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ASSOCIAZIONE ITALIANA PSICOGERIATRIA

ASL CITTÀ DI TORINO

# Lo Spettro FTD-SLA


## Adriano Chiò

*Dipartimento di Neuroscienze 'Rita Levi Montalcini', Università degli Studi di Torino, Torino*

*Istituto di Scienze e Tecnologie della Cognizione, CNR, Roma*


CNR ISTC ISTITUTO DI SCIENZE E TECNOLOGIE DELLA COGNIZIONE

CME

# Are amyotrophic lateral sclerosis patients cognitively normal?

NEUROLOGY 2003;60:1094–1097

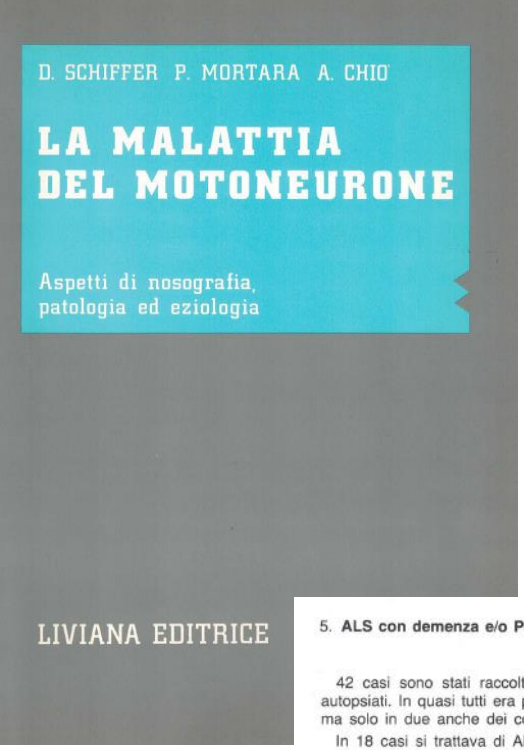
C. Lomen-Hoerth, MD, PhD; J. Murphy, PhD; S. Langmore, PhD; J.H. Kramer, PsyD; R.K. Olney, MD; and B. Miller, MD

***Table 2** Patient characteristics of 44 ALS patients who underwent detailed neuropsychological testing*

| Characteristics | ALS with FTLD | ALS without FTLD |
|---|---|---|
| No. of subjects | 23 | 21 |
| Age, y | 65, range 42–80 | 54, range 37–81 |
| Sex | 14M, 9F | 13M, 8F |
| Site of onset | 11 bulbar, 12 limb | 8 bulbar, 13 limb |
| Family history | 6 dementia, 2 PD, 4 ALS | 3 ALS, 1 PD |
| FVC | 66% predicted, range 0*–117 | 95% predicted, range 32–157 |
| ALSFRS score | 34, range 17–46 | 37, range 22–47 |

* The one patient with an unrecordable FVC presented to our clinic already on a ventilator.

- Il 52% dei pazienti studiati soddisfaceva i criteri per una FTLD possibile o probabile.




# 1985


5. **ALS con demenza e/o Parkinsonismo**

42 casi sono stati raccolti da Hudson (1981) e di questi 27 sono stati autopsiati. In quasi tutti era presente una degenerazione dei fasci piramidali, ma solo in due anche dei cordoni posteriori.

In 18 casi si trattava di ALS-D. Vi era un'atrofia variabile, specie frontale e temporale, con scomparsa di neuroni, gliosi, specie nel II e III strato dove vi era pure una modica spongiosi. Da notare che nella maggior parte dei casi vi erano degenerazioni neuronali e gliosi anche nello striato, pallido, talamo, corpo del Luys, sostanza nera, nucleo dentato, ecc., senza corrispettiva evidenza clinica. Non si trovarono né NFD, né inclusioni argentofile; in un solo caso erano presenti placche senili. In 8 casi si trattava di ALS-PD.

Oltre alle degenerazioni corticali, come perdita di neuroni, gliosi e degenerazione spongiosa, vi era interessamento della sostanza nera, del pallido e, in alcuni casi, anche di altre strutture (Wechsler e Davidson, 1932; Caidus et al, 1966; Poudouresques et al, 1967; Tsujiyama et al, 1967; Bonduelle et al, 1968; Kaiya e Mehraein, 1974). Tre casi sono stati recentemente descritti da Wikström et al (1982) ed avvicinati a quello descritto da Mitsuyama e Takamiya (1979) in Giappone.

In linea generale il sovraffollarsi di reperti contrastanti rende questo capitolo estremamente confuso. Tyler (1982) ha cercato di mettere ordine distinguendo casi con semplice difficoltà del linguaggio e casi con demenza e parkinsonismo (5%).

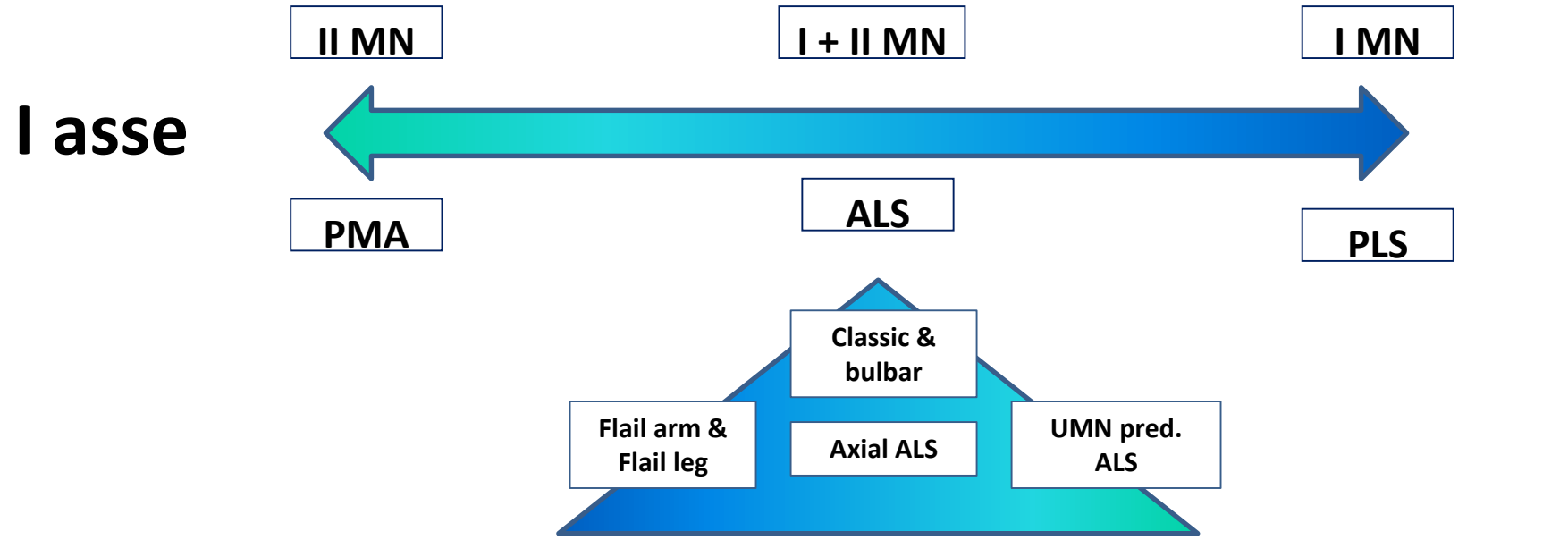
Tra questi ultimi tiene ancora separati i casi con prevalente quadro di ALS da quelli con prevalente quadro di rapida demenza presenile. Nel gruppo ALS egli considera ancora tre tipi di patologia. Vi sono casi con alterazioni corticali e/o spongiotiche, degenerazioni neuronali e proliferazione astrocitaria nella corteccia, nello striato, nei nuclei motori e nelle corna anteriori; casi che si presentano come ALS del tipo CJ con corpi di Bunina, perdita di neuroni, gliosi corticale, del pallido, della amigdala e del talamo, lieve stato spongioso (Hirano et al, 1967; Finlayson e Martin, 1973; Metcalf ed Hirano, 1971; Takahashi et al, 1977; Hart et al, 1977); altri ancora erano simili ma senza inclusioni (Delay et al, 1959; Castaigne et al, 1972; Michaux et al, 1977). Infine vi sono casi con alterazioni tipo morbo di Alzheimer.

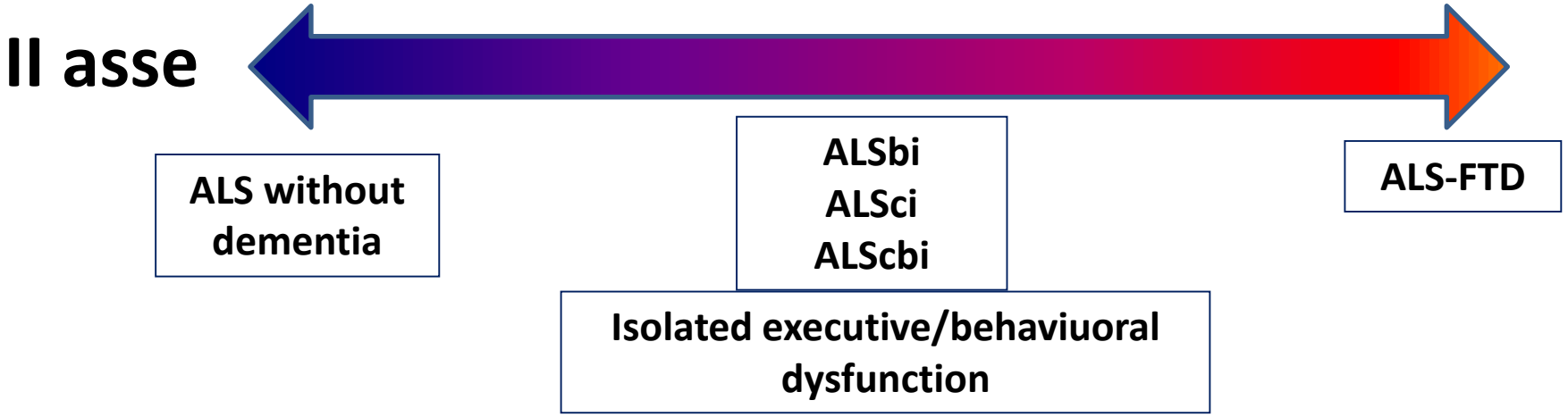
Nel gruppo con rapida demenza, miocloni e lieve amiotrofia, vi è una spongiosi corticale. Ciò induce a discutere dei rapporti fra CJ e ALS, vista anche la frequenza con cui nella prima malattia compaiono amiotrofie. Van Rossum (1965) ha rilevato che nel 21% dei casi di CJ vi sono atrofie muscolari, mentre nel 50% delle autopsie sono presenti degenerazioni delle corna anteriori e demielinizzazione delle vie piramidali. È importante rilevare che in alcuni casi sono stati descritti fratelli con morbo di Alzheimer, Parkinson o ALS (Friede e De Jong, 1964; Van Rossum, 1965). Tyler (1982) ricorda che in nessun caso del gruppo con prevalente ALS la demenza è risultata trasmissibile, mentre questa lo era nel gruppo con prevalente demenza. In linea con questa osservazione sta quella di Roos et al (1973) i quali hanno calcolato che il 17% dei casi con demenza trasmissibile avevano amiotrofie. In pratica, i casi diagnosticati come «forma amiotrofica della CJ» appartengono al secondo gruppo. Questo è confermato da Salazar et al (1983): su 60 casi di «forma amiotrofica di CJ» nessuno ha demenza trasmissibile e la patologia non dimostra spongiosi. Per contro 20 su 140 casi di CJ con trasmissione hanno amiotrofia, ma questa non è né precoce né significativa. Su 2000 casi della letteratura e personali, Salazar et al (1983) hanno trovato 231 casi con precoci segni di interessamento del motoneurone periferico. Questi differivano però dai casi classici di CJ perché la malattia ha più lunga durata, non c'è spongiosi e l'inoculazione ai primati ha dato 2 volte sole su 33 una encefalopatia spongiosa. Perciò i casi con compromissione precoce del motoneurone periferico sono più affini alla ALS che alla CJ, in cui tali segni sono tardivi.

Sono stati descritti casi di ALS con lesioni diffuse, NFD e placche senili del tipo morbo di Alzheimer (Barrett, 1913; Bertrand e Van Bogaert, 1925; Matzdorf, 1925; Sodenbergh e Sjorval, 1929; Lowenberg e Waggoner, 1934; Van Bogaert et al, 1940; Castaigne et al, 1972), ma Tyler (1982) ritiene che l'associazione sia coincidentale. Allo stesso modo egli considera le associazioni descritte tra ALS e morbo di Pick. In tutto sono 12 segnalate in letteratura (Von Braunmühl, 1937; Von Bagh, 1941; Van Mansvelt, 1954; Van Reeth et al, 1961; Minauf e Jellinger, 1969; Poppe e Tennstedt, 1963; Kuràch et al, 1979). In uno di questi casi vi erano lesioni anche a carico della sostanza nera (De Morsier, 1967). Brion et al (1980) considerano tutti i casi cui aggiungono il loro e concludono con tre ipotesi: coincidenza semplice, demenza primitiva con ALS secondaria, ALS con estensione corticale grave.

Un caso di associazione tra demenza presenile ed ALS, senza NFD e placche, è riportato da Mitsuyama e Takamiya (1979), simile a quelli descritti in Giappone da Harada et al (1966), Ynasa (1964, 1970), Tsujiyama et al (1967), Shirabe et al (1970). Questi casi sarebbero diversi da quelli di Guam e secondo Mitsuyama e Takamiya (1979) potrebbero costituire una entità clinico-patologica autonoma. Recentemente lo stesso autore ha raccolto in Giappone 26 casi con questa associazione (Mitsuyama, 1984) ed ha ribadito la possibilità che si tratti di una nuova entità nosografica.

# Le dimensioni fenotipiche della SLA

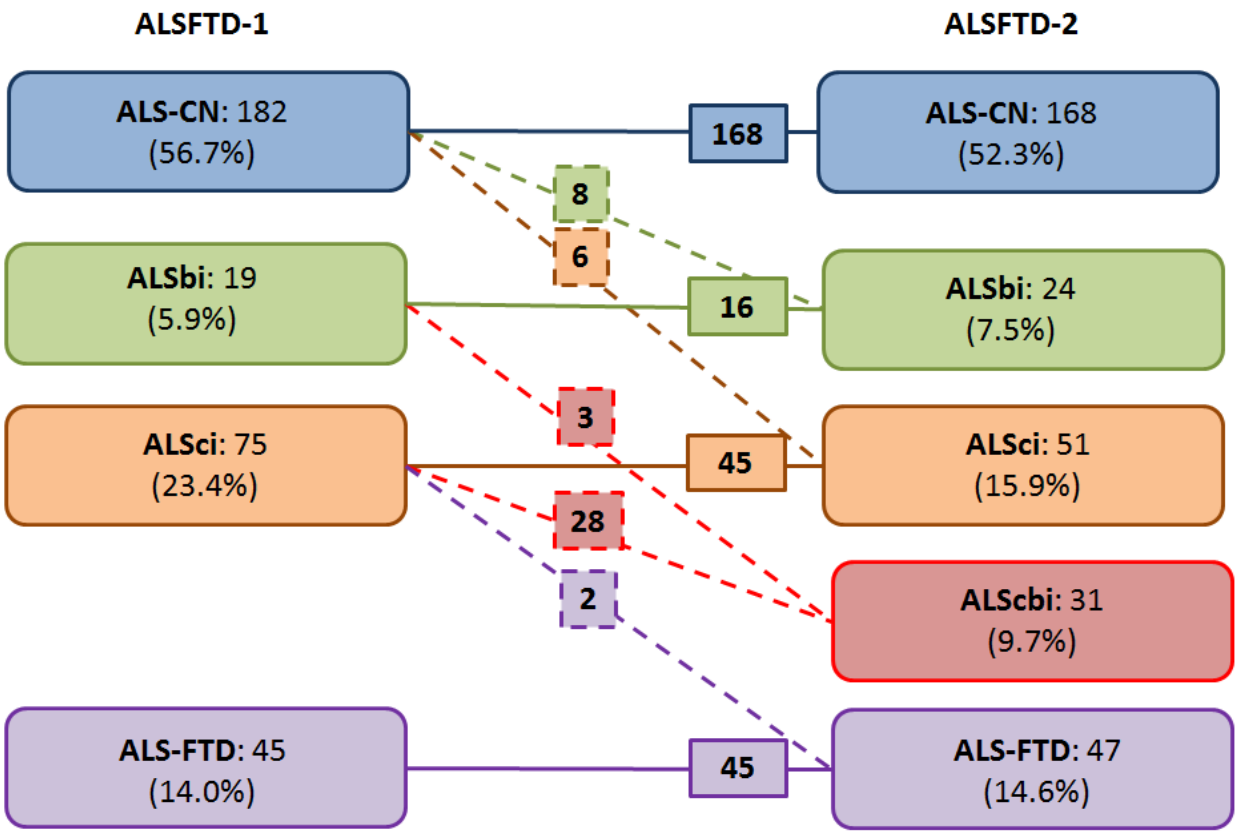


# I nuovi criteri per i disturbi cognitivi nella SLA
## (Strong et al, ALS 2016)

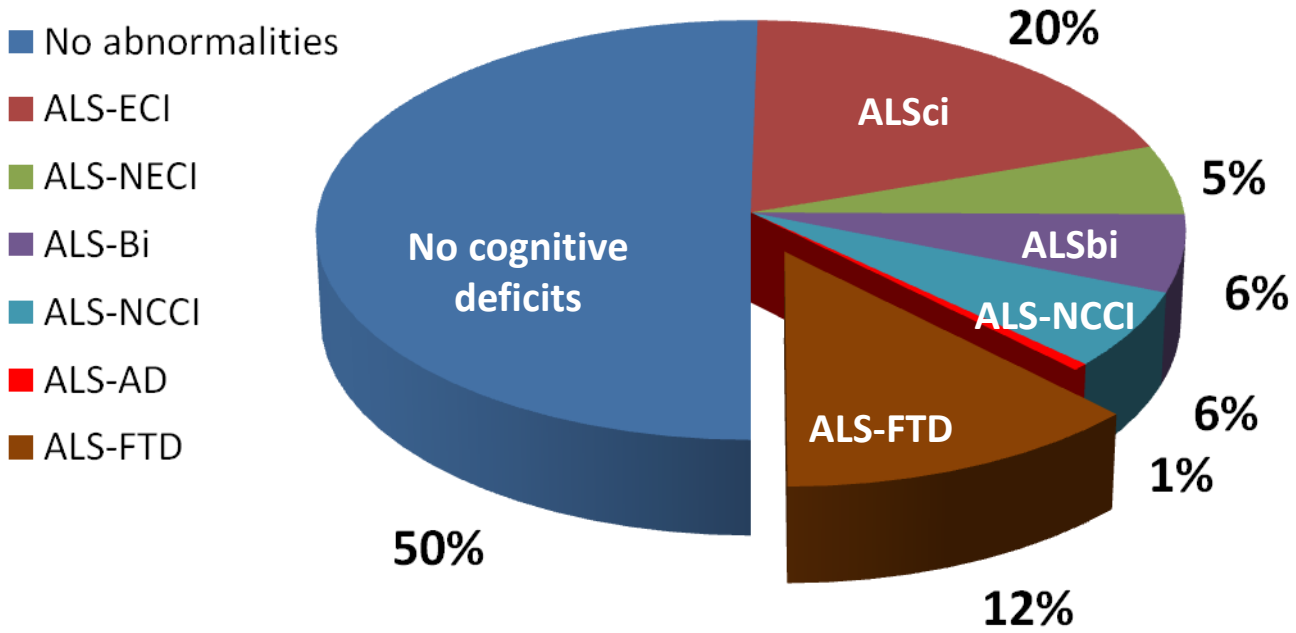
| | |
|---|---|
| **ALSbi** | Apatia *OPPURE* almeno due fra i sintomi elencati fra i criteri di Raskovsky et al (Brain 2011) |
| **ALSci** | Disturbo disesecutivo *OPPURE* disturbo del linguaggio |
| **ALScbi** | Presenza dei criteri sia di ALSbi sia di ALSbi |
| **ALS-FTD** | Evidenza di deterioramento progressivo del comportamento o della cognizione mediante osservazione o storia clinica<br>*E*<br>1. Almeno 3 fra i sintomi cognitivi elencati fra i criteri di Raskovsky et al (Brain 2011)<br>*OPPURE*<br>2. Sintomi cognitivi/comportamentali, associati a perdita di insight e/o sintomi psicotici<br>*OPPURE*<br>3. Sintomi compatibili con demenza semantica/variante semantica di PPA o variante non fluente di PPA |
| **ALS-demenza** | SLA associata ad AD o a demenza vascolare |

# Cambio di categoria tra i criteri ALSFTD-1 e ALSFTD-2: dati del registro piemontese

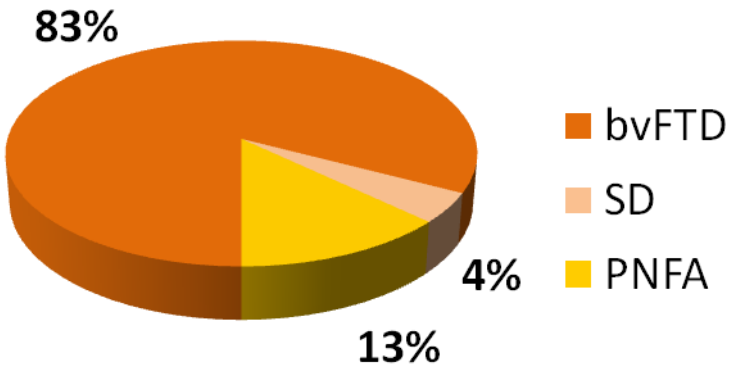



Iazzolino et al, *J Neurol Neurosurg Psychiatry* 2019

# Frequenza dei disturbi cognitivi nella SLA: i dati del registro piemontese




**Dati del registro Piemontese per la SLA (PARALS)**




Montuschi et al, J Neurol Neurosurg Psychiatry 2014

# Eterogeneità fenotipica nella SLA
# La disfunzione cognitiva

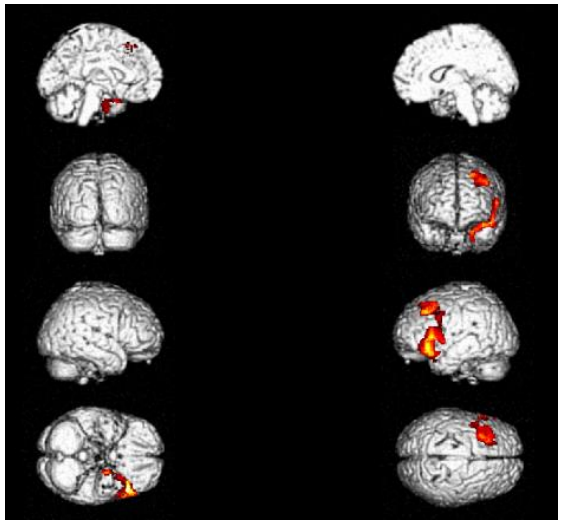
**ALS cognitivamente normali**

**ALS Bi**
**ALS Ci**
**ALScbi**

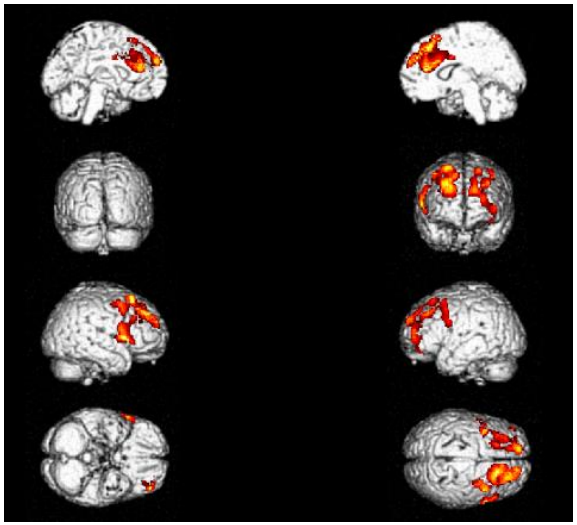
**ALS-FTD**

**Disfunzione esecutiva isolata**

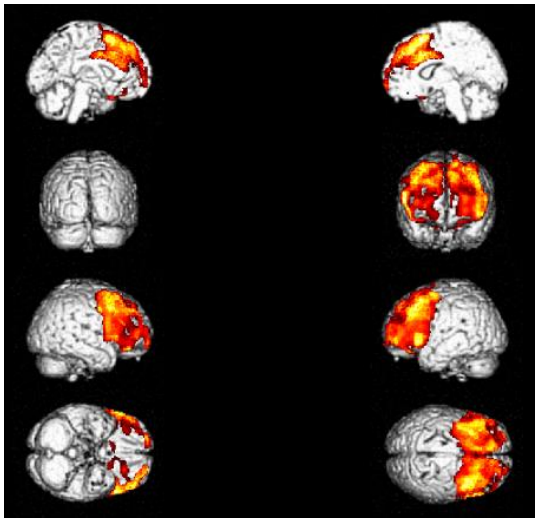
**ALSci**



**ALScbi**



**ALS-FTD**



Canosa et al, submitted

# Con quale frequenza i pazienti con FTD presentano un’evoluzione verso SLA?

# Incidence of early-onset dementias in Cambridgeshire, United Kingdom

L. Mercy, MFPH
J.R. Hodges, MD, FRCP

Neurology® 2008;71:1496–1499

ABSTRACT

**Objective:** To estimate the incidence of early-onset dementias in a defined area of Cambridgeshire served by Addenbrooke's Hospital.

- Tasso di incidenza di FTD <65 anni 3,5/100.000 (2.0-5.7)
- 1 caso su 16 con MND associata

**Table 1** Diagnosis by sex for incident cases of dementia, Cambridgeshire, 2000–2006

| | Age at diagnosis <65 y (n = 54) | | |
|---|---|---|---|
| Clinical diagnosis | Men | Women | Total |
| Alzheimer disease | 9 | 10 | 19 |
| FTD (all types) | 9 | 7 | 16 |
| bv-FTD | 7 | 5 | 12 |
| FTD-MND | 0 | 1 | 1 |
| PNFA | 1 | 0 | 1 |
| Semantic dementia | 1 | 1 | 2 |
| Parkinsonian syndromes (PSP, PD, CBD, DLB, MSA, PPS) | 2 | 3 | 5 |
| Vascular dementia | 2 | 1 | 3 |
| Huntington disease | 5 (2 with dementia) | 4 (2 with dementia) | 9 |
| Secondary dementias | 1 | 1 | 2 |
| Total | 28 | 26 | 54 |

FTD = frontotemporal dementia; bv-FTD = behavioral variant FTD; MND = motor neuron disease; PNFA = progressive nonfluent aphasia; PSP = progressive supranuclear palsy; PD = Parkinson disease; CBD = corticobasal degeneration; DLB = diffuse Lewy body disease; MSA = multisystem atrophy; PPS = parkinsonism-plus syndromes.

# The overlap of amyotrophic lateral sclerosis and frontotemporal dementia

Catherine Lomen-Hoerth, MD, PhD; Thomas Anderson, MD; and Bruce Miller, MD

**Abstract**—Patients with frontotemporal dementia (FTD) with no known diagnosis of ALS or family history of ALS were clinically and electrophysiologically assessed for the presence of ALS. Of 36 patients studied, five met criteria for a definite diagnosis of ALS and two had EMG findings suggestive of denervation in one limb. An additional five patients had prominent fasciculations and six other patients had trouble swallowing but all had normal results on EMG studies. One of the patients with fasciculations and a normal EMG study progressed to definite ALS over the course of 1 year.

NEUROLOGY 2002;59:1077–1079

- Studio su 36 pazienti con **FTD**
- Analisi da parte di esperti di SLA con valutazione neurofisiologica
  - 5 (16%) avevano i criteri per SLA definita
  - 13 (36%) avevano i criteri per SLA possibile
    - 1 di questi pazienti aveva sviluppato SLA definita dopo 1 anno

***Table** Clinical characteristics of 36 patients with sporadic FTD*

| Characteristic | FTD, n = 30 | ALS–FTD, n = 6 |
|---|---|---|
| Age, y | 64 (43–82) | 56 (46–71) |
| Sex, F/M | 13/17 | 4/2 |
| Duration of dementia symptoms, y | 4 (1–9) | 3 (2–5) |
| EMG | Normal | Diffuse motor neuron disease |

* Average values are listed with the range in parentheses.

FTD = frontotemporal dementia.

# Prevalence, characteristics, and survival of frontotemporal lobar degeneration syndromes

Ian T.S. Coyle-Gilchrist, MBBS
Katrina M. Dick, BSc
Karalyn Patterson, FMedSci

OPEN

Neurology® 2016;86:1736-1743

Studio epidemiologico in due contee UK (Cambridgeshire and Norfolk)

**Table 1** Clinical features at the time of detailed clinical assessment for 200 of 204 cases identified during the PiPPIN Study

| | All | bvFTD | PSP | CBS | nfvPPA | svPPA | PPA |
|---|---|---|---|---|---|---|---|
| Total cases | 200 | 42 | 48 | 48 | 28 | 23 | 11 |
| M/F | 93/107 | 19/23 | 29/19 | 17/31 | 11/17 | 12/11 | 5/6 |
| Mean age at assessment, y (SD) | 69.4 (8.7) | 63.7 (7.9) | 72.6 (7.8) | 70.8 (8.5) | 70.6 (9.8) | 66.7 (6.7) | 72.6 (7.8) |
| Mean years from onset to assessment (SD) | 4.3 (2.9) | 4.4 (3.0) | 4.7 (3.5) | 4.4 (2.7) | 3.7 (2.5) | 4.4 (2.7) | 4.2 (2.3) |
| Behavioral changes, n (%) | 158 (79) | 42 (100.0) | 40 (83.3) | 36 (75.0) | 13 (46.4) | 22 (95.7) | 5 (45.5) |
| Language impairment, n (%) | 138 (69.0) | 31 (73.8) | 13 (27.1) | 32 (66.7) | 28 (100.0) | 23 (100.0) | 11 (100.0) |
| Akinesia, n (%) | 110 (55.0) | 27 (64.3) | 43 (89.6) | 30 (62.5) | 5 (17.9) | 3 (13.0) | 2 (18.2) |
| Rigidity (%) | 85 (42.5) | 9 (21.4) | 41 (85.4) | 33 (68.8) | 1 (3.6) | 0 (0.0) | 1 (9.1) |
| Dystonia, n (%) | 58 (29.0) | 4 (9.5) | 28 (58.3) | 26 (54.2) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Apraxia, n (%) | 108 (54.0) | 12 (28.6) | 25 (52.1) | 45 (93.8) | 16 (57.1) | 2 (8.7) | 8 (72.7) |
| Supranuclear gaze paresis, n (%) | 76 (38.0) | 3 (7.1) | 47 (97.9) | 22 (45.8) | 2 (7.1) | 0 (0.0) | 2 (18.2) |
| Postural instability/falls, n (%) | 89 (44.5) | 7 (16.7) | 47 (97.9) | 32 (66.7) | 2 (7.1) | 0 (0.0) | 1 (9.1) |
| Features of motor neuron disease, n (%) | 9 (4.5) | 8 (19.0) | 0 (0.0) | 1 (2.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) |

# Incidence of frontotemporal lobar degeneration in Italy

## The Salento-Brescia Registry study

Giancarlo Logroscino, MD, PhD, Marco Piccininni, MSc, Giuliano Binetti, MD, Chiara Zecca, MSc, Rosanna Turrone, PhD, Rosa Capozzo, MD, Rosanna Tortelli, MD, PhD, Petronilla Battista, PhD, Eriola Bagoj, MSc, Roberta Barone, MSc, Silvia Fostinelli, PhD, Luisa Benussi, PhD, Roberta Ghidoni, PhD, Alessandro Padovani, MD, PhD, Stefano F. Cappa, MD, Antonella Alberici, MD, and Barbara Borroni, MD

**Correspondence**
Dr. Logroscino
giancarlo.logroscino@uniba.it

*Neurology*® 2019;92:e2355-e2363. doi:10.1212/WNL.0000000000007498

- 1/1/2017-31/12/2017, 2.100.000 abitanti
- 63 casi di FTD
- Incidenza 3,05 (2.3-3.9)/100.000 abitanti
- 2 casi (3.2%) con diagnosi di FTD-ALS
- 2 casi con segni di motoneurone (1 bvFTD, 1 PSP)

**Table 1** Clinical and demographic characteristics of incident cases of FTLD at the time of assessment (Salento-Brescia Registry, 2017)

| Variable | All | bvFTD | CBS | FTD-ALS | nfvPPA | uPPA | PSP |
|---|---|---|---|---|---|---|---|
| Total cases, n | 63 | 23 | 7 | 2 | 19 | 3 | 9 |
| M/F, n | 31/32 | 15/8 | 4/3 | 1/1 | 6/13 | 1/2 | 4/5 |
| Age at diagnosis, (mean ± SD), y | 71.29 ± 7.82 | 68.39 ± 6.40 | 69.86 ± 8.65 | 70.00 ± 9.90 | 73.37 ± 9.41 | 72.00 ± 10.15 | 75.44 ± 3.43 |
| Education, mean ± SD, y | 7.54 ± 3.64 | 7.61 ± 4.23 | 8.00 ± 3.37 | 9.00 ± 1.41 | 7.16 ± 3.42 | 5.00 ± 0.00 | 8.33 ± 4.47 |
| Onset-diagnosis interval, mean ± SD, mo | 32.89 ± 26.81 | 38.26 ± 29.46 | 33.00 ± 32.67 | 11.89 ± 12.46 | 29.71 ± 10.65 | 45.54 ± 25.76 | 38.91 ± 38.10 |
| Behavioral symptoms, % (n)[a] | 80.65 (50) | 100.00 (23) | 85.71 (6) | 100.00 (2) | 63.16 (12) | 33.33 (1) | 75.00 (6) |
| Reduction in speech fluency, % (n)[a] | 55.17 (32) | 33.33 (7) | 42.86 (3) | 0.00 (0) | 100.00 (19) | 0.00 (0) | 50.00 (3) |
| Impaired single-word comprehension, % (n)[a] | 15.69 (8) | 18.75 (3) | 16.67 (1) | 0.00 (0) | 16.67 (3) | 33.33 (1) | 0.00 (0) |
| Phonemic paraphasia, % (n)[a] | 33.33 (19) | 4.76 (1) | 50.00 (3) | 50.00 (1) | 68.42 (13) | 33.33 (1) | 0.00 (0) |
| Stuttering, % (n)[a] | 3.45 (2) | 0.00 (0) | 16.67 (1) | 0.00 (0) | 5.26 (1) | 0.00 (0) | 0.00 (0) |
| Bradykinesia, % (n) | 28.57 (18) | 13.04 (3) | 71.43 (5) | 50.00 (1) | 5.26 (1) | 0.00 (0) | 88.89 (8) |
| Muscular rigidity, % (n) | 30.16 (19) | 13.04 (3) | 85.71 (6) | 0.00 (0) | 5.26 (1) | 0.00 (0) | 100.00 (9) |
| Dystonia, % (n) | 3.17 (2) | 4.35 (1) | 14.29 (1) | 0.00 (0) | 0.00 (0) | 0.00 (0) | 0.00 (0) |
| Motoneuron symptoms/signs, % (n) | 6.35 (4) | 4.35 (1) | 0.00 (0) | 100.00 (2) | 0.00 (0) | 0.00 (0) | 11.11 (1) |
| Apraxia, % (n)[a] | 28.33 (17) | 13.04 (3) | 83.33 (5) | 0.00 (0) | 21.05 (4) | 33.33 (1) | 57.14 (4) |
| Supranuclear gaze palsy, % (n) | 14.29 (9) | 0.00 (0) | 0.00 (0) | 0.00 (0) | 0.00 (0) | 0.00 (0) | 100.00 (9) |
| Postural instability/falls, % (n)[a] | 16.13 (10) | 0.00 (0) | 33.33 (2) | 50.00 (1) | 0.00 (0) | 0.00 (0) | 77.78 (7) |

Abbreviations: bvFTD = behavioral variant of frontotemporal dementia; CBS = corticobasal syndrome; FTD-ALS = frontotemporal dementia–amyotrophic lateral sclerosis; FTLD = frontotemporal lobar degeneration; nfvPPA = nonfluent agrammatic variant primary progressive aphasia; PSP = progressive supranuclear palsy; uPPA = unspecified primary progressive aphasia, other language and speech disorder (not classifiable as nfvPPA or semantic variant PPA).
[a] Because of the presence of missing values, percentages are not computed from the whole sample size.

# Predicting Development of Amyotrophic Lateral Sclerosis in Frontotemporal Dementia

Journal of Alzheimer's Disease 58 (2017) 163–170

Tim Van Langenhove[a,b,c,d,e,*], Olivier Piguet[a,b,c], James R. Burrell[a,b,c], Cristian Leyton[a,b,f,g],

Table 3
Clinical characteristics of FTD patients who developed ALS compared with those that did not develop ALS

| | Developed ALS | Did not develop ALS | Comparison |
|---|---|---|---|
| Number | 8 | 144 | — |
| Male, *n* (%) | 3 (37.5) | 86 (60.1) | $p=0.27$ |
| Age at onset, y, mean ± SD | 63.1 ± 8.9 | 59.6 ± 9.0 | $p=0.35$ |
| Survival, m, mean ± SD | 56.2 ± 25.5 | 99.7 ± 42.9 | $p=\mathbf{0.01}$ |
| Family history, *n* (%) | 1 (12.5) | 27 (18.8) | $p=1$ |
| *C9orf72* positive, *n* (%) | 3 (37.5) | 10 (6.9) | $p=\mathbf{0.02}$ |
| Behavior changes, *n* (%) | | | |
| Disinhibition | 5 (62.5) | 68 (47.5) | $p=0.48$ |
| Eating habit changes | 5 (62.5) | 75 (52.4) | $p=0.44$ |
| Stereotypical behavior | 7 (87.5) | 87 (60.8) | $p=0.67$ |
| Apathy | 6 (75.0) | 101 (70.6) | $p=0.63$ |
| Loss of empathy | 7 (87.5) | 93 (65.0) | $p=1$ |
| Hallucinations or delusions | 0 (0.0) | 16 (11.2) | $p=0.58$ |
| Language changes, *n* (%) | | | |
| Impaired naming | 7 (75.0) | 73 (23.8) | $p=0.067$ |
| Impaired comprehension | 3 (38.5) | 58 (15.9) | $p=1$ |
| Apraxia of speech | 5 (62.5) | 36 (16.8) | $p=\mathbf{0.03}$ |
| Agrammatism | 5 (62.5) | 27 (22.4) | $p=\mathbf{0.01}$ |
| Neuropsychological assessment | | | |
| ACE-III (/100) | 67.3 ± 11.9 | 72.8 ± 2.8 | $p=0.21$ |
| Digit span, forward | 5.3 ± 0.8 | 5.7 ± 1.7 | $p=0.43$ |
| Digit span, backward | 3.2 ± 0.4 | 3.9 ± 1.5 | $p=0.11$ |
| FAS letter fluency | 9.6 ± 2.6 | 21.2 ± 12.8 | $p=\mathbf{0.02}$ |
| RCF copy | 24.9 ± 7.4 | 29.2 ± 5.8 | $p=0.09$ |
| RCF recall | 13.2 ± 10.5 | 10.9 ± 6.8 | $p=0.64$ |
| Emotion selection task (/42) | 21.6 ± 8.4 | 29.2 ± 7.4 | $p=\mathbf{0.04}$ |
| SYDBAT, naming (/30) | 18.6 ± 5.9 | 16.9 ± 8.5 | $p=0.81$ |
| SYDBAT, repetition (/30) | 20.7 ± 9.3 | 27.8 ± 3.9 | $p=\mathbf{0.006}$ |
| SYDBAT, comprehension (/30) | 24.4 ± 4.4 | 24.0 ± 5.9 | $p=0.74$ |
| SYDBAT, semantic assoc. (/30) | 23.8 ± 2.6 | 22.2 ± 6.0 | $p=0.86$ |

ACE-III, Addenbrooke's Cognitive Examination third version; RCF, Rey Complex Figure; SYDBAT, Sydney Language Battery

Table 2
Yearly incidence of ALS in FTD patients according to duration of FTD symptoms

| Duration of FTD symptoms, years | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
|---|---|---|---|---|---|---|---|---|---|---|
| FTD patients at risk | 7 | 30 | 55 | 81 | 82 | 70 | 52 | 41 | 32 | 16 |
| Developed ALS | – | 2 | 3 | 2 | 1 | – | – | – | – | – |
| Incidence/100 patient-years | – | 6.7 | 5.5 | 2.5 | 1.2 | – | – | – | – | – |

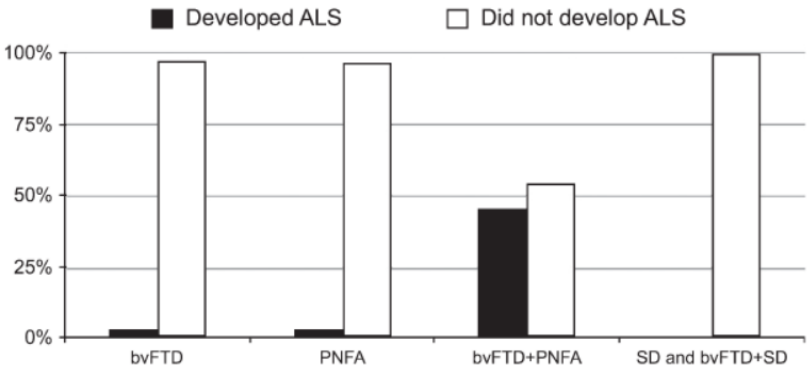



Fig. 1. Frequency of development of ALS according to FTD subtypes.

# ECAS: uno strumento di screening cognitivo specificamente disegnato per la SLA

# Screening for cognition and behaviour changes in ALS

SHARON ABRAHAMS[1,2,3,4], JUDITH NEWTON[1,3,4], ELAINE NIVEN[3], JENNIFER FOLEY[3] & THOMAS H. BAK[1,2,3,4]

*Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration*, 2014; 15: 9–14

Table I. Normative data on the ECAS.

| | Mean (SD) | Range | Abnormality cut-off |
|---|---|---|---|
| Executive functions (max 48) | 40.48 (3.54) | 33–46 | 33 |
| Language functions (max 28) | 27.63 (0.70) | 26–28 | 26 |
| Fluency (max 24) | 19.85 (2.50) | 14–24 | 14 |
| ALS-Specific functions (max 100) | 87.95 (4.98) | 75–97 | 77 |
| Memory functions (max 24) | 18.68 (2.73) | 12–23 | 13 |
| Visuospatial functions (max 12) | 11.85 (0.48) | 10–12 | 10 |
| ALS Non-specific functions (max 36) | 30.53 (2.96) | 22–35 | 24 |
| ECAS Total score (max 136) | 118.48 (6.64) | 99–128 | 105 |

Max: maximum score; ALS-Specific functions consists of the total score of Executive, Language and Fluency scores. ALS Non-specific functions consist of the total score of Memory and Visuospatial functions. ECAS Total score is the combined score for ALS-Specific and ALS Non-specific functions. Cut-off is based on 2 SD from the mean. A score at or below this value indicates impairment.

Table III. ECAS scores: frequency of abnormal performance in ALS group.

| | Frequency of abnormality | Percentage of Total ALS Group falling below cut-off |
|---|---|---|
| ALS-Specific functions | 14 | 29.17% |
| ALS Non-specific functions | 3 | 6.25% |
| ECAS Total score | 14 | 29.17% |

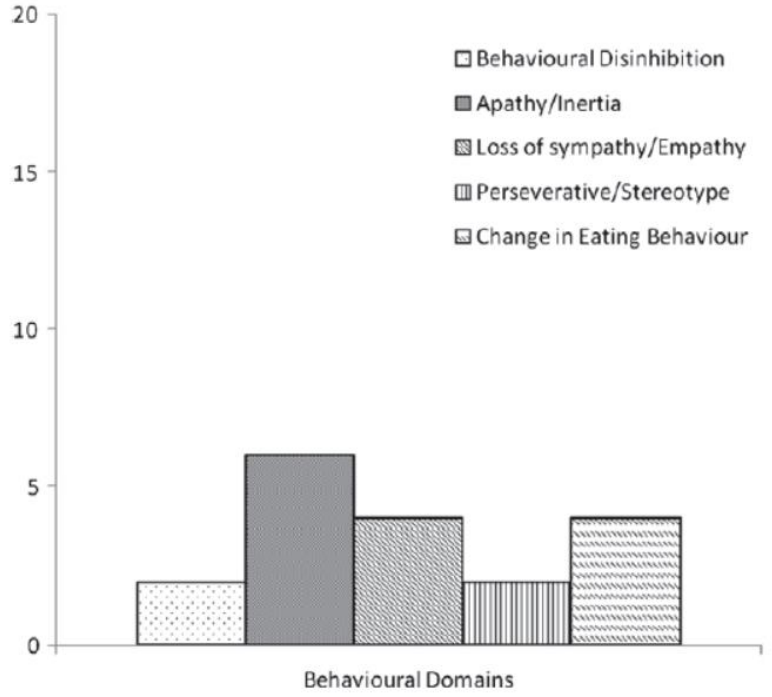


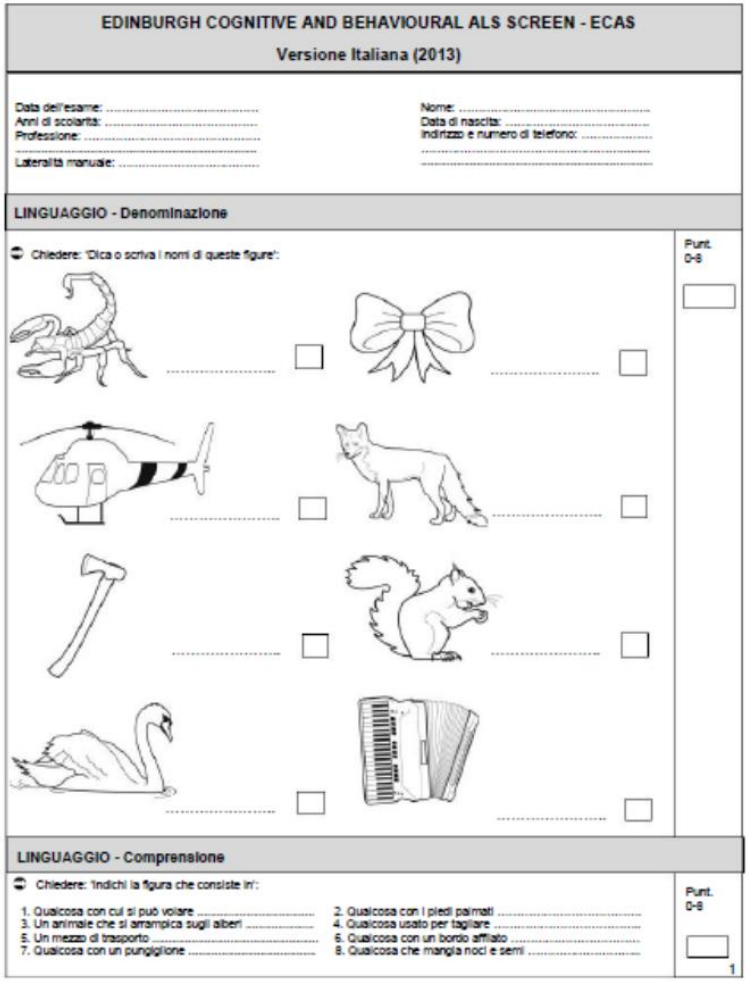

Figure 2. Behaviour domains: frequency of behavioural impairment.

Screening comportamentale compilato dai caregiver

# The validation of the Italian Edinburgh Cognitive and Behavioural ALS Screen (ECAS)

BARBARA POLETTI[1]*, FEDERICA SOLCA[1]*, LAURA CARELLI[1],
FABIANA MADOTTO[2], ANNALISA LAFRONZA[1], ANDREA FAINI[3], ALESSIA MONTI[4],
STEFANO ZAGO[5], DANIELA CALINI[1], CINZIA TILOCA[1], ALBERTO DORETTI[1,6],
FEDERICO VERDE[1,6], ANTONIA RATTI[1,6], NICOLA TICOZZI[1,6],
SHARON ABRAHAMS[7]* & VINCENZO SILANI[1,6]*

*Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration*, 2016; 17: 489–498



EDINBURGH COGNITIVE AND BEHAVIOURAL ALS SCREEN - ECAS

Versione Italiana (2013)

Data dell'esame: ..... Nome: .....
Anni di scolarità: ..... Data di nascita: .....
Professione: ..... Indirizzo e numero di telefono: .....
..... .....
Lateralità manuale: ..... .....

LINGUAGGIO - Denominazione

Chiedere: 'Dica o scriva i nomi di queste figure':

Punt. 0-8

LINGUAGGIO - Comprensione

Chiedere: 'Indichi la figura che consiste in':

1. Qualcosa con cui si può volare .....
2. Qualcosa con i piedi palmati .....
3. Un animale che si arrampica sugli alberi .....
4. Qualcosa usato per tagliare .....
5. Un mezzo di trasporto .....
6. Qualcosa con un bordo affilato .....
7. Qualcosa con un pungiglione .....
8. Qualcosa che mangia noci e semi .....

Punt. 0-8

1

- ❑ PUNTI DI FORZA:
  Test di Screening di facile e rapida somministrazione (15 minuti circa)

- ❑ PUNTI DI DEBOLEZZA:
  Sintetico

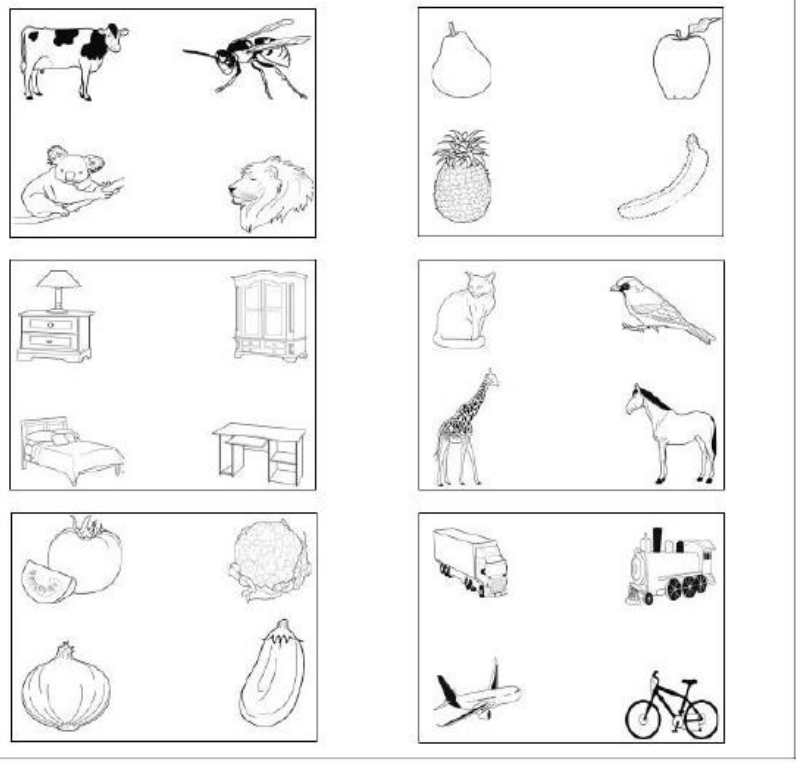
Il test analizza i diversi domini cognitivi
sia specifici per la SLA (Linguaggio, Fluenza Verbale, Funzioni Esecutive)
sia non specifici per la SLA (Memoria,Abilità Visuo Spaziali)

| PUNTEGGI | | |
|---|---|---|
| **Linguaggio** | Denominazione, Comprensione, Spelling | / 28 |
| **Fluenza Verbale** | Fluenza Fonemica S, Fluenza Fonemica C | / 24 |
| **Funzioni Esecutive** | Digit Span Inverso, Alternanza, Completamento di frasi, Cognizione Sociale | / 48 |
| | **TEST SPECIFICI SLA:** | **/100** |
| | | |
| **Memoria** | Rievocazione Immediata, Ritenzione Differita, Riconoscimento Differito | / 24 |
| **Abilità visuo-spaziali** | Conteggio di punti, Conteggio di cubi, Posizione di numeri | / 12 |
| | **TEST NON SPECIFICI SLA:** | **/ 36** |
| | | |
| | **PUNTEGGIO TOTALE ECAS:** | **/ 136** |

# Di particolare interesse è l'inserimento del subtest sulla Cognizione Sociale

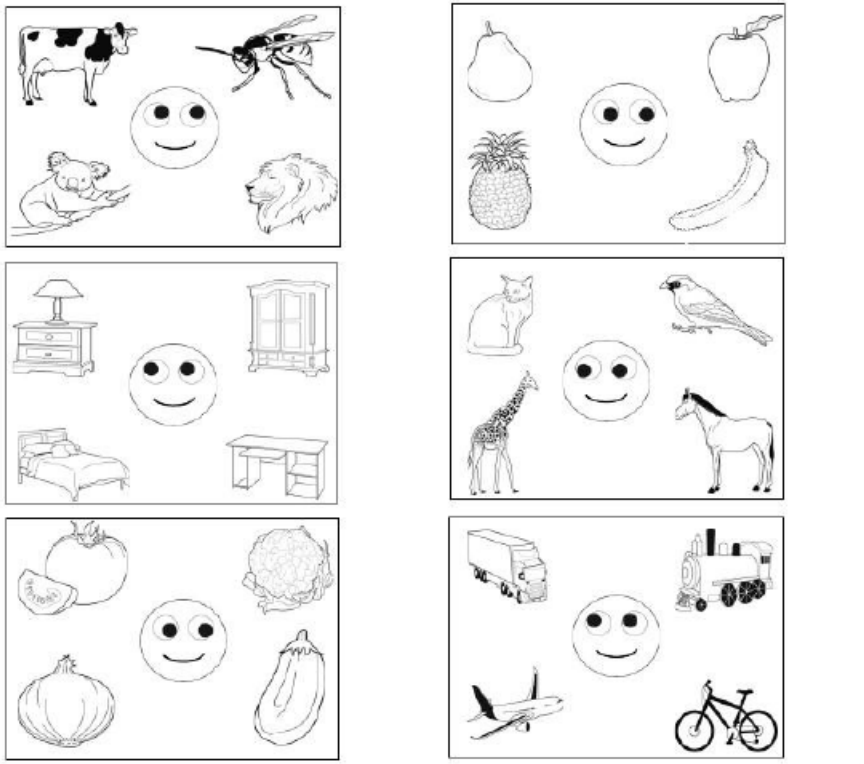
**COGNIZIONE SOCIALE – Parte A**

Dire: 'Vedrà alcune figure, ciascuna posta in ogni angolo di un riquadro. Le chiedo di scegliere **la figura che le piace di più**. Indichi o dica a voce quale figura preferisce. Le chiedo di rispondere il più velocemente possibile'. Cerchiare la scelta della persona.



**COGNIZIONE SOCIALE – Parte B**

Dire: 'Vedrà alcune figure, ciascuna posta in ogni angolo di un riquadro. Le chiedo di scegliere qual è la **figura preferita dalla faccia**. Indichi o dica a voce qual è la **figura preferita dalla faccia**. Le chiedo di rispondere il più velocemente possibile'. Cerchiare la scelta della persona. Item corretti = 2 punti, errori = 1 punto, errori egocentrici = 0 punti.



# Caratteristiche cognitive della demenza associata alla SLA

# Cognitive impairment in amyotrophic lateral sclerosis

*Julie Phukan, Niall P Pender, Orla Hardiman*

*Lancet Neurol* 2007; 6: 994–1003

**Amyotrophic lateral sclerosis (ALS) is a motor neuron disease that has sporadic and inherited forms. ALS is the most common neurodegenerative disorder of young and middle-aged adults, and few treatments are available. Although**

- Fluenza verbale
- Flessibilità
- Attenzione
- Working memory

- Linguaggio
- Funzione visuopercettiva

- Disturbo del comportamento (soprattutto apatia)

| | Patients (n) | Neuropsychological test performance that showed impairment | Neuropsychological test performance in the normal range |
|---|---|---|---|
| Gallassi, 1985[18] | 22 | Verbal fluency (COWA), verbal reasoning, visual attention (Barrage test), short-term verbal memory (Rey's), short-term visual recall | Long-term verbal memory (Rey's), memory spans (verbal and spatial) |
| David, 1986[43] | 14 | Set shifting (WCST), episodic memory (VPAL), picture recall | Attention (digit span), visual recall (RCFT), prose recall |
| Neary, 1990[44] | 4 | Verbal fluency (letter and category), set shifting (WCST and WBT), intelligence (WAIS-R), interpretation of proverbs, episodic memory (VPAL) | Visuoperception (Money road map), intelligence (KBF), memory (Warrington memory test), delayed verbal recall |
| Kew, 1993[16]<br>Kew, 1993[15] | 12<br>16 | Verbal fluency (written), free picture recall, recall memory (KOLT) | Cognitive inhibition (Stroop), recognition memory, visuoperceptual battery, set shifting (WCST), episodic memory (VPAL) |
| Ludolph, 1992[11] | 18 | Verbal fluency | Set shifting (WCST), cognitive inhibition (Stroop), visual recall (RCFT), attention (digit span), naming (modified test), visual concentration (d2 test) |
| Massman, 1996[45] | 146 | Verbal fluency (COWA), immediate free recall (CVLT), continuous recognition memory (CRMT, major deficiency in some patients), attention (VSAT), set shifting (WCST) | Delayed verbal recognition memory (CVLT), visuoperception (Benton JLO), confrontation naming (BNT) |
| Abrahams, 1997[46] | 52 | Verbal fluency (written), executive function and intrinsic generation (RMJT; noted in pseudobulbar palsy only), planning and working memory (CTH), set shifting (WCST), word recognition memory test, Stroop negative priming (trend towards significance) | Episodic memory (VPAL), recall memory (KOLT) |
| Rakowicz, 1998[47] | 18 | Verbal fluency, attention (reverse digit span), conceptual semantic processing (pyramids and palm trees test), syntactic comprehension (TROG), MMSE, confrontation naming (graded naming test) | Attention (forward digit span), picture naming, word-picture matching |
| Moretti, 2002[48] | 14 | Verbal fluency (letter), set shifting (WCST), cognitive inhibition (Stroop), attention (PASAT), interpretation of proverbs, bilingual, aphasia test–B, MMSE | Intellectual ability (RSPM, WAIS-R, KBF), attention (digit span), story retrieval, past events retrieval, visuoperception (JLO) |
| Abrahams, 2005[49] | 20 | Verbal fluency (written and spoken), computerised sentence-completion task | Confrontation naming (graded naming test), fluency (category and design), attention (PASAT, letter span), set shifting (WCST), episodic memory (VPAL), recognition memory test, recall memory (KOLT), visuoperception (Benton JLO), object decision, position discrimination |
| Ringholz, 2005[50] | 279 | Verbal fluency, VSAT, visual recall, logical memory (verbal recall), confrontation naming (BNT) | Visuoperceptual ability (Benton facial recognition test), MMSE (except severely impaired patients), cognitive inhibition (Stroop) |

COWA=controlled oral word association test. WCST=Wisconsin card-sorting test. VPAL=verbal paired associate learning. RCFT=Rey complex figure test. WBT=Weigl's block task. KBF=Koh's block figures. WAIS-R=Weschler adult intelligence scale. KOLT=Kendrick object learning task. CVLT=California verbal learning test. CRMT=continuous recognition memory test. VSAT=verbal series attention test. JLO=judgment of line orientation. BNT=Boston naming test. RMJT=random movement joystick test. CTH=computerised Tower of Hanoi test. TROG=test for the reception of grammar. MMSE=mini mental state examination. PASAT=paced auditory serial addition test. RSPM=Raven's standard progressive matrices.

*Table 3:* **Neuropsychological test performance in ALS**

# Metanalisi di 44 studi su SLA e cognitività (1986-2014)

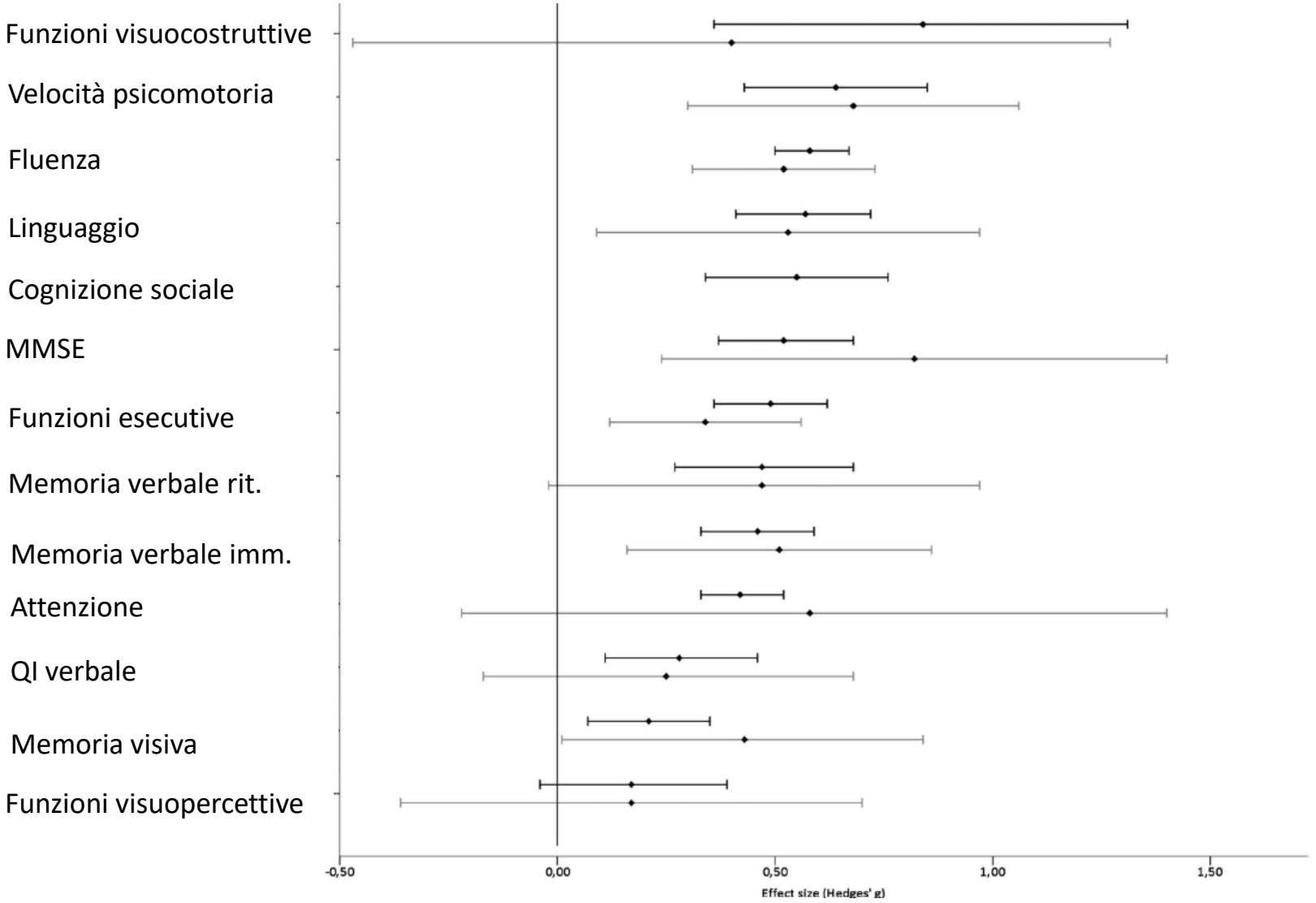



Figure 2 Effect size per cognitive domain. Effect size is expressed as Hedges' g, larger values indicate more impairment in patients with ALS compared to healthy volunteers. Black line: meta-analysis update; grey line: meta-analysis 2010. For a description of the neuropsychological tests included in each domain, see online supplementary table S5. ALS, amyotrophic lateral sclerosis.

Beeldman et al, *J Neurol Neurosurg Psychiatry* 2016

ORIGINAL CONTRIBUTION

Arch Neurol. 2010;67(7):826-830.

# Neurobehavioral Features in Frontotemporal Dementia With Amyotrophic Lateral Sclerosis

*Patricia Lillo, MD; Beatrice Garcin, MD; Michael Hornberger, PhD; Thomas H. Bak, MD; John R. Hodges, MD, FRCP*

- Maggiore frequenza di disturbi della memoria nei pazienti con bvFTD e di difficoltà di reperimento di parole in quelli con FTD/ALS

- Inoltre i pazienti con FTD/ALS avevano una maggiore frequenza di deliri e allucinazioni

**Table 2. Summary of Onset Symptoms in bvFTD vs FTD/ALS Groups**

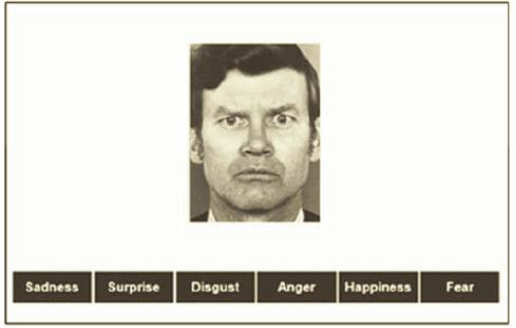
| Symptom at Onset | No. (%) of Patients: bvFTD Group (n=43) | No. (%) of Patients: FTD/ALS Group (n=18) | *P* Value |
|---|---|---|---|
| Memory problems | 27 (63) | 3 (17) | .003 |
| Word-finding problems | 3 (7) | 8 (44) | .002 |
| Delusions | 8 (19) | 9 (50) | .03 |
| Reduced speech output | 10 (23) | 9 (50) | .79 |
| Hallucinations | 5 (12) | 5 (28) | .12 |
| Executive problems | 21 (49) | 12 (67) | .20 |
| Behavioral changes | | | |
| Loss of insight | 40 (93) | 18 (100) | .25 |
| Disinhibition | 23 (53) | 7 (39) | .29 |
| Apathy | 34 (79) | 11 (61) | .14 |
| Lack of empathy | 17 (40) | 3 (17) | .83 |
| Stereotypical behavior | 28 (65) | 11 (61) | .77 |
| Food preference/ dietary change | 21 (49) | 11 (61) | .38 |

Abbreviations: bvFTD, behavioral variant frontotemporal dementia; FTD/ALS, FTD with amyotrophic lateral sclerosis.

# Cognitività sociale

*Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration*, 2013; Early Online: 1–8

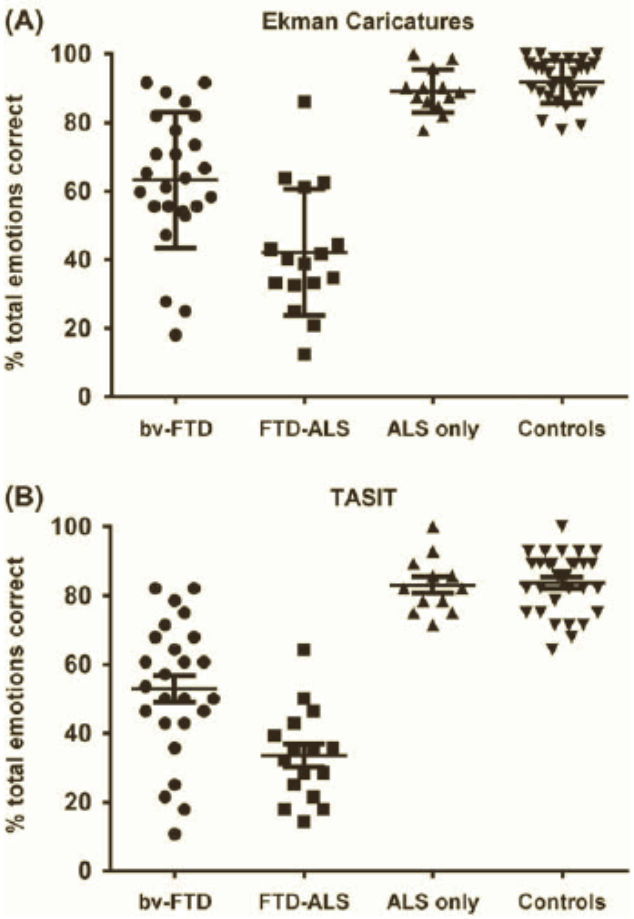
informa
healthcare




ORIGINAL ARTICLE

# Emotion processing deficits distinguish pure amyotrophic lateral sclerosis from frontotemporal dementia

SHARON A. SAVAGE[1,2], PATRICIA LILLO[1], FIONA KUMFOR[1,2], MATTHEW C. KIERNAN[1,3], OLIVIER PIGUET[1,2] & JOHN R. HODGES[1,2]



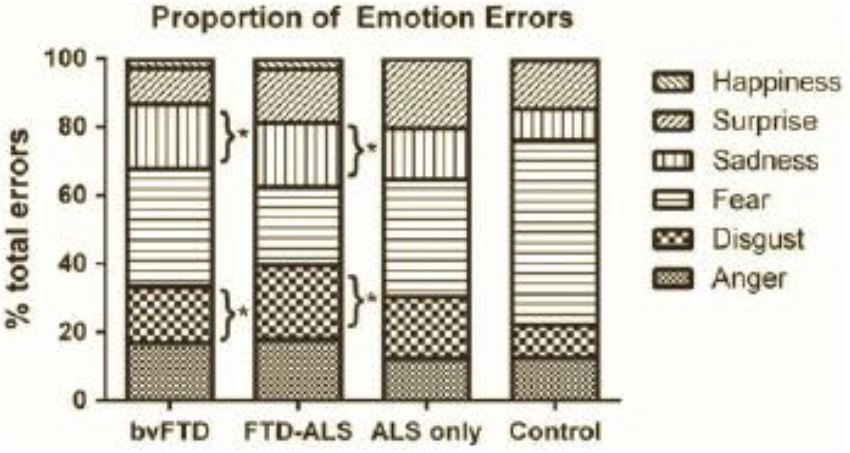




Figure 3. Group error patterns for individual emotions. Scores represent the distribution of errors across each emotion as a proportion of the total errors. Asterisks (*) indicate significant differences in the proportion of errors made on Disgust and Sadness for the bv-FTD and FTD-ALS groups, compared to healthy controls. The profile of errors seen in ALS-only patients was not significantly different to any groups.

# Processing emozionale di scene

Dorothée Lulé
Anja Kurt
Reinhart Jürgens
Jan Kassubek
Volker Diekmann
Eduard Kraft
Nicola Neumann
Albert C. Ludolph
Niels Birbaumer
Silke Anders

## Emotional responding in amyotrophic lateral sclerosis

J Neurol (2005) 252 : 1517–1524

- 12 casi di SLA sporadica ad esordio spinale e progressione lenta
- 18 controlli sani appaiati per età
- 104 immagini di persone in situazione sociali per valutare l'arousal, la valenza emozionale e l'associazione del movimenti con alcuni parametri fisiologici (startle response, risposta cutanea galvanica e frequenza cardiaca)
- I casi di SLA valutavano le immagini come di valenza più positiva, indipendentemente dalla valenza reale, e le scene neutrali e calme erano maggiormente arousing rispetto ai controlli

frontiers in
HUMAN NEUROSCIENCE

ORIGINAL RESEARCH ARTICLE
published: 21 May 2013
doi: 10.3389/fnhum.2013.00178

# Exploring sarcasm detection in amyotrophic lateral sclerosis using ecologically valid measures

*Mathew Staios[1,2]*, Fiona Fisher[2], Annukka K. Lindell[1], Ben Ong[1], Jim Howe[2] and Katrina Reardon[2]*

[1] School of Psychological Science, La Trobe University, Melbourne, VIC, Australia
[2] Calvary Health Care Bethlehem, Melbourne, VIC, Australia

# Teoria della mente

Dopo aver controllato per le difficoltà esecutive, i pazienti con SLA presentavano ancora significative difficoltà nei compiti che valutavano la comprensione di frasi **sarcastiche e paradossali**

**Table 2 | Neuropsychological data for ALS and control participants.**

| Variable | ALS ($N = 35$) mean ($SD$) | Controls ($N = 30$) mean ($SD$) | η2 | $P$-Value |
|---|---|---|---|---|
| ACE-R | 79.60 (3.64) | 81.23 (3.61) | | >0.05 |
| Brixton | 20.02 (8.06) | 13.43 (3.86)* | 0.21 | <0.05 |
| **EMOTION DISCRIMINATION** | | | | |
| Positive emotions | 4.40 (1.06) | 4.6 (0.723) | 0.012 | >0.05 |
| Negative emotions | 6.77 (1.28) | 7.00 (0.909) | 0.01 | >0.05 |
| **TEST OF SOCIAL INFERENCE** | | | | |
| Sincere | 8.94 (2.38) | 9.66 (1.95) | 0.027 | >0.05 |
| Simple sarcasm[rnl] | 9.40 (2.46) | 11.10 (1.32)* | 0.192 | <0.05 |
| Paradoxical sarcasm[rnl] | 9.82 (1.85) | 11.23 (1.16)* | 0.205 | <0.05 |

*Note: *p <0.05; rnl, median and interquartile range; Brixton, Brixton Spatial Anticipation Test.*

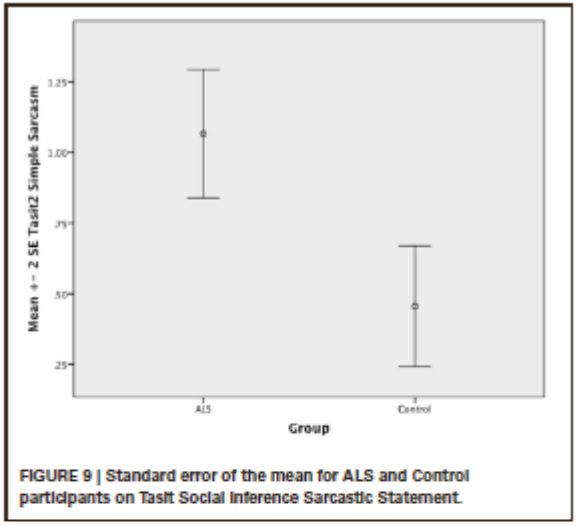



**FIGURE 9 | Standard error of the mean for ALS and Control participants on Tasit Social Inference Sarcastic Statement.**

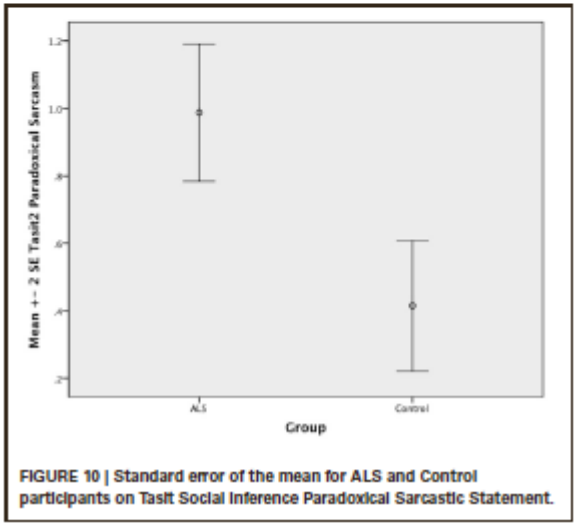



**FIGURE 10 | Standard error of the mean for ALS and Control participants on Tasit Social Inference Paradoxical Sarcastic Statement.**

1. Mancanza di studi di popolazione
2. Bias di selezione (% di casi bulbari; rapporto m/f; variabilità di età di esordio e durata di malattia; esclusione dei casi familiari/genetici)
3. Piccola dimensione dei campioni
4. Valutazione neuropsicologica limitata
5. Pochi studi con correlati di neuroimmagine

# SLA, FTD
# e sintomi psicotici

doi:10.1093/brain/awr366 Brain 2012: 135; 784–793 | 784

BRAIN
A JOURNAL OF NEUROLOGY

# SLA familiari con e senza mutazione *C9ORF72*

## Clinical characteristics of patients with familial amyotrophic lateral sclerosis carrying the pathogenic GGGGCC hexanucleotide repeat expansion of *C9ORF72*

Adriano Chiò,[1,*] Giuseppe Borghero,[2,*] Gabriella Restagno,[3,*] Gabriele Mora,[4,*]

Table 2 Gender, site of onset, frequency of cognitive impairment and median age at onset (IQR) of index mainland Italian patients with familial ALS with different gene mutations

| Gene | Number of cases | Gender (female) (%) | Bulbar onset (%) | Cognitive impairment (%) | Median age at onset (IQR) |
|---|---|---|---|---|---|
| *C9ORF72* | 45 | 23 (51.1) | 19 (42.2) | 21 (46.7) | 59.0 (50.6–62.9) |
| *FUS* | 6 | 2 (33.3) | 1 (16.7) | 0 | 35.3 (30.4–39.6) |
| *SOD1* | 38 | 20 (52.6) | 3 (7.9) | 1 (2.6) | 50.0 (42.8–62.6) |
| *TARDBP* | 13 | 4 (30.8) | 4 (30.8) | 4 (30.8) | 66.0 (58.0-70.6) |
| Unknown gene | 75 | 32 (42.7) | 25 (33.3) | 7 (9.3) | 60.7 (53.0–68.9) |
| Overall | 177[a] | 81 (45.8) | 52 (29.4) | 32 (18.1) | 58.0 (47.7–67.5) |
| *P*-value | – | 0.54 | 0.011 | 0.0001 | 0.0001 |

a Two index cases were not included: one with *optineurin* missense mutation and one with *valosin containing protein* missense mutation.

- ‘psychotic symptoms (delusions and hallucinations) were reported more commonly among patients carrying the chromosome 9p21 repeat expansion compared with nonexpanded cases.’

ORIGINAL STUDY

# Psychosis and Hallucinations in Frontotemporal Dementia with the *C9ORF72* Mutation: A Detailed Clinical Cohort

*Andrew Kertesz, MD,* Lee Cyn Ang, MD,† Sarah Jesso, BA,* Julia MacKinley, BA,* Matt Baker, BA,‡ Patricia Brown, BA,‡ Christen Shoesmith, MD,* Rosa Rademakers, PhD,‡ and Elizabeth C. Finger, MD**

*Cogn Behav Neurol* • Volume 26, Number 3, September 2013

## Psicosi e allucinazioni sono relativamente specifici della FTD associata a C9ORF72

- 6 pazienti su 8 con FTD e *C9ORF72* rispetto a 8 pazienti su 44 con FTD senza *C9ORF72* avevano disturbi psicotici ($p<0.005$)

**TABLE 1.** Clinical Details and Neuroanatomic Findings in Patients with Frontotemporal Dementia (FTD) and *C9ORF72* Expanded Repeats

| Patient #/Sex | Age at Onset | Mode of Onset | Nature of Psychosis | Other bvFTD-Related Symptoms | Aphasia | Motor Neuron Disease | Neuroimaging Findings | Family History | FBI Score* | Age at Death, Autopsy Findings |
|---|---|---|---|---|---|---|---|---|---|---|
| 1/Man | 57 | Behavior change | Visual hallucinations, psychotic delusions | Food, poor hygiene, impulsiveness, indifference | Anomia | No | Left parietal, bifrontal, and temporal atrophy | Brother (Patient 2) had FTLD-U; mother and maternal uncle had early-onset dementia, probably FTD; maternal aunt had ALS | 45 | |
| 2/Man | 52 | Behavior change | | Food, poor hygiene, indifference, compulsions | Echolalia | No | No testing | Brother (Patient 1) had FTD; same family history as Patient 1 | 43 | 59, FTLD-U + TDP-43 type B |
| 3/Man | 43 | Behavior change | | Food, poor hygiene, irritability, indifference | Anomia, conduction | Possible bulbar | Left > right frontal and temporal atrophy | Maternal uncle had Pick disease | 42 | 46, declined |
| 4/Man | 56 | Behavior change | Auditory hallucinations | Food, irritability, indifference, compulsions | Mild anomia | Yes | Bifrontal and left temporal atrophy | No family history | 32 | 60, declined |
| 5/Woman | 53 | Depression | Bizarre delusions | Food, poor hygiene, indifference, inappropriate behavior | Echolalia | No | Medial frontal and anterior temporal atrophy | Sister had ALS and cognitive deficits; mother had early-onset dementia | 39 | |
| 6/Man | 67 | Aphasia | Paranoid delusions | Food, compulsions, irritability, disinhibition, impulsiveness | Semantic paraphasias | No | Mild bifrontal, temporal, and parietal atrophy | Sister had FTD/ALS: FTLD-U + TDP-43 type B | 32 | |
| 7/Man | 52 | Behavior change | Visual and auditory hallucinations | Food, poor hygiene, inappropriate behavior, indifference, obsessions | Dysarthria | Yes | Right temporal and inferior frontal atrophy | Sister (Patient 8) had bvFTD; mother had ALS and suspected behavioral changes; 2 maternal uncles and 1 cousin had ALS; another maternal uncle had dementia | 46 | |
| 8/Woman | 47 | Behavior change | Visual and auditory hallucinations | Food, inappropriate behavior, compulsions | Decreased speech output | Yes | Bifrontal and right > left temporal atrophy | Brother (Patient 7) had bvFTD; same family history as Patient 7 | 46 | 64, FTLD-U + TDP-43 type B |

ANN NEUROL 2013;00:000–000

# Aggregation of Neurologic and Neuropsychiatric Disease in Amyotrophic Lateral Sclerosis Kindreds: A Population-Based Case–Control Cohort Study of Familial and Sporadic Amyotrophic Lateral Sclerosis

Susan Byrne, PhD,[1,2] Mark Heverin, MSc,[2] Marwa Elamin, PhD,[2] Peter Bede, MD,[1,2] Catherine Lynch, MSc,[1] Kevin Kenna, BSc,[3] Russell MacLaughlin, PhD,[1] Cathal Walsh, PhD,[4] Ammar Al Chalabi, PhD,[5] and Orla Hardiman, FRCPI[1,2]

- Aumento di rischio di disturbi psicotici e suicidio nei familiari di pazienti con SLA

**TABLE 4. Comparison of Relatives of All Cases and All Controls Demonstrates a Significant Relative Risk of Schizophrenia and Suicide in Relatives of All Amyotrophic Lateral Sclerosis Patients Compared to Controls**

| Disease | Relatives of Cases, n = 4,050 | Relatives of Controls, n = 5,634 | Risk Ratio | Chi-Square, *p* | HR | *p* | 95% CI |
|---|---|---|---|---|---|---|---|
| Parkinson disease | 24 affected | 35 affected | 1.0 | 0.3, 0.858 | 0.8 | 0.298 | 0.5–1.2 |
| Dementia | 152 affected | 186 affected | 1.1 | 1.4, 0.255 | 1.2 | 0.052 | 0.9–1.4 |
| Depression | 24 affected | 31 affected | 1.1 | 0.1, 0.891 | 1.1 | 0.684 | 0.7–1.7 |
| Schizophrenia/ psychotic illness | 13 affected | 5 affected | 3.6 | 6.9, 0.009 | 4.1 | <0.0001[a] | 2.5–6.7 |
| Suicide | 14 affected | 4 affected | 4.9 | 9.6, 0.004 | 5.6 | <0.0001[a] | 2.4–12.9 |

[a]Statistically significant.
CI = confidence interval; HR = hazard ratio.

**TABLE 5. Relatives of C9-Positive Cases and C9-Negative Cases Compared to Controls in a Cox Regression Proportional Model**

| Disease | Relatives | HR | 95% CI | *p* |
|---|---|---|---|---|
| Parkinson disease | Relatives of C9-positive patients | 1.3 | 0.5–3.7 | 0.570 |
| | Relatives of C9-negative patients | 0.7 | 0.4–1.1 | 0.126 |
| Dementia | Relatives of C9-positive patients | 1.6 | 1.1–2.4 | 0.017[a] |
| | Relatives of C9-negative patients | 1.2 | 0.9–1.4 | 0.100 |
| Depression | Relatives of C9-positive patients | 3.3 | 1.6–7.0 | 0.002[a] |
| | Relatives of C9-negative patients | 0.6 | 0.3–1.1 | 0.075 |
| Schizophrenia/psychotic illness | Relatives of C9-positive patients | 9.9 | 4.8–20.5 | <0.0001[a] |
| | Relatives of C9-negative patients | 3.9 | 2.4–6.5 | <0.0001[a] |
| Suicide | Relatives of C9-positive patients | 16.6 | 5.6–49.4 | <0.0001[a] |
| | Relatives of C9-negative patients | 5.1 | 2.2–12.1 | <0.0001[a] |

[a]Statistically significant.
CI = confidence interval; HR = hazard ratio.

- Tale aumento è prevalentemente ma non totalmente dovuto ai pazienti portatori di mutazione *C9ORF72*

nature COMMUNICATIONS

ARTICLE

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# Genetic correlation between amyotrophic lateral sclerosis and schizophrenia

Russell L. McLaughlin[1,2,*], Dick Schijven[3,4,*], Wouter van Rheenen[3], Kristel R. van Eijk[3], Margaret O'Brien[1],

Correlazione genetica fra SLA e schizofrenia: 14.3% (7-22%)

Gli score di rischio poligenico della schizofrenia spiegano lo 0,12% della varianza della SLA

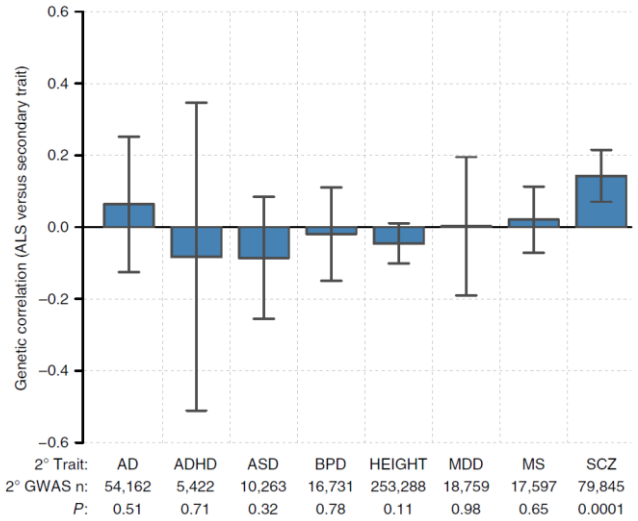


**Figure 1 | Genetic correlation between ALS and eight secondary traits.** Error bars indicating 95% confidence intervals and *P*-values were calculated by the LD score regression software using a block jackknife procedure. Secondary traits are: AD, Alzheimer's disease; ADHD, attention deficit-hyperactivity disorder; ASD, autism spectrum disorder; BPD, bipolar disorder; MDD, major depressive disorder; MS, multiple sclerosis; SCZ, schizophrenia.

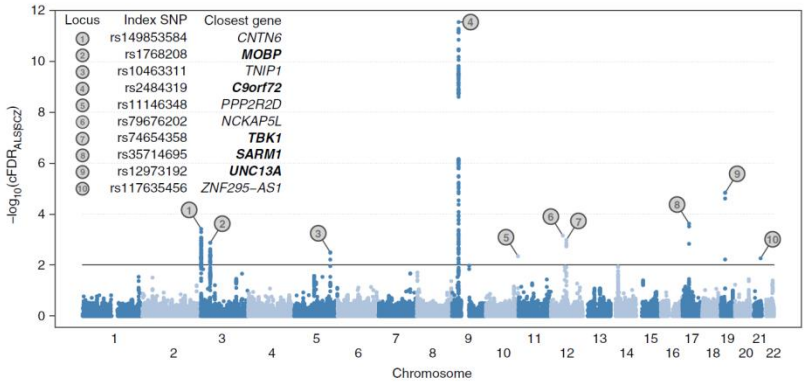


**Figure 4 | Pleiotropy-informed ALS risk loci determined by analysis of cFDR in ALS GWAS *P*-values given schizophrenia GWAS *P*-values ($cFDR_{ALS|SCZ}$).** Each point denotes a SNP; its *x* axis position corresponds to its chromosomal location and its height indicates the extent of association with ALS by cFDR analysis. The solid line indicates the threshold cFDR = 0.01. Any gene whose role in ALS is already established is in bold. A complete list of all loci at cFDR ≤ 0.05 is provided in Supplementary Table 8.

# Esiste una progressione del danno cognitivo nella SLA?

ALS and other motor neuron disorders 2004 5, 46-54




# A longitudinal study of the evolution of cognitive function and affective state in patients with amyotrophic lateral sclerosis

M Kilani,[1] J Micallef,[1] C Soubrouillard,[1] D Rey-Lardiller,[5] C Dematteï,[1] M Dib,[2] P Philippot,[4] M Ceccaldi,[3] J Pouget[5] and O Blin[1]

- 'CONCLUSIONI: Questo studio fornisce ulteriori prove di un lieve difetto nella funzione frontale nei pazienti con SLA **che evolve solo lentamente o non evolve affatto col tempo**'

| | M0 | | M6 | | M12 | |
|---|---|---|---|---|---|---|
| | ALS ($n$=18) | Controls ($n$=19) | ALS ($n$=14) | Controls ($n$=19) | ALS ($n$=13) | Controls ($n$=19) |
| Trail Making Test | | | | | | |
| A Form | 49.9 [19.4] | 41.3 [13.1] | 46.2 [20.0] | 40.2 [12.7] | 51.3 [20.5] | 35.5 [9.6] |
| B Form | 120.3 [71.5] | 86.1 [49.9] | 113.3 [44.0] | 77.1 [24.6] | 117.0 [46.1] | 76.7 [28.9] |
| 95% CL for group effect Form B | [3.9;82.3] | | [6.8;56.3] | | [19.6;70.8] | |
| 95% CL for group effect Form B-A | [5.6;69.5] | | [11.6;44.3] | | [11.8;49] | |
| without patients under benzodiazepines | | | | | | |
| 95% CL for group effect Form B | [17.9;121.3] | | [1.4;70.3] | | [13.8;78.6] | |
| 95% CL for group effect Form B-A | [20.8;101.3] | | [8.4;52.3] | | [9.6;49.9] | |
| Empan Test | | | | | | |
| Direct | 7.71 [1.79] | 8.11 [1.56] | 7.38 [2.36] | 8.26 [1.56] | 7.18 [1.72] | 8.21 [1.40] |
| Indirect | 5.18 [1.88] | 5.79 [1.13] | 5.77 [1.48] | 6.32 [1.53] | 5.73 [1.49] | 6.05 [1.43] |
| Total | 12.88 [3.26] | 13.9 [2.28] | 13.15 [3.65] | 14.58 [2.67] | 12.91 [2.02] | 14.26 [2.35] |
| WCST | | | | | | |
| Categories | 4.39 [1.79] | 5.42 [1.35] | 5.00 [1.83] | 5.68 [1.00] | 5.67 [1.44] | 5.56 [1.20] |
| Errors | 12.1 [7.31] | 7.37 [4.98] | 8.64 [8.09] | 5.21 [3.78] | 6.42 [7.29] | 5.95 [5.77] |
| Perseverations | 6.56 [5.53] | 4.00 [3.56] | 4.57 [4.88] | 2.84 [2.09] | 3.50 [5.49] | 2.47 [2.93] |
| Rey Word Recall | | | | | | |
| List A: Correct - immediate recall | 51.9 [10.5] | 58.2 [8.51] | 49.1 [12.2] | 56.2 [8.0] | 48.8 [12.1] | 56.6 [7.6] |
| List A: Double – immediate | 4.59 [4.50] | 2.37 [1.64] | 4.08 [3.95] | 2.37 [1.95] | 3.64 [3.17] | 2.52 [1.87] |
| List A: Incorrect – mmediate recall | 0.47 [0.87] | 1.56 [2.64] | 1.42 [1.68] | 0.63 [1.07] | 0.91 [1.30] | 1.21 [1.72] |
| List A: Correct – delayed recall | 10.0 [3.41] | 11.7 [2.45] | 9.85 [3.85] | 11.68 [2.45] | 8.27 [4.71] | 11.33 [2.09] |
| List A: Double – delayed recall | 0.94 [1.20] | 0.68 [0.95] | 0.31 [0.63] | 0.68 [0.95] | 0.36 [0.67] | 0.56 [0.62] |
| List A: Incorrect – delayed recall | 0.06 [0.24] | 0.42 [0.84] | 0.38 [0.96] | 0.42 [0.84] | 0.82 [1.08] | 0.28 [0.67] |
| List B: Correct – immediate recall | 5.88 [1.65] | 6.47 [1.68] | 6.62 [2.26] | 8.21 [2.15] | 7.18 [3.06] | 7.33 [2.03] |
| List B: Double – immediate | 0.29 [0.47] | 0.2 [0.48] | 0.31 [0.63] | 0.25 [0.58] | 0.45 [0.93] | 0.47 [0.61] |
| List B: Incorrect – immediate recall: | 0.38 [0.62] | 0.47 [0.96] | 0.38 [0.65] | 0.37 [0.68] | 0.55 [0.82] | 0.33 [0.59] |
| Proactive interference | 11.0 [–] | 3.50 [5.69] | 0.00 [–] | 0.17 [0.41] | 0.33 [0.58] | 0.09 [0.30] |
| Delayed recognition – correct | 14.5 [0.87] | 14.5 [0.77] | 14.4 [0.77] | 14.8 [0.50] | 14.8 [0.63] | 14.8 [0.38] |
| Delayed recognition – errors | 1.41 [1.73] | 0.79 [1.08] | 0.37 [0.65] | 0.41 [1.02] | 1.10 [1.20] | 1.06 [1.26] |
| Benton Test | 11.9 [1.2] | 12.3 [1.8] | 12.6 [1.7] | 13.1 [1.4] | 13.1 [1.4] | 13.2 [1.8] |
| Raven Progressive Matrix | 36.2 [9.6] | 42.9 [7.6] | 38.4 [10.9] | 43.1 [7.4] | 40.3 [9.5] | 44.0 [7.0] |
| Boston Test | 27.5 [1.42] | 28.44 [0.62] | 27.8 [1.4] | 28.4 [0.7] | 28.7 [0.5] | 28.4 [0.7] |

Scores are presented at baseline. Data are presented as mean values [SE]. WCST: Wisconsin Card Sorting Test. There were no statistically significant inter-group differences except for the Trail Making Test and the Boston test.

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ORIGINAL COMMUNICATION

Herbert Schreiber
Tanja Gaigalat
Ursula Wiedemuth-Catrinescu
Michael Graf
Ingo Uttner
Rainer Muche
Albert Christian Ludolph

# Cognitive function in bulbar- and spinal-onset amyotrophic lateral sclerosis

## A longitudinal study in 52 patients

- 'Concludiamo che vi è un pattern di disfunzione cognitiva nella SLA che si manifesta **precocemente** nel corso della malattia soprattutto con le **forme bulbari**.'

- I deficit cognitivi non progrediscono in sincronia con il declino motorio, ma molto più lentamente

**Table 2** **a:** Means of longitudinal test profiles at study entry and follow-up examinations in the complete patient sample. **b:** Longitudinal statistical analysis (Friedman exact)

| | 2a: means at baseline and at follow-up | | | | | | | | 2b: Friedman-test | |
|---|---|---|---|---|---|---|---|---|---|---|
| | E1 (n = 52) | | E2 (n = 32) | | E3 (n = 24) | | E4 (n = 19) | | Number (n) | E1-E4 (p) |
| Test | mean | SD | mean | SD | mean | SD | mean | SD | | |
| *Clinical parameters and behavioral data* | | | | | | | | | | |
| VC | **94.5** | 9.2 | **87.5** | 3.5 | **79.5** | 9.2 | **80.0** | 2.8 | 10 | **0.01** |
| Norris | **74.9** | 11.6 | **72.1** | 6.0 | **64.0** | 9.7 | **61.6** | 9.8 | 10 | **0.002** |
| BDI | **10.8** | 7.0 | **9.0** | 7.1 | **11.2** | 7.1 | **10.3** | 6.9 | 12 | n. s. |
| *Executive functions* | | | | | | | | | | |
| CWIT1 | **33.0** | 8.6 | **33.6** | 8.0 | **37.1** | 8.2 | **35.8** | 6.8 | 9 | n. s. |
| CWIT2 | **43.9** | 6.7 | **44.1** | 6.6 | **48.1** | 6.5 | **47.5** | 9.1 | 9 | **0.004** |
| CWIT3 | **87.1** | 16.7 | **84.7** | 13.3 | **80.5** | 14.6 | **82.2** | 14.3 | 9 | n. s. |
| CWIT4 | **3.0** | 2.6 | **4.1** | 5.4 | **1.9** | 2.3 | **2.5** | 3.3 | 9 | n. s. |
| COWAT 1 | **21.2** | 9.7 | **24.1** | 9.8 | **26.7** | 12.6 | **29.4** | 12.2 | 13 | n. s. |
| COWAT2 | **2.7** | 3.1 | **1.5** | 1.6 | **2.2** | 2.3 | **2.8** | 2.9 | 13 | n. s. |
| COWAT3 | **0.13** | 0.15 | **0.06** | 0.06 | **0.08** | 0.06 | **0.09** | 0.08 | 13 | **0.009** |
| 5-PFT1 | **24.6** | 8.4 | **24.9** | 7.2 | **25.9** | 12.3 | **26.6** | 11.1 | 8 | n. s. |
| 5-PFT2 | **3.0** | 3.1 | **2.1** | 2.0 | **1.9** | 2.6 | **2.5** | 3.6 | 8 | **0.01** |
| 5-PFT3 | **0.11** | 0.09 | **0.09** | 0.11 | **0.07** | 0.09 | **0.08** | 0.11 | 8 | **0.03** |
| WCST1 | **2.0** | 1.5 | **2.0** | 1.1 | **2.7** | 1.0 | **2.7** | 1.4 | 6 | n. s. |
| WCST2 | **22.3** | 9.2 | **23.7** | 7.0 | **16.8** | 9.11 | **19.5** | 9.1 | 6 | n. s. |
| WCST3 | **21.0** | 12.8 | **17.0** | 1.6 | **15.4** | 13.4 | **9.6** | 9.1 | 6 | n. s. |
| *Memory functions* | | | | | | | | | | |
| DS | **5.5** | 0.7 | **5.6** | 1.0 | **5.8** | 1.0 | **5.8** | 1.1 | 13 | **0.009** |
| RFT | **27.0** | 8.2 | **25.1** | 9.9 | **27.7** | 14.0 | **25.9** | 8.7 | 12 | n. s. |
| AVLT1 | **5.1** | 0.9 | **5.4** | 1.8 | **7.0** | 2.4 | **5.8** | 1.3 | 13 | n. s. |
| AVLT2 | **11.9** | 1.6 | **10.9** | 1.9 | **12.5** | 2.4 | **11.3** | 1.9 | 13 | n. s. |
| AVLT3 | **7.0** | 2.0 | **5.5** | 2.5 | **5.5** | 2.3 | **5.5** | 1.5 | 13 | **0.05** |
| AVLT4 | **3.4** | 2.4 | **2.3** | 1.7 | **2.8** | 1.9 | **3.1** | 1.4 | 13 | **0.03** |
| AVLT5 | **8.7** | 2.4 | **7.8** | 2.0 | **10.0** | 2.5 | **8.3** | 2.8 | 13 | n. s. |
| AVLT6 | **45.9** | 1.9 | **45.0** | 3.8 | **46.8** | 4.3 | **45.0** | 4.3 | 13 | n. s. |
| *Attentional control* | | | | | | | | | | |
| Alert.1 | **283** | 100 | **334** | 119 | **351** | 121 | **395** | 156 | 6 | n. s. |
| Alert.2 | **294** | 115 | **311** | 110 | **325** | 114 | **385** | 153 | 6 | **0.03** |
| DivAtt1 | **705** | 145 | **735** | 108 | **717** | 113 | **708** | 125 | 5 | n. s. |
| DivAtt2 | **2.0** | 2.6 | **2.7** | 2.9 | **3.0** | 1.7 | **1.0** | 0 | 5 | n. s. |

Exact Friedman test; level of significance $p < 0.05$. *VC* Vital capacity; *BDI* Beck Depression Inventory; *CWIT* Colour Word Interference Test: 1 reading-time (sec), 2 naming-time (sec), 3 interference-time (sec), 4 error score; *COWAT* Controlled Word Association Test: 1 number of words, 2 number of errors, 3 ratio number/errors; 5-PFT, 5-Point Fluency Test: 1 number of designs (figures), 2 number of errors, 3 ratio number/errors; *WCST* Wisconsin Card Sorting Test: 1 number of categories, 2 number of errors, 3 number of perseverating errors; *DS* Digit span: number; *RFT* Recurring Figures Test of Kimura: number of errors; *AVLT* Auditory Verbal Learning Test: 1 words at I. presentation, 2 words at V. presentation, 3 learning achievement, 4 loss by interference, 5 recall after 30 min, 6 recognition; *Alertness1* reaction time without warning tone (in ms), *Alertness2* reaction time with warning tone (in ms); *Divided Attention*, *1* reaction time (ms), *2* missing outs

# Cognitive changes predict functional decline in ALS

## A population-based longitudinal study

Marwa Elamin, MRCP

ABSTRACT

Neurology® 2013;80:1590-1597

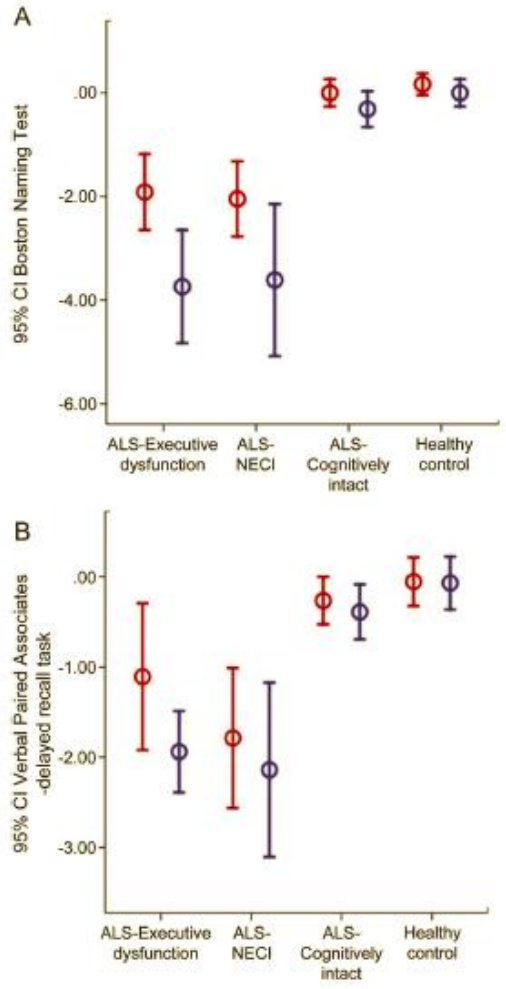
- I pazienti che alla diagnosi non hanno alterazioni cognitive non tendono a svilupparle successivamente

**Table 4** Summary of evolution of cognitive status in the patients with ALS who did not have dementia

| First assessment (n at T1) | Second assessment (n at T2) | Third assessment (n at T3) | Fourth assessment (n at T4) |
|---|---|---|---|
| No cognitive impairment (n = 94) | n = 60 | n = 37 | n = 9 |
| | 49/60 (81.7%): normal cognition | 30/37 (81.1%): normal cognition | 7/9: normal cognition |
| | 6/60 (10%): language dysfunction | 2/37 (5.4%): language dysfunction | 1/9: executive function[a] |
| | 3/60 (5.0%): impaired visuoconstruction | 3/37 (8.1%): impaired visuoconstruction | |
| | 2/60 (3.3%): executive dysfunction | 2/37 (5.4%): executive dysfunction | |
| Executive dysfunction (n = 47) | n = 17 | n = 5 | |
| Single domain (n = 17) | 1/5: no change | 2/2: no new change in cognitive status | |
| | 4/5: language/memory dysfunction | | |
| Multidomain (n = 30) | 11/12 (91.7%): no change | 3/3: no new change in cognitive status | |
| | 1/12 (8.3%): developed Bv-FTD | | |
| Nonexecutive cognitive impairment (n = 23) | n = 14 | n = 3 | n = 1 |
| | 9/14 (64.2%): no change in cognitive status | 3/3: no new change in cognitive status | 1/1: no new change in cognitive status |
| | 3/14 (21.4%): executive dysfunction | | |
| | 2/14 (14.3%): spread to previously unaffected nonexecutive domains | | |

Abbreviations: ALS = amyotrophic lateral sclerosis; Bv-FTD = behavioral variant-frontotemporal lobar degeneration.
[a] The second patient with abnormal cognitive function at this assessment had executive dysfunction that had emerged at T3 and thus was not new.

Figure 1 Mean z scores on BNT and VPA-II




BNT: Boston Naming Test
VPA: Verbal Paired Associated Test

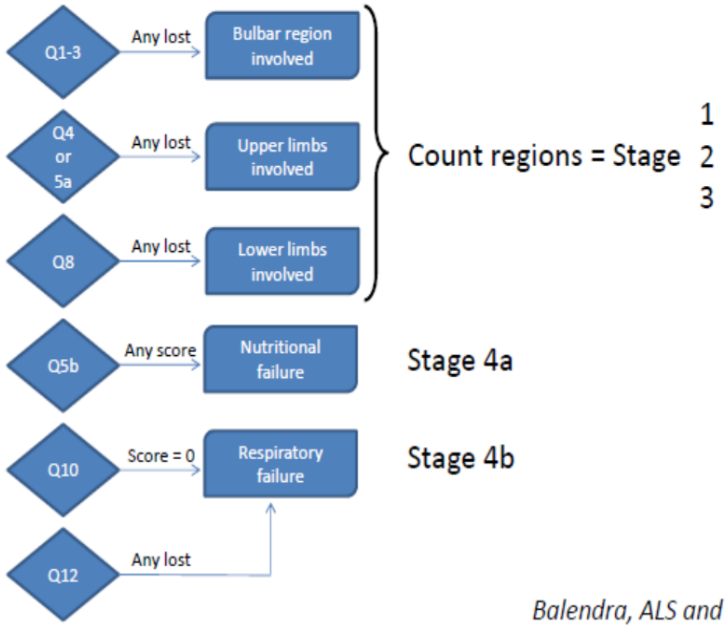
# Sono credibili questi risultati?

# Gli stadi King's ricapitolano la diffusione di malattia

## King's method

- Based on neurological regions
- Modified from regions used in El Escorial criteria
- Additional nutritional and respiratory failure criteria
  - Defined rules
  - Still works if loosely defined
- Highest stage wins

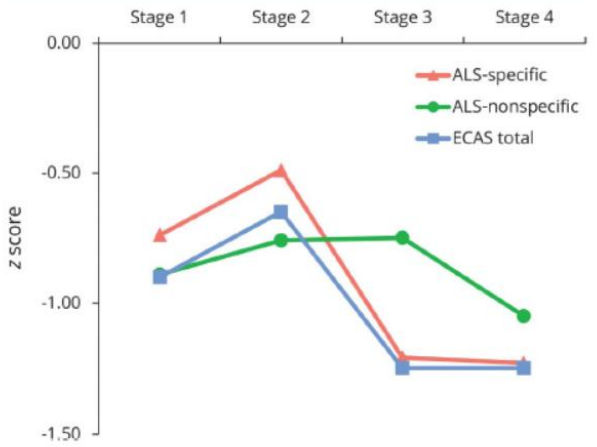

## Mapping ALSFRS to King's Stage



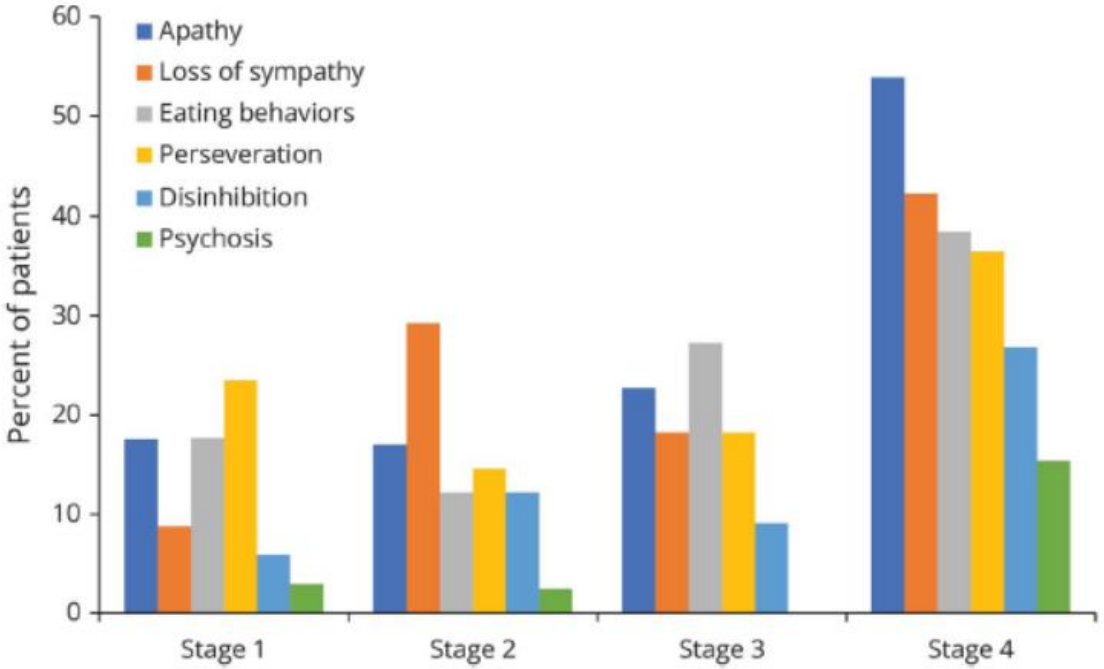

*Balendra, ALS and FTD 2014*

# Stadi clinici King's e compromissione cognitiva e comportamentale valutata con la scala ECAS

**Figure 1** Cognitive performance across King's clinical disease stages

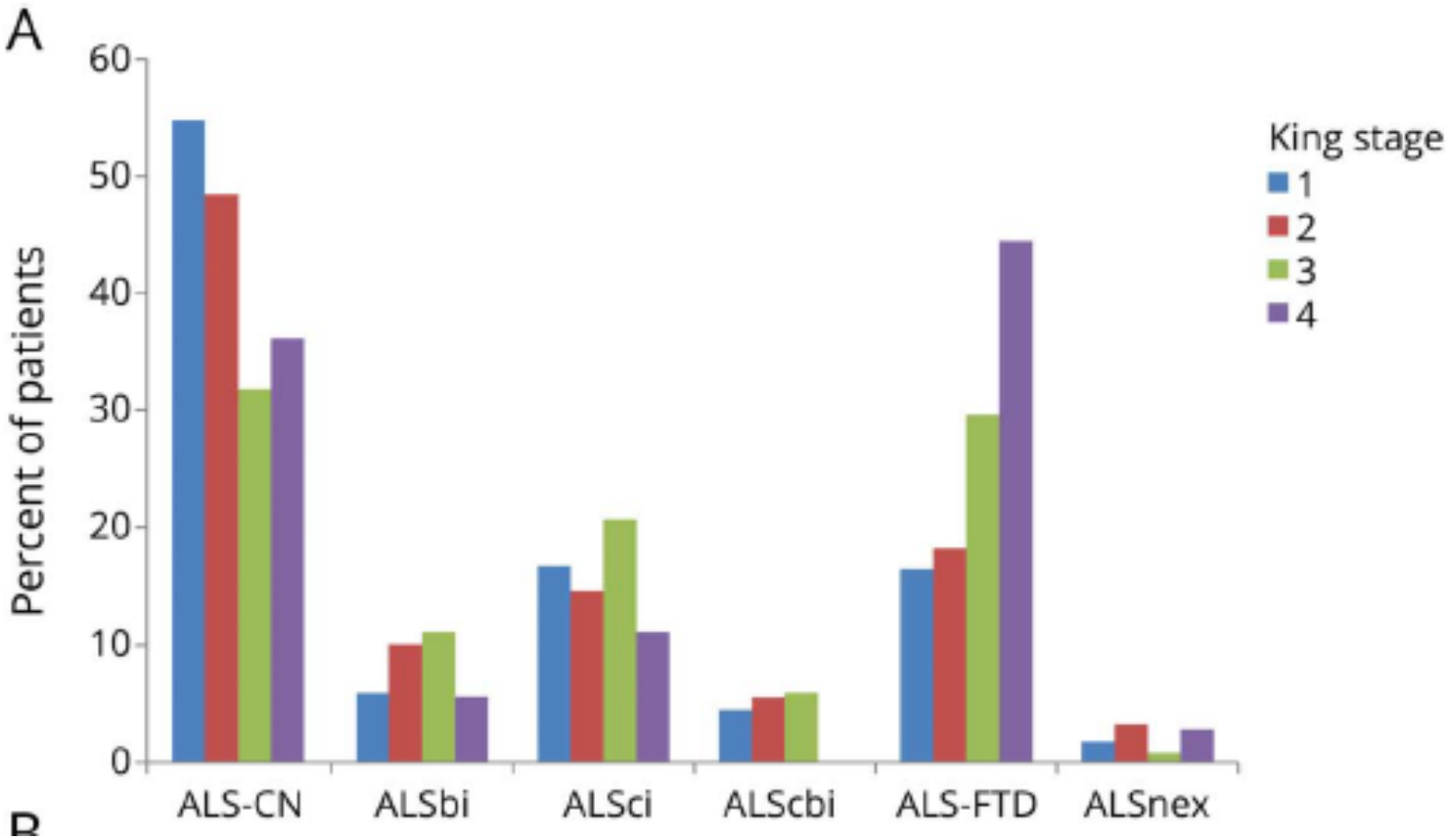



Patient performance is scaled to a standardized score (*z* score) on the basis of the mean and SD of local UK and Irish control groups. ALS = amyotrophic lateral sclerosis; ECAS = Edinburgh Cognitive and Behavioural ALS Screen.



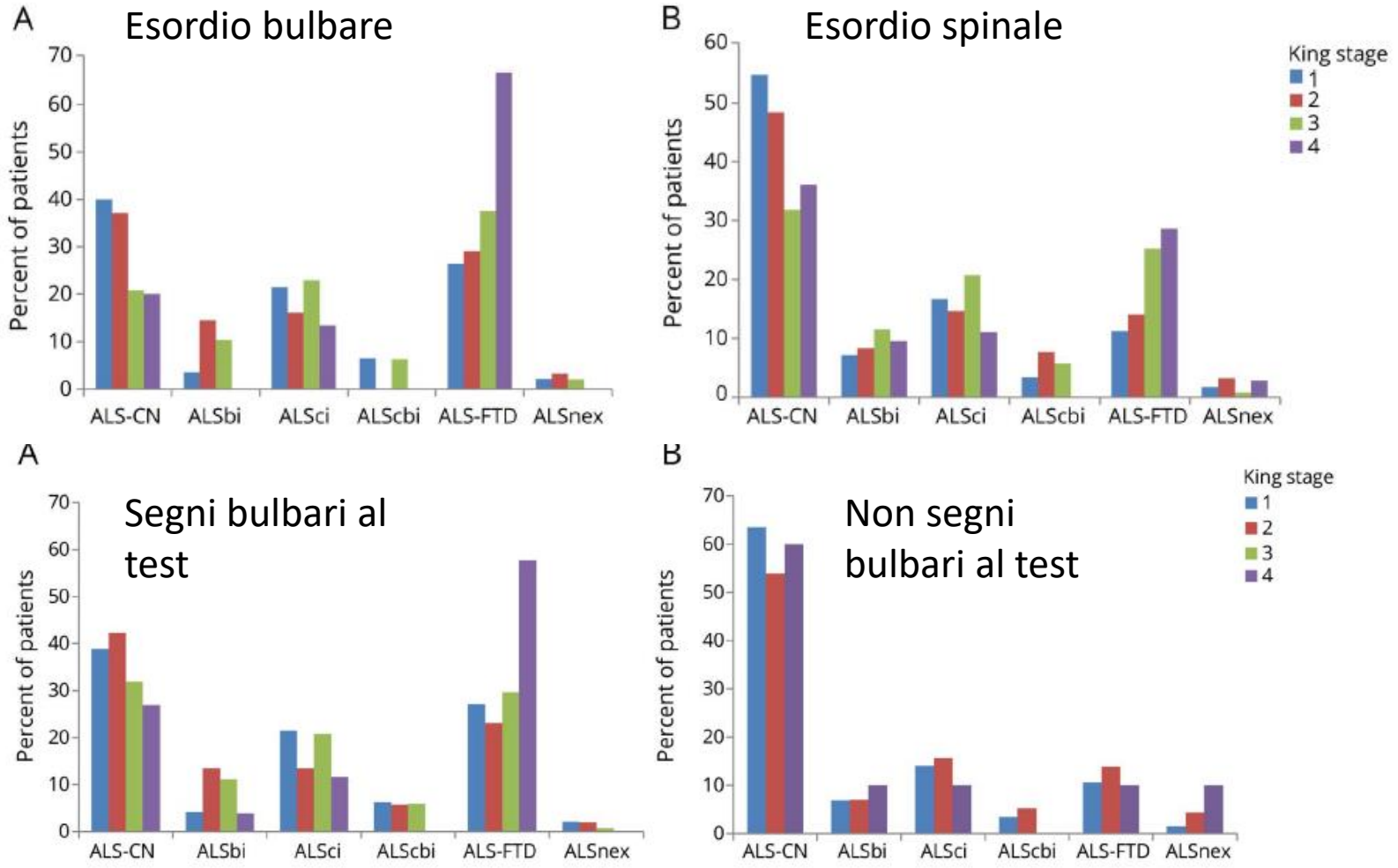

Crockford et al, *Neurology* 2018

# La compromissione cognitiva aumenta con il peggioramento dello stadio di malattia




Chiò et al, *Neurology* 2019

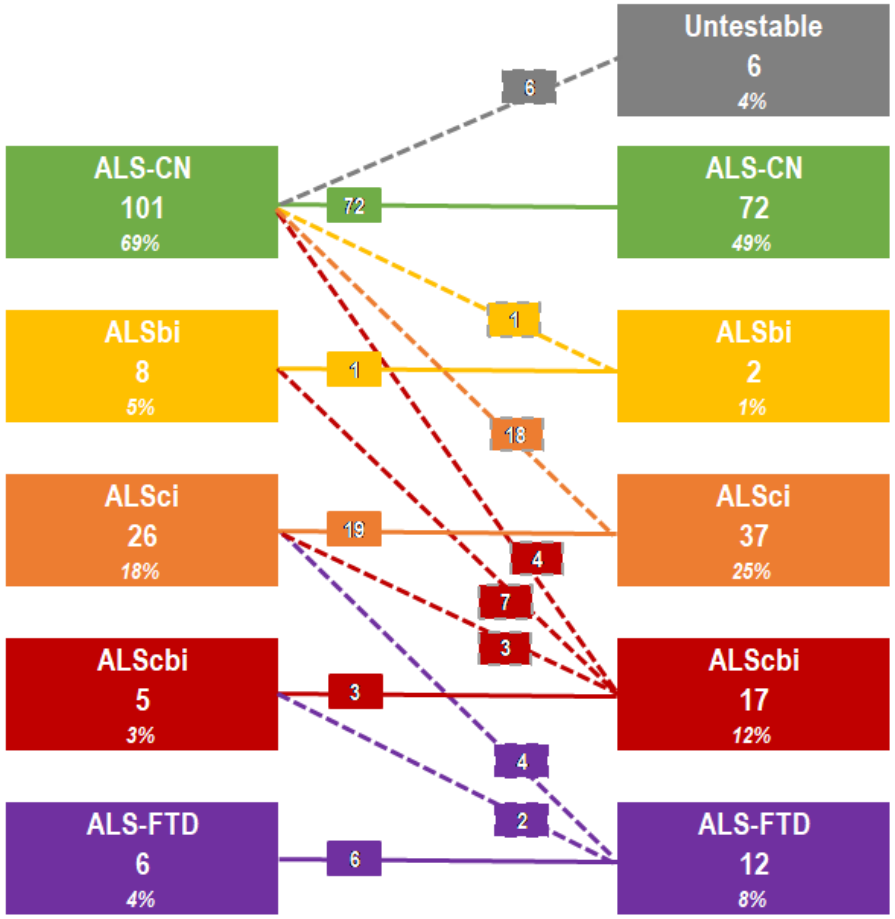
# Classificazione cognitiva e presenza di segni bulbari




Chiò et al, *Neurology* 2019

# Lo studio longitudinale Novara-Torino

| Cognitive status | t0 | t1 |
|---|---|---|
| Normal cognition | 101 | 72 |
| ALSbi | 8 | 2 |
| ALSci | 26 | 37 |
| ALScbi | 5 | 17 |
| ALS-FTD | 6 | 12 |
| Untestable | 0 | 6 |
| Median ALSFRS-r score | 43 | 34 |
| Median FVC (%) | 96 | 80 |
| Median BMI | 24.5 | 23.2 |
| Bulbar sign in spinal-onset patients | 33 | 44 |




Bersano et al, *Amyotrophic Lateral Sclerosis* submitted

# Influenza dei disturbi cognitivi sulla prognosi

ORIGINAL CONTRIBUTION

Arch Neurol. 2010;67(7):826-830.

# Neurobehavioral Features in Frontotemporal Dementia With Amyotrophic Lateral Sclerosis

Patricia Lillo, MD; Beatrice Garcin, MD; Michael Hornberger, PhD; Thomas H. Bak, MD; John R. Hodges, MD, FRCP

La prognosi dei pazienti con FTD/ALS è nettamente peggiore di quelli con bvFTD senza segni motori

Sopravvivenza mediana:

FTD/ALS: 2.4 anni
bvFTD: 6.6 anni

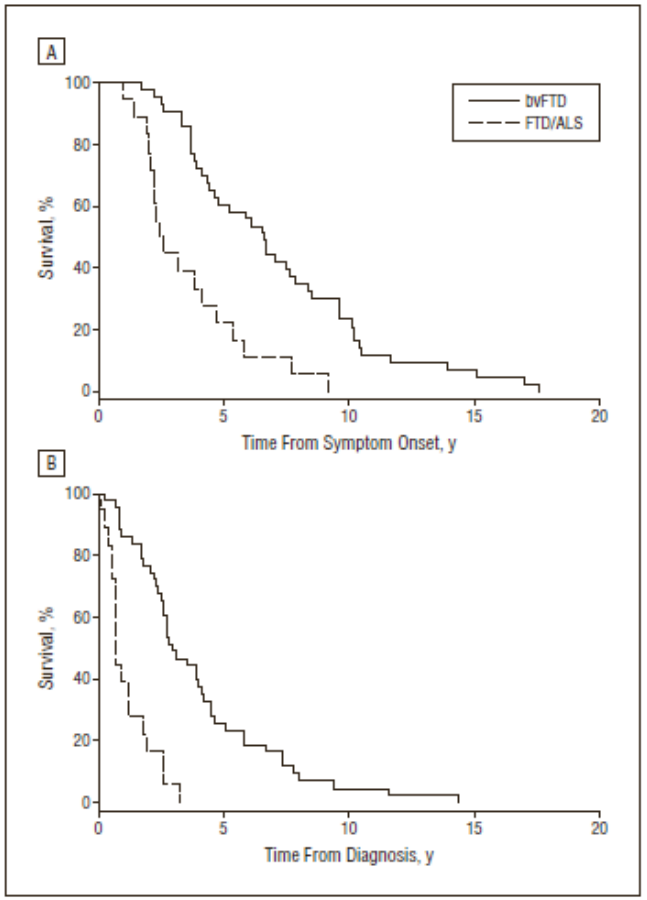
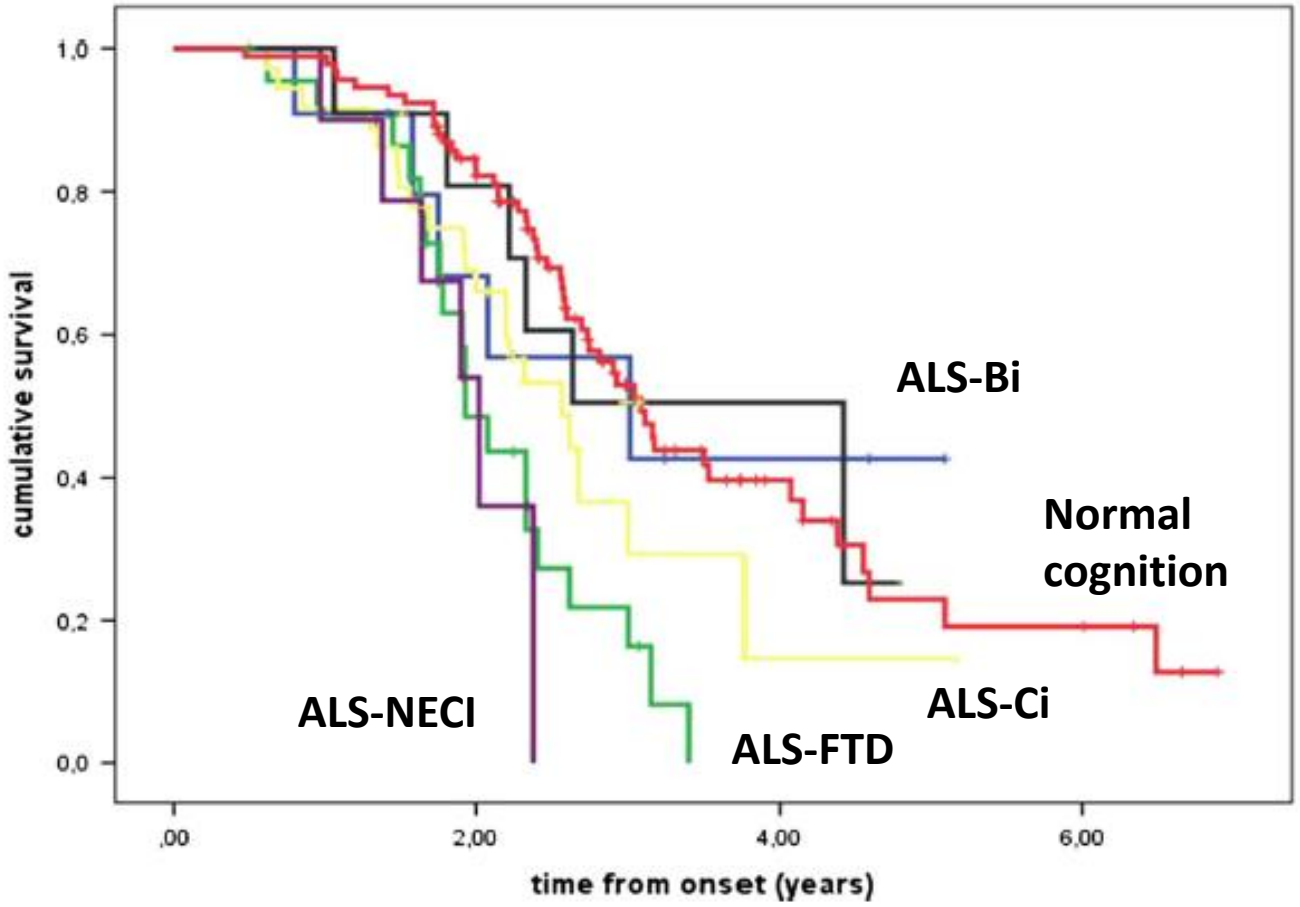



**Figure.** Survival curves in patients with behavioral variant frontotemporal dementia (bvFTD group) and patients with FTD who developed amyotrophic lateral sclerosis (FTD/ALS group). A, Kaplan-Meier survival curve from symptom onset to death in the bvFTD and FTD/ALS groups ($P<.001$). B, Kaplan-Meier survival curve from diagnosis to death in the bvFTD and FTD/ALS groups ($P<.001$).

# Influenza della cognitività sulla prognosi nella SLA




Montuschi et al, J Neurol Neurosurg Psychiatry 2014

# Cognitive changes predict functional decline in ALS

## A population-based longitudinal study

Marwa Elamin, MRCP

ABSTRACT

Neurology® 2013;80:1590-1597

- La presenza di alterazioni cognitive (FTD e sindrome disesecutiva) si associa a un più rapido declino delle funzioni motorie

**Table 3** Results of direct comparisons of median decline in ALSFRS-R over time in 4 cognitive subgroups (segregated based on cognitive status at initial visit) using the Kruskal-Wallis test

| | | | No dementia or executive impairment | | |
|---|---|---|---|---|---|
| Cognitive function at baseline | Comorbid FTD | Executive dysfunction | Nonexecutive cognitive impairment | No cognitive abnormality | *p* |
| Functional decline T1–T2 | | | | | |
| No. | 5 | 17 | 14 | 61 | |
| Median change in total ALSFRS-R score (points/mo) | −1.29 | −1.20 | −1.05 | −0.83 | 0.117 |
| Median change in bulbar subscores (points/mo) | −0.20 | −0.20 | 0.00 | 0.00 | 0.026 |
| Functional decline T1–T3 | | | | | |
| No. | | 5 | 3 | 38 | |
| Median decline in total ALSFRS-R score (points/mo) | | −0.76 | −0.66 | 0.42 | 0.025 |
| Median decline in bulbar subscores (points/mo) | | −0.25 | −0.10 | 0.00 | 0.064 |

Abbreviations: ALSFRS-R = revised Amyotrophic Lateral Sclerosis Functional Rating Scale; FTD = frontotemporal lobar degeneration; T1 = first assessment; T2 = second assessment; T3 = the third assessment.

# Executive dysfunction is a negative prognostic indicator in patients with ALS without dementia

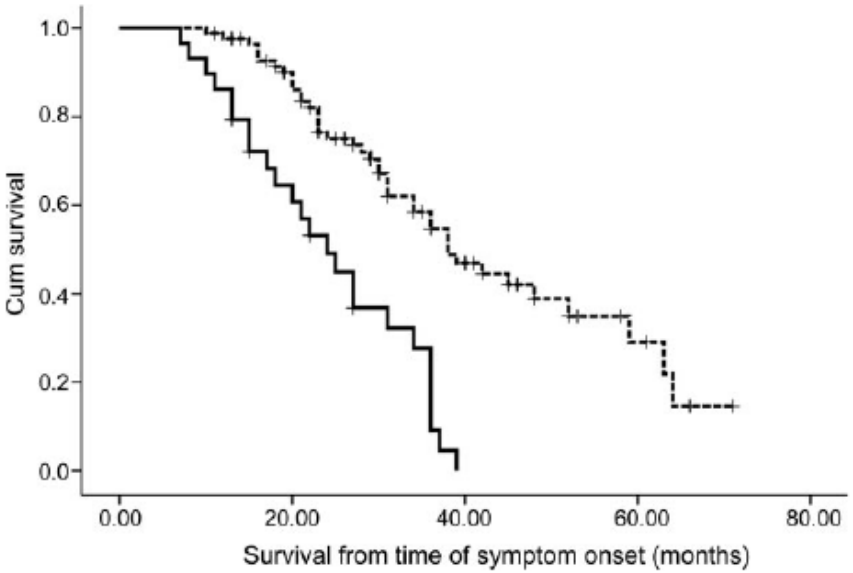
M. Elamin, MRCP
J. Phukan, PhD
P. Bede, MRCP

Neurology® 2011;76:1263–1269

ABSTRACT

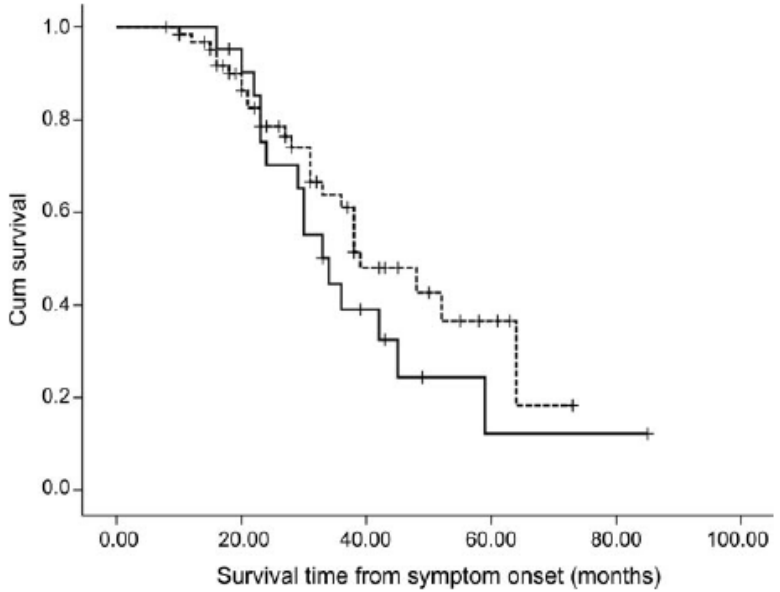
**Background:** The prognostic implications of cognitive impairment in amyotrophic lateral sclerosis (ALS) are not established.

**Figure 3** Kaplan-Meier plots of survival probabilities for 113 patients with amyotrophic lateral sclerosis stratified by presence of executive dysfunction




Log-rank test for equality of survival functions, $p < 0.0001$. Black line: patients with executive dysfunction (n = 29); dotted line: patients without executive dysfunction (n = 84); +: censored cases.

**Figure 4** Kaplan-Meier plots of survival probabilities for 84 patients with amyotrophic lateral sclerosis stratified by presence of nonexecutive cognitive impairment




Log-rank test for equality of survival functions, $p = 0.377$. Black line: patients with nonexecutive cognitive impairment (n = 21); dotted line: patients in whom no abnormality was detected (n = 63); +: censored cases.

Pazienti con compromissione esecutiva isolata vs. cognitivamente normali

Pazienti con compromissione non esecutiva isolata vs. cognitivamente normali

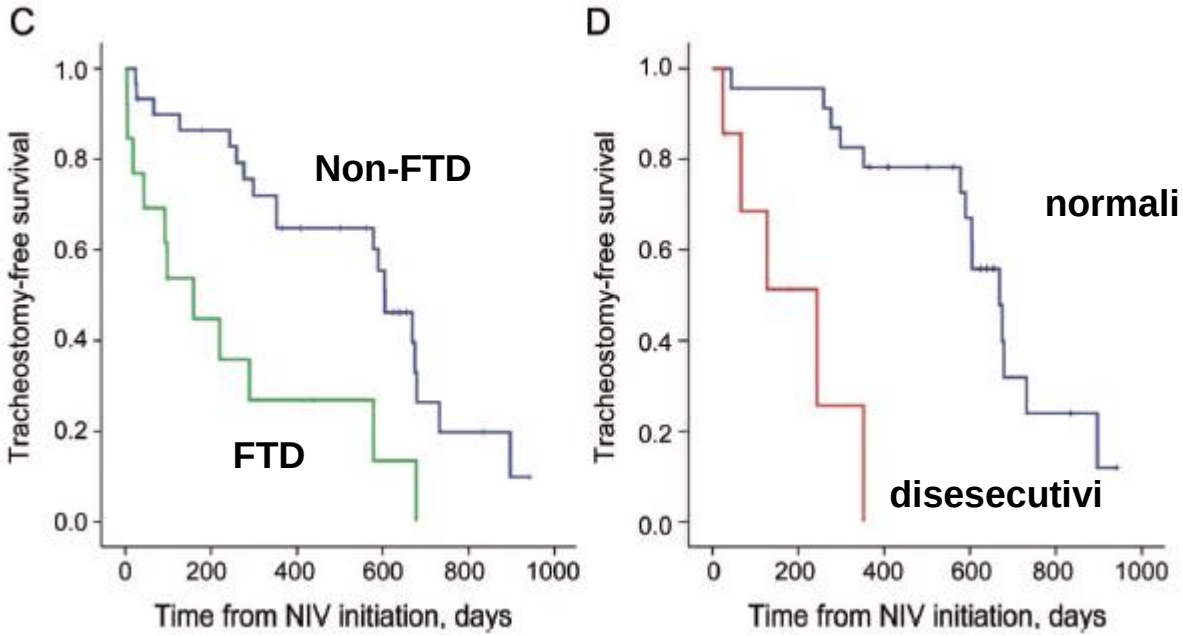
Neurobehavioral dysfunction in ALS has a negative effect on outcome and use of PEG and NIV

A. Chiò, MD

ABSTRACT

Neurology© 2012;78:1085-1089

# Influenza della disfunzione neurocomportamentale sull'uso di PEG e NIV




I pazienti con FTD o disturbo disesecutivo non si adattano alla NIV

ORIGINAL CONTRIBUTION

Arch Neurol. 2009;66(11):1359-1364

# Survival Profiles of Patients With Frontotemporal Dementia and Motor Neuron Disease

*William T. Hu, MD, PhD; Harro Seelaar; Keith A. Josephs, MST, MD; David S. Knopman, MD; Bradley F. Boeve, MD; Eric J. Sorenson, MD; Leo McCluskey, MD; Lauren Elman, MD; Helenius J. Schelhaas, MD, PhD; Joseph E. Parisi, MD; Benno Kuesters, MD, PhD; Virginia M.-Y. Lee, PhD; John Q. Trojanowski, MD, PhD; Ronald C. Petersen, MD, PhD; John C. van Swieten, MD; Murray Grossman, MD*

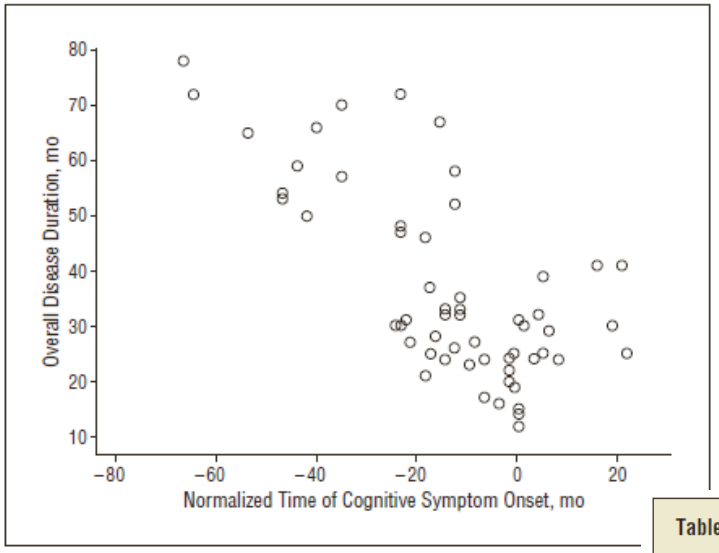



**Figure 1.** Relationship between normalized time of cognitive symptom and overall disease survival among deceased patients. Normalized tim cognitive symptom onset was derived by subtracting the date of cogni symptom onset from the date of motor symptom onset. A negative va indicates cognitive onset; a positive value, motor onset.

- I pazienti con esordio cognitivo (FTD-ALS) hanno una prognosi migliore di quelli con esordio motorio (ALS-FTD)

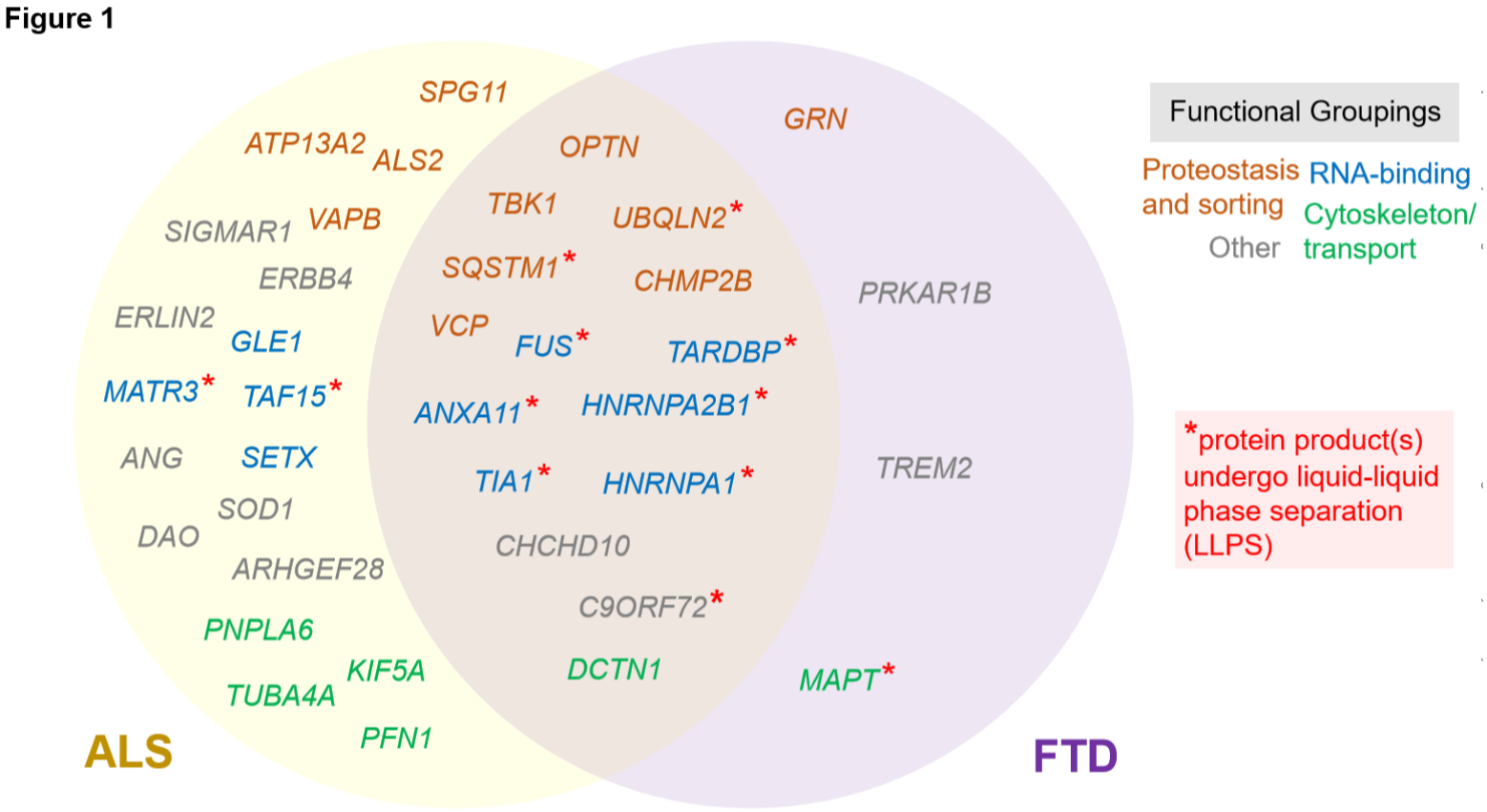
**Table 2. Characteristics of Patients According to Survival Patterns**

| Characteristic | Typical Survivors: Simultaneous Onset (n=8) | Typical Survivors: Cognitive Onset or Motor Onset (n=54) | Long-term Survivors (n=25) | *P* Value[a] |
|---|---|---|---|---|
| Female, No. (%) | 5 (62) | 21 (39) | 8 (32) | .31 |
| Died, No. (%) | 4 (50) | 39 (72) | 16 (64) | .40 |
| Age at onset, mean (SD), y | 63.0 (12.9) | 58.7 (10.2) | 58.5 (10.3) | .28 |
| Cognitive onset, No. (%) | 0 | 37 (69) | 22 (88) | <.001 |
| Bulbar onset, No. (%) | 5 (63) | 34 (63) | 7 (28) | .01 |
| Language-dominant cognitive symptoms, No. (%) | 3 (38) | 16 (30) | 7 (28) | .88 |
| Overall disease duration, mean (SD), mo | 19.2 (6.4) | 28.6 (8.8) | 69.3 (21.1) | <.001 |
| Disease duration until secondary symptom onset, mean (SD), mo | 0 | 12.4 (7.9) | 44.5 (21.6) | <.001 |
| Disease duration after secondary symptom onset, mean (SD), mo | 19.2 (6.4) | 15.1 (7.4) | 24.0 (15.5) | .01 |

[a]We used $\chi^2$ test and 1-way analysis of variance to determine differences between dichotomous and continuous variables, respectively.

# Compromissione cognitiva e mutazioni genetiche

# L’interrelazione genetica fra SLA e FTD




Fernandopulle et al, *Human Mol Genet 2019*

# I geni e la neuropatologia della SLA

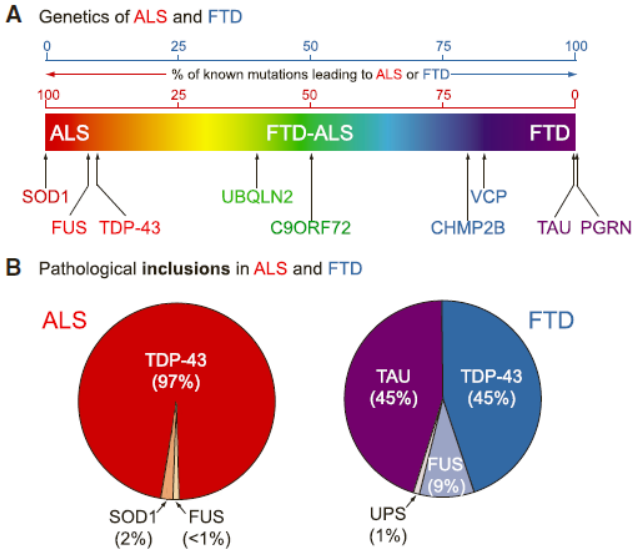



Figure 1. Clinical, Genetic, and Pathological Overlap of ALS and FTD

Ling et al, *Neuron* 2013

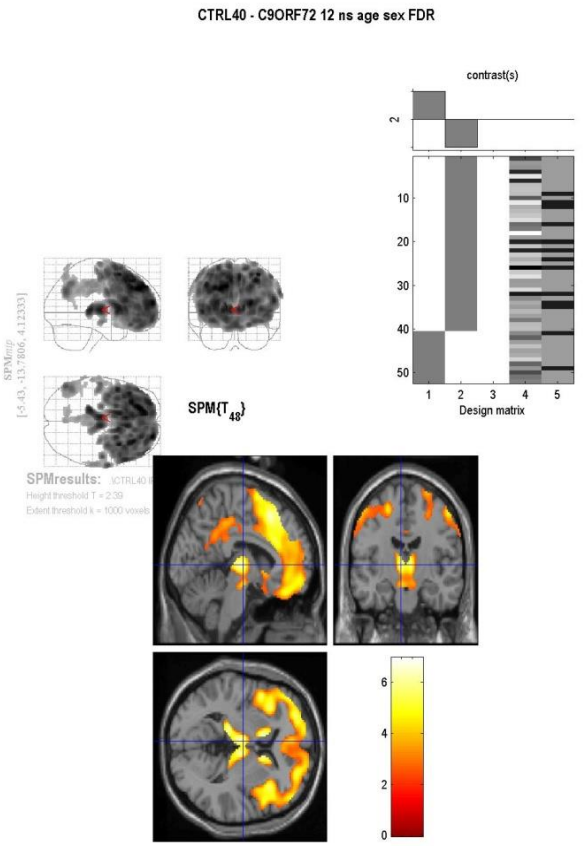
| | Predominant pathology | Associated genes |
|---|---|---|
| Classic ALS | TDP-43 | *ALS2, SETX, TARDBP, VAPB, CHMP2b, ANG, UBQLN2, OPTN, PFN1, TUBA4a, UNC13a, FIG4, ELP3, NEK1, C21orf2, SIGMAR1, DCTN1, MATR3, CHCHD10, VCP, hnRNPA1, hnRNPA2b1, NIPA1, SMN1, TBK1, ATXN2, MOBP, SARM1, UBQLN2, SQSTM1* |
| Classic ALS | SOD1 | *SOD1* |
| Classic ALS | FUS | *FUS* |
| ALS with cognitive or behavioural impairment or comorbid FTD | TDP-43 | *TARDBP, CHMP2b, TBK1, UBQLN2, SQSTM1, DCTN1, UNC13a* |
| Classic ALS, ALS-FTD, FTD | TDP-43, p62, dipeptide repeats, RNA foci | *C9orf72* |
| Multi-system proteinopathy* | TDP-43 | *VCP, hnRNPA1, hnRNPA2b1, SQSTM1* |
| Behavioural variant FTD | TDP-43 | *CHMP2, GRN* |
| Behavioural variant FTD | FUS | - |
| Behavioural variant FTD | Tau | *MAPT* |
| Semantic variant primary progressive aphasia | TDP-43 | *GRN, C9orf72* |
| Semantic variant primary progressive aphasia | Tau | *MAPT* |
| Logopenic and non-fluent variant primary progressive aphasia | Tau | *MAPT* |

ALS=amyotrophic lateral sclerosis. FTD=frontotemporal dementia. *A familial disorder in which patients present with ALS, FTD, inclusion body myositis, Paget's disease of the bone, or combinations thereof.

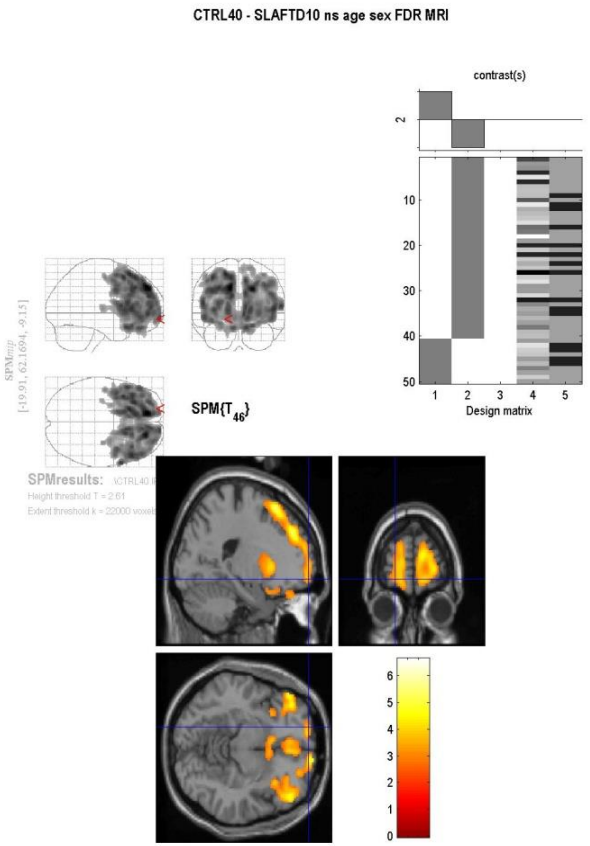
***Table 3*: The complex correlations between genes, pathology, and phenotypes**

Van Es al, *Lancet* 2017

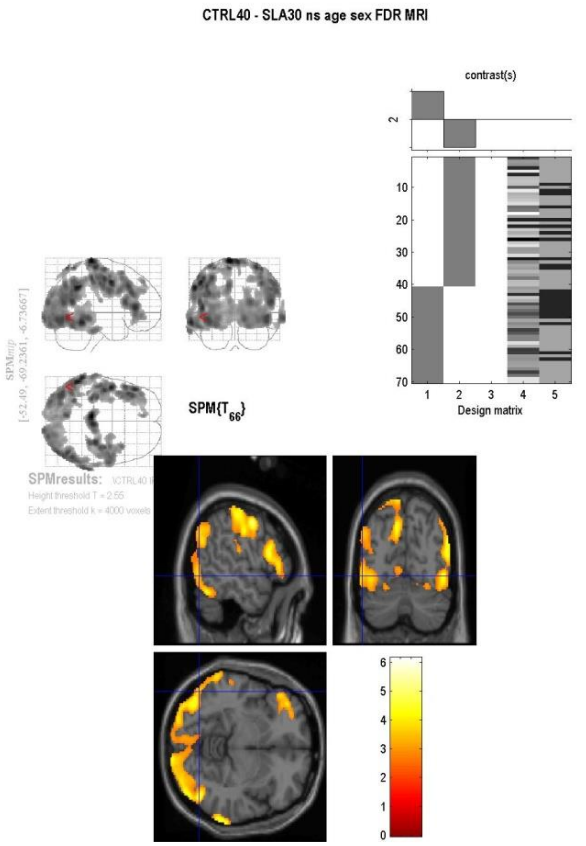
# 18F-FDG-PET nei pazienti con mutazione C9ORF72 e nei pazienti ALS-FTD




**ALS-C9ORF72**




**ALS-FTD non-mutated**




**ALS cognitively normal non-mutated**

Cistaro et al, EJNMN, 2014

# APOE E2 è un fattore di rischio per disturbi cognitivi nella SLA?

Table 1. Patients With ALS and Age- and Sex-Matched Population Control Individuals

| APOE | No. (%) Patients With ALS (n = 357) | Controls (n = 223) | P Value |
|---|---|---|---|
| Genotype | | | |
| ε2/ε2 | 2 (0.6) | 0 | .73 |
| ε2/ε3 | 36 (10.1) | 24 (10.8) | |
| ε3/ε3 | 275 (77.0) | 169 (75.8) | |
| ε3/ε4 | 37 (10.4) | 22 (9.9) | |
| ε2/ε4 | 6 (1.7) | 7 (3.1) | |
| ε4/ε4 | 1 (0.3) | 1 (0.4) | |
| Alleles[a] | | | |
| ε2 | 46 (6.4) | 31 (7.0) | .85 |
| ε3 | 623 (87.3) | 384 (86.1) | |
| ε4 | 45 (6.3) | 31 (7.0) | |

Abbreviation: ALS, amyotrophic lateral sclerosis.

[a] Data were obtained for 714 patients with ALS and 446 controls.

Table 4. Multivariate Logistic Regression[a]

| | Odds Ratio (95% CI) | P Value |
|---|---|---|
| **Patients With ALS-FTD** | | |
| *C9ORF72* vs non-*C9ORF72* | 13.08 (4.75-36.02) | <.001 |
| *APOE* | | |
| ε2 vs non-ε2 | 2.61 (1.14-6.10) | .03 |
| ε4 vs non-ε4 | 0.68 (0.25-1.85) | .46 |
| Sex, female vs male | 1.25 (0.63-2.48) | .53 |
| Site of onset, bulbar vs spinal | 1.97 (0.98-3.93) | .05 |
| Age group, y | | |
| ≥70 vs <50 | 7.43 (1.61-34.71) | .01 |
| 60-69 vs <50 | 3.00 (0.64-14.04) | .16 |
| 50-59 vs <50 | 1.46 (0.29-7.28) | .64 |
| **Patients With ALS-Ci** | | |
| *C9ORF72* vs non-*C9ORF72* | 2.85 (1.11-7.31) | .03 |
| *APOE* | | |
| ε2 vs non-ε2 | 1.01 (0.45-2.20) | .99 |
| ε4 vs non-ε4 | 0.68 (0.33-1.42) | .30 |
| Sex, female vs male | 1.27 (0.76-2.13) | .36 |
| Site of onset, bulbar vs spinal | 0.93 (0.54-1.61) | .80 |
| Age group, y | | |
| ≥70 vs <50 | 2.88 (1.01-8.21) | .048 |
| 60-69 vs <50 | 2.85 (1.01-7.99) | .047 |
| 50-59 vs <50 | 1.74 (0.59-5.13) | .31 |

Abbreviations: ALS, amyotrophic lateral sclerosis; ALS-Ci, ALS with cognitive impairment; ALS-FTD, ALS with comorbid frontotemporal dementia.

[a] Data for patients with ALS with behavioral impairment are not reported because all values were nonsignificant.

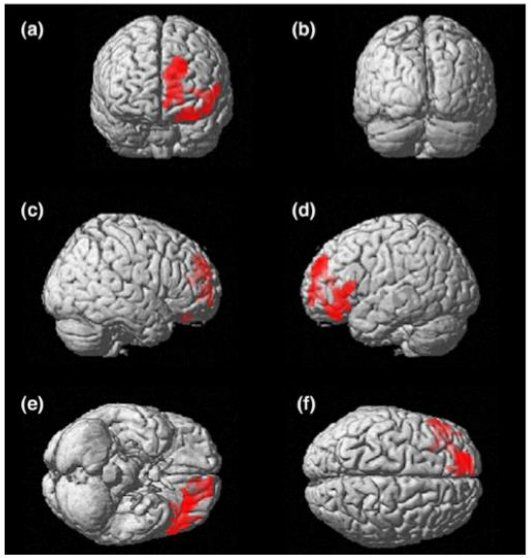



**Figure 1** Glass brain rendering of multiple regression of *Apolipoprotein E* genotype, as transformed into rank variable, against whole brain metabolism. The clusters showing a statistically significant positive correlation are projected on brain surface. (a) Frontal view; (b) posterior view; (c) right view; (d) left view; (e) view from below; (f) view from above.

**Table 2** Results of the positive correlation between whole brain metabolism and *Apolipoprotein E* genotypes

| Cluster extent | $P$ ($FDR_{corrected}$) | $Z$-score | Talairach coordinates | | | Lobe | Cortical region | BA |
|---|---|---|---|---|---|---|---|---|
| 774 | 0.05 | 4.270 | −20 | 56 | 25 | Frontal | Left superior frontal gyrus | 10 |
| | | 3.087 | −16 | 58 | 4 | Frontal | Left medial frontal gyrus | 10 |
| | | 2.943 | −8 | 41 | 9 | Frontal | Left anterior cingulate | 32 |
| 698 | 0.05 | 3.589 | −30 | 36 | −20 | Frontal | Left middle frontal gyrus | 11 |
| | | 3.315 | −48 | 32 | −12 | Frontal | Left inferior frontal gyrus | 47 |
| | | 3.286 | −55 | 24 | 6 | Frontal | Left inferior frontal gyrus | 45 |

BA, Brodmann area.

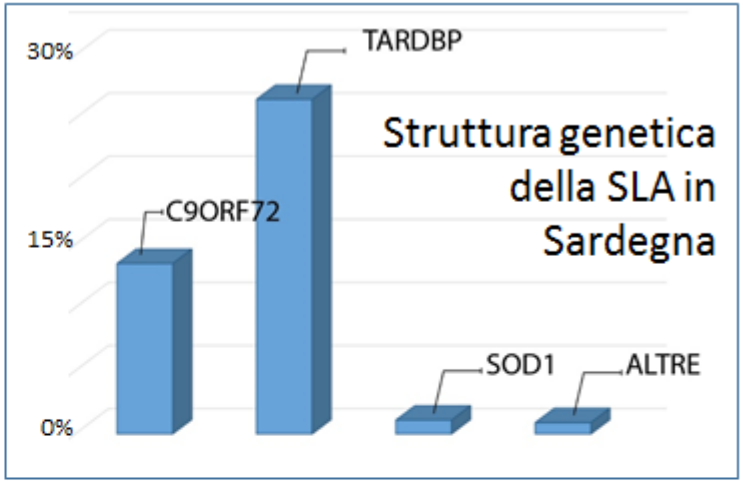
Chiò et al, JAMA Neurol 2016

Canosa et al, Eur J Neurol 2019

# Oligogenicità nella popolazione sarda con SLA mediante exome sequencing

## Popolazione

186 casi SLA
84 controlli sani } origine **sarda**




## Metodi

1) Sequenziamento dell'esoma: 6 geni maggiori, 38 geni minori

2) Confronto con i database genetici di riferimento per SNP: *6500Genomes, 1000Genomes, ExAc, dbSNP*

3) Predizioni di patogenicità (*SIFT, PolyPhen*)

# Oligogenic cases - prevalence and clinical phenotype

Oligogenic subjects: carriers of multiple rare or novel variants in either Group 1 or Group 2 genes
Prevalence among cases 22.6%: the co-occurence of multiple variants is higher than previously reported and than expected by mutation frequency
Evidence for a possible influence on ALS phenotype

| | Controls | ALS | FALS | | FTD | ONSET | |
|---|---|---|---|---|---|---|---|
| | | | SALS | FALS | | Spinal | Bulbar |
| **Oligogenic cases** | 7/84 (8.3%) | 42/186 (22.6%) | 29/154 (18.8%) | 13/32 (40.6%) | 7/16 (43.8%) | 29/149 (19.5%) | 13/37 (35.1%) |
| **P** | **-** | **0.006** | **0.010** | | **0.024** | **0.049** | |

Grassano et al, Motor Neuron Disease session





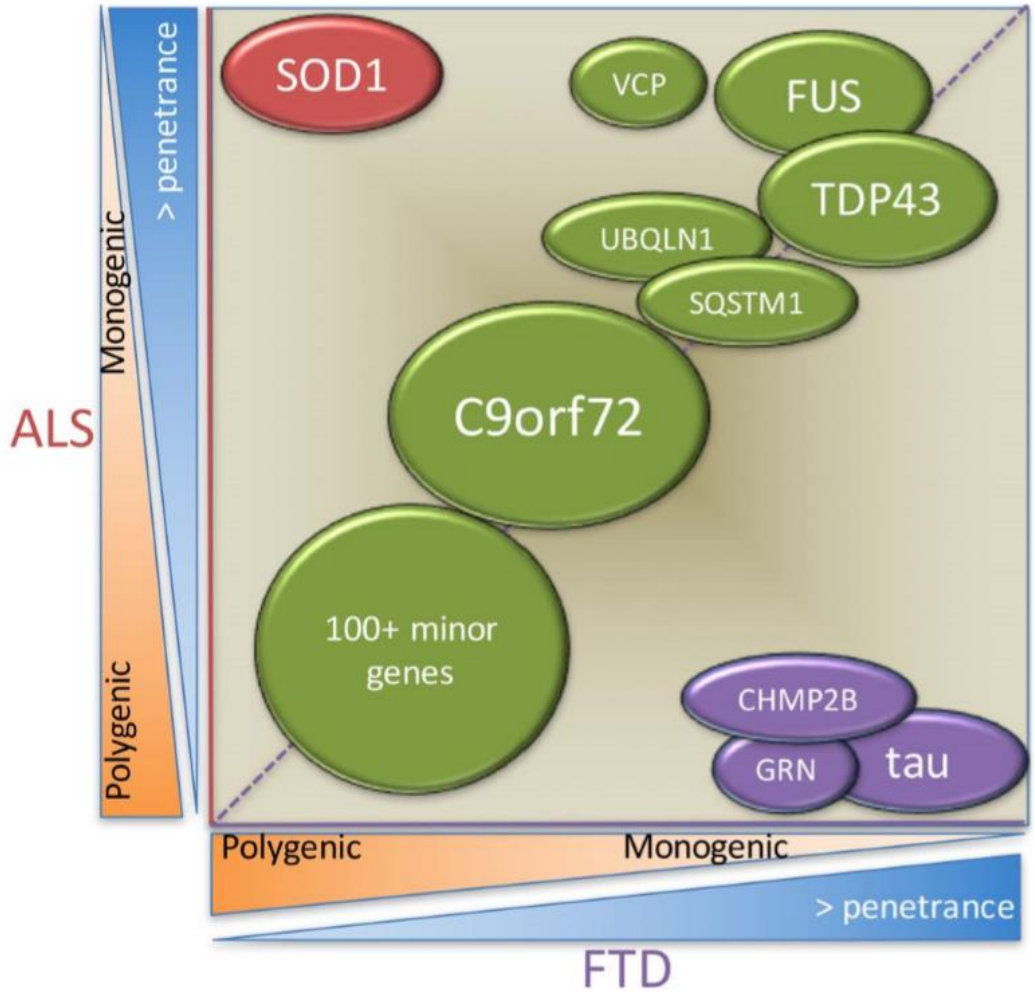







# Grazie per l’attenzione!


# L’interrelazione genetica fra SLA e FTD




Ji et al, *J Neurol Neurosurg Psychiatry 2017*