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To cite this version:

Juliette Ortholand, Igor Koval, Pierre-François Pradat, Sophie Tezenas Du Montcel, Stanley Durrleman. Gender and spinal/bulbar onset interaction on ALS progression. ENCALS 2022 - European Network to Cure ALS meeting, Jun 2022, Edinburgh, United Kingdom. hal-03782549

HAL Id: hal-03782549

https://hal.science/hal-03782549v1

Submitted on 21 Sep 2022

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GENDER AND SPINAL/BULBAR ONSET INTERACTION ON ALS PROGRESSION

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Background & Objectives

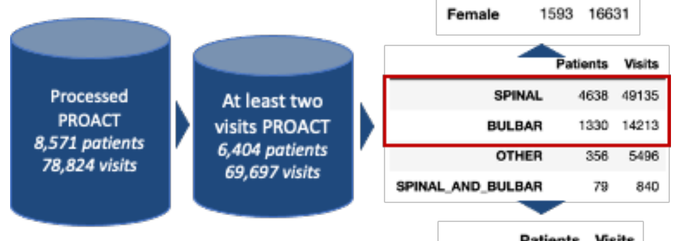
ALS is an adult onset heterogeneous neurodegenerative disease that occurs at a younger age than AD or PD (55 , 60, 60 respectively). Descriptive studies show that the mean age and gender/ratio is different according to the phenotype. Compared to spinal onset form, bulbar-onset form, which represent 26 % of ALS cases, are more frequent in women (gender ratio of 1/2 vs 1/3 in spinal forms) and occurs later. The progression of bulbar forms is more rapid in bulbar-onset form with a mean survival of 24 months (vs 40 months in spinal forms). (Tysnes, Acta Neurol Scand 1991)

However the interaction betwen **gender** and **spinal/bulbar onset** on ALS progression remains under study.

To investigate this issue , we used a multivariate disease progression model in PROACT, a large dataset of ALS patients.

Methods

Population:



	Patients	Visits
Male	3045	32504
Female	1593	16631

	Patients	Visits
SPINAL	4638	49135
BULBAR	1330	14213
OTHER	356	5496
SPINAL_AND_BULBAR	79	840

	Patients	Visits
Male	669	7092
Female	661	7121

Clinical Endpoints:

- BMI
- ALSFRS-R Respiratory
- ALSFRS-R Bulbar
- ALSFRS-R Gross Motor
- ALSFRS-R Fine Motor
- Percent Forced Vital Capacity (PFVC) (Brändli, Thorax 1996)

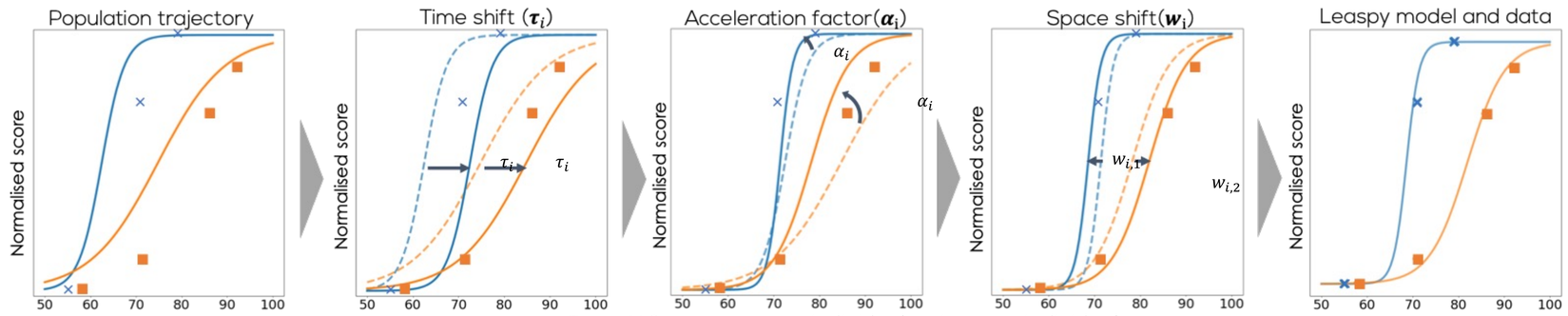
Statistical Methods:

leaspy — *J-B. Schiratti 2017 (Bayesian mixed-effect model)*

Useful for:

- **Temporal progression**
- **Continuous endpoints**
- **Multivariate analysis**
- **Robust to missing data**

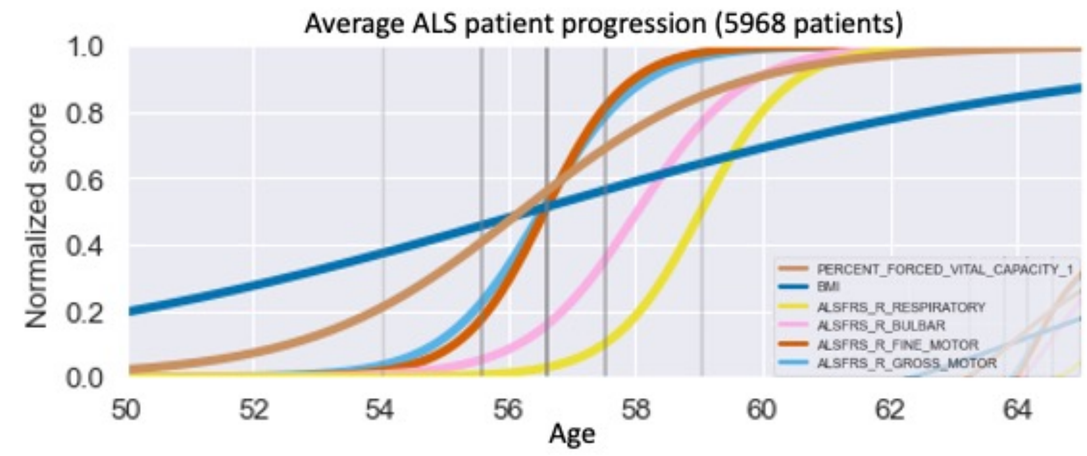
Scores are normalized thanks to there scales, and BMI and PFVC thanks to box-cox transformation and [-3,3] normalization.



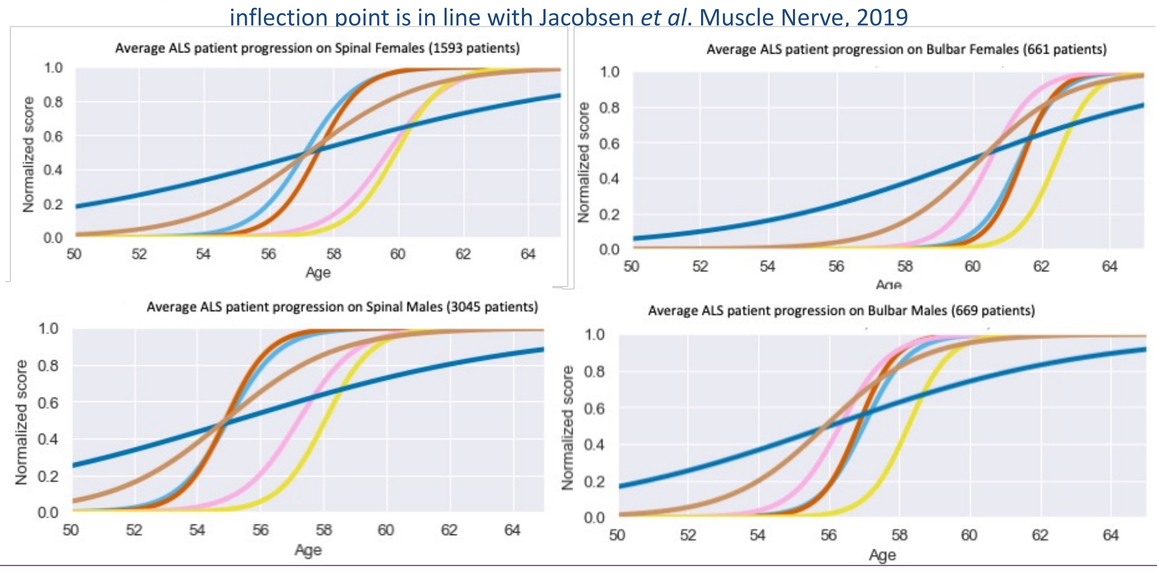
From ALS course map to individual trajectory : individual parameters

Results

Endpoints	Spinal Male	Bulbar Male	Spinal Female	Bulbar Female	Interaction p-value	Subgroup relations
Age at baseline (y)	53.9 ± 11.8	55.7 ± 11.5	56.8 ± 11.1	60.5 ± 9.6	7.5e-03	SM<(BM,SF)<BF
Follow up (y)	1.0 ± 0.5	0.9 ± 0.4	0.9 ± 0.5	1.0 ± 0.4	1.3e-01	
Number of visits	10.6 ± 5.9	10.6 ± 4.7	10.4 ± 5.5	10.7 ± 5.0	2.4e-01	
Active arm	1836 (60.3 %)	382 (57.1 %)	957 (60.1 %)	360 (54.5 %)		
Placebo arm	951 (31.2 %)	242 (36.2 %)	503 (31.6 %)	232 (35.1 %)		
Observational arm	258 (8.5 %)	45 (6.7 %)	133 (8.3 %)	69 (10.4 %)		
Age at first symptoms (y)	51.8 ± 11.7 (91.3 %)	54.1 ± 11.5 (90.7 %)	54.6 ± 11.2 (91.3 %)	58.7 ± 9.7 (91.7 %)	1.8e-02	SM<(BM,SF)<BF
Age at diagnosis (y)	52.4 ± 11.8 (52.1 %)	54.8 ± 11.4 (53.4 %)	55.2 ± 11.5 (52.2 %)	59.4 ± 10.0 (52.6 %)	6.1e-02	SM<BM<SF<BF
Patients with gastrostomy	19.8 %	45.4 %	21.4 %	58.5 %		
Patients dead	26.9 %	35.1 %	30.3 %	38.1 %		
Length of the disease (y)	2.6 ± 1.2 (25.7 %)	2.2 ± 0.8 (32.7 %)	2.7 ± 1.1 (29.1 %)	2.4 ± 0.8 (36.0 %)	8.8e-02	BM<BF<SM<SF
Time betw. sympt. and bsl (y)	1.9 ± 1.5 (91.3 %)	1.5 ± 0.9 (90.7 %)	2.0 ± 1.3 (91.3 %)	1.5 ± 0.9 (91.7 %)	7.8e-01	



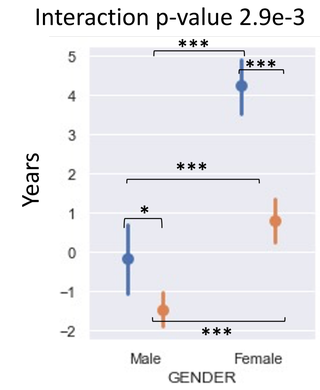
disease progression of the typical patient: Symptoms develop between the age of 55 and 75. Slope at inflection point is in line with Jacobsen *et al*. Muscle Nerve, 2019



Legend:

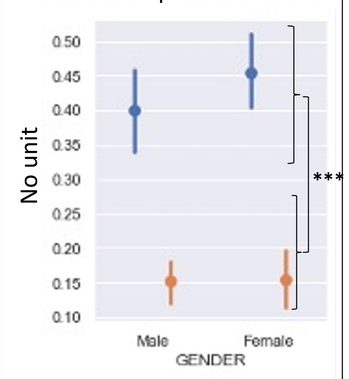
- B: Bulbar,
- S: Spinal,
- M: Male,
- F: Female,
- PFVC: Percent of Forced Vital Capacity,
- <: earlier or slower
- *: <5e-2
- **: <1e-2
- ***: <1e-3

Time-shift distributions
Interaction p-value 2.9e-3



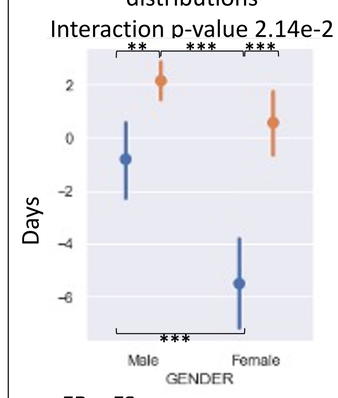
SM < (BM, SF) < BF

Log acceleration factor distributions
Interaction p-value 3.19e-1



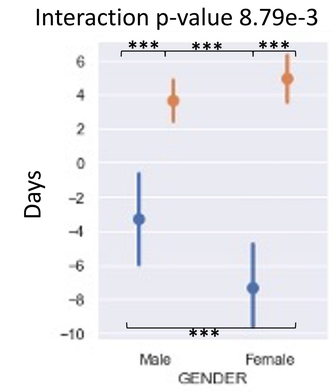
S < B

BMI inter-marker spacing distributions
Interaction p-value 2.14e-2



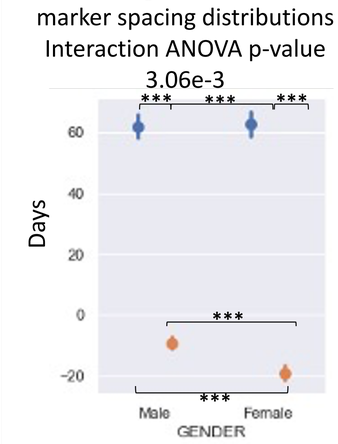
FB < FS
MB < MS
FB < MB

PFVC inter-marker spacing distributions
Interaction p-value 8.79e-3



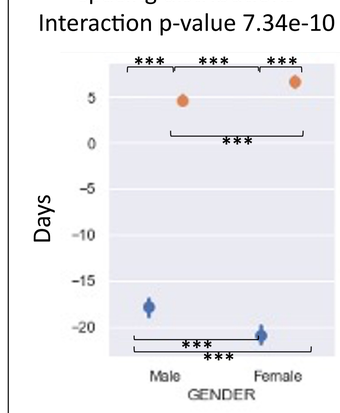
FB < FS
MB < MS

ALSFRS-R gross motor inter-marker spacing distributions
Interaction ANOVA p-value 3.06e-3



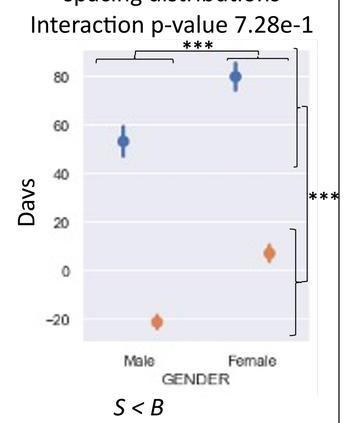
SF < SM < (BM, BF)

ALSFRS-R bulbar inter-marker spacing distributions
Interaction p-value 7.34e-10



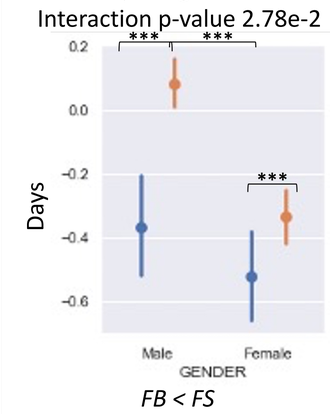
BF < BM < SM < SF

ALSFRS-R Fine motor inter-marker spacing distributions
Interaction p-value 7.28e-1



S < B
M < F

ALSRS_R Respiratory inter-marker spacing distributions
Interaction p-value 2.78e-2



FB < FS
MB < MS

Distribution of relative timing of endpoints on the different subgroups

Discussion

- Our method allows to validate that patients with bulbar onset have a faster progression although the disease starts later (Chio, Neurology 2020) and that for both gross and fine motor scores progression starts earlier (and bulbar score and BMI later) for spinal patients regardless of the gender (Rooney, J Neurol Neurosurg Psychiatry 2016) (Moglia, J Neurol Neurosurg Psychiatry 2019), with a **large number of patients** and **a methodology not based on survival model** that allows to use **six major outcome of ALS**.
- We exhibited, that **female starts later in both spinal and bulbar onset**, which might be linked to hormone protection as suggested in Trosji, Int J Mol Sci. 2020.
- We show that, **fine motor progression starts earlier for spinal male patients** and **gross motor progression starts earlier for spinal female patients**, which might be associated to gender early socialization as suggested in Dinkel, Infant Behav Dev 2020.

https://gitlab.com/icm-institute/aramislab/leaspy
http://www.aramislab.fr/
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