripheral nerves
    - no features of diffuse demyelination (CIDP)

- NEEDLE EMG
  - active denervation (fibrillation potentials) and fasciculation potentials in upper, lower limb, and bulbar muscles
  - reinnervation of motor unit potentials (polyphasic, long duration, high amplitude) with reduced recruitment

Focality of upper and lower motor neuron degeneration at the clinical onset of ALS

ABSTRACT Objective: To localize and analyze the anatomic distribution of upper motor neuron (UMN) and lower motor neuron (LMN) loss in patients with ALS early in their disease when motor manifestations were still relatively focal using clinical examination signs. **Methods:** We reviewed records of 100 patients with ALS who were evaluated when the diagnosis was first established or suspected. From the patient history, we ascertained the body region of first symptoms and the time course. From the physical examination, we separately graded severity of UMN and LMN signs in each body region, indexed these to the body region of first symptoms, and sorted and analyzed the data. **Results:** Motor manifestations began in one body region in 98% of patients. UMN and LMN signs were both maximal in these same body regions, but they were independent of each other in severity and their outward distribution, which conformed to neuronal anatomy. The outward distribution of both UMN and LMN signs seemed more directed to caudal body regions than to rostral ones. **Conclusions:** Motor neuron degeneration in ALS is a focal process at both upper and lower motor neuron levels of the motor system. At each level, it begins corresponding to the same peripheral body region and then advances contiguously and separately to summate over time. **NEUROLOGY 2007;68:1571-1575**

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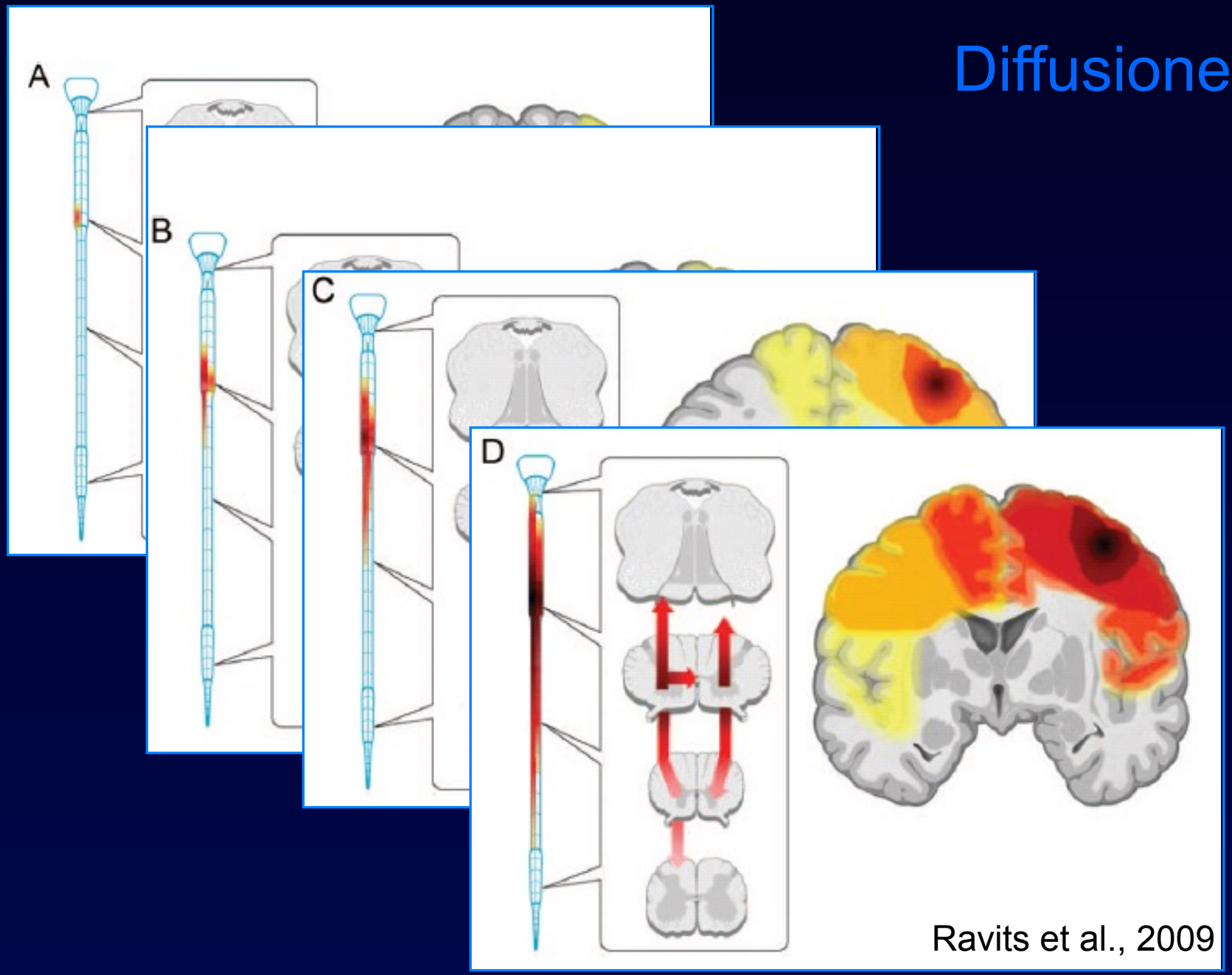
Focalità all' esordio: nuove riflessioni

Table Composite severity scores showing distribution of motor neuron deficits indexed to region of onset

Body region of onset	Body region evaluated	Composite LMN severity scores	Composite UMN severity scores
Bulbar (n = 29)	Bulbar*	102	94
	Both arms	40	40
	Both legs	8	41
Arms (n = 34)	Onset arm (focus)	85	38
	Contralateral arm	41	13
	Ipsilateral leg	14	25
	Contralateral leg	6	20
	Bulbar	6	4
Trunk (n = 6)	Trunk*	24	NA
	Both arms	17	4
	Both legs	8	7
Legs (n = 29)	Onset leg (focus)	66	34
	Contralateral leg	37	24
	Ipsilateral arm	19	17
	Contralateral arm	16	14
	Bulbar	4	3

*Scores are doubled to normalize with limbs.
LMN = lower motor neuron; UMN = upper motor neuron; NA = not applicable.

Diffusione



Ravits et al., 2009

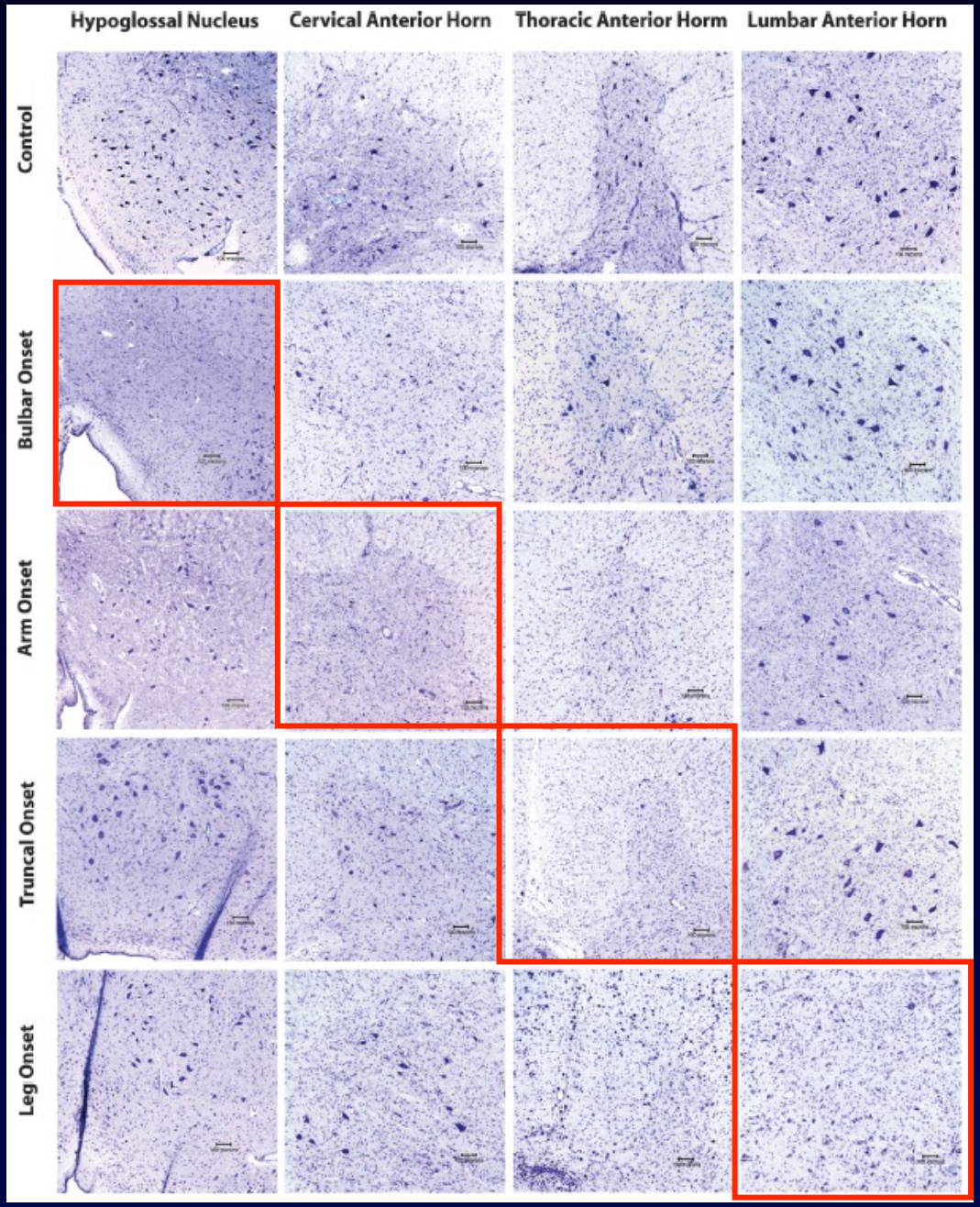
Table Comparison of UMN and LMN 3-dimensional neuroanatomy

Anatomic feature	UMN	LMN
Location	Cerebral cortex	Brainstem and spinal cord
Motor neurons	Giant cells of Betz	Alpha motor neurons
Nuclei	M1 (~Brodmann area 4)	Motor nuclei and anterior gray horn
Microenvironment	Layer V	Rexed lamina IX
3-D arrangement	Laminar	Columnar
Somatotopic arrangement	Lateral to medial	Rostral to caudal
Anatomic span	12 cm per hemisphere	46 cm midbrain to sacral cord
Origination in neurodevelopment	Anterior (rostral) portion of neural tube in line with LMN progenitors	Posterior (caudal) portion of neural tube in line with UMN progenitors
Functional integrations	Prefrontal networks; convergence and divergence with LMNs	Convergence and divergence from UMNs; motor units

UMN = upper motor neuron; LMN = lower motor neuron.

Ravits et al., 2009

Diffusione



Ravits et al., 2007