



HAL
open science

Gender and spinal/bulbar onset interaction on ALS progression

Juliette Ortholand, Igor Koval, Pierre-François Pradat, Sophie Tezenas Du Montcel, Stanley Durrleman

► **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-03782549>

Submitted on 21 Sep 2022

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

GENDER AND SPINAL/BULBAR ONSET INTERACTION ON ALS PROGRESSION

J. ORTHOLAND¹, I. KOVAL¹, P.-F. PRADAT^{2,3}, S. TEZENAS DU MONTCEL¹, S. DURRLEMAN¹

1. Inria, centre of Paris, ARAMIS team, Sorbonne Université, Institut du Cerveau/Paris Brain Institute AP-HP, INSERM, CNRS, University Hospital, Paris, France

2. APHP, Centre de Référence Maladies Neuromusculaires Paris-Est, Institut de Myologie, Hôpital Pitié-Salpêtrière, Sorbonne Université, CNRS, INSERM, Laboratoire d'Imagerie Biomédicale, Paris, France

3. Northern Ireland Centre for Stratified Medicine, Biomedical Sciences Research Institute Ulster University, C-TRIC, Altnagelvin Hospital, Derry/Londonderry, United Kingdom

Background & Objectives

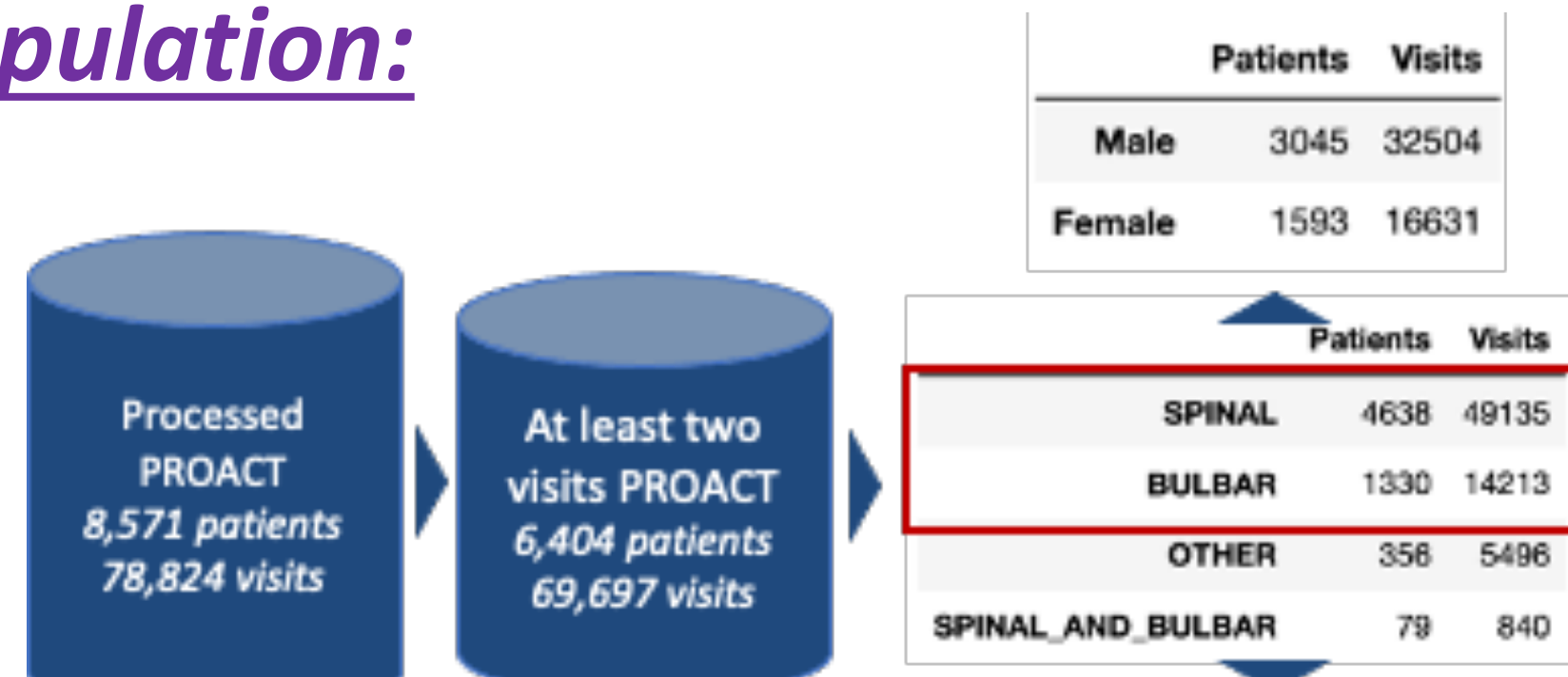
ALS is an adult onset heterogeneous neurodegenerative disease that occurs at a younger age than AD or PD (55, 60, 60 respectively). Descriptive studies show that the mean age and gender/ratio is different according to the phenotype. Compared to spinal onset form, bulbar-onset form, which represent 26 % 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 between **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:



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)

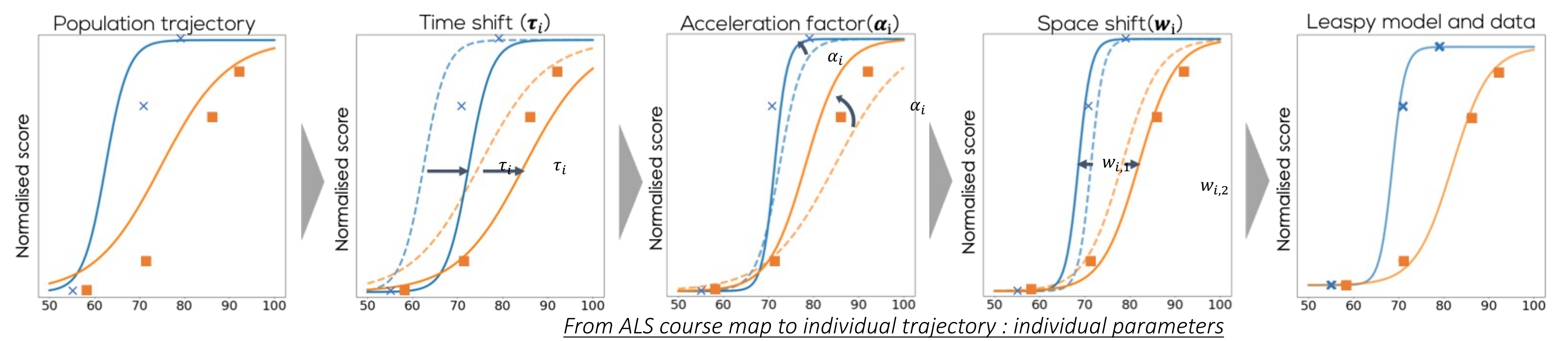
Statistical Methods:

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

Useful for:

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

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



Results

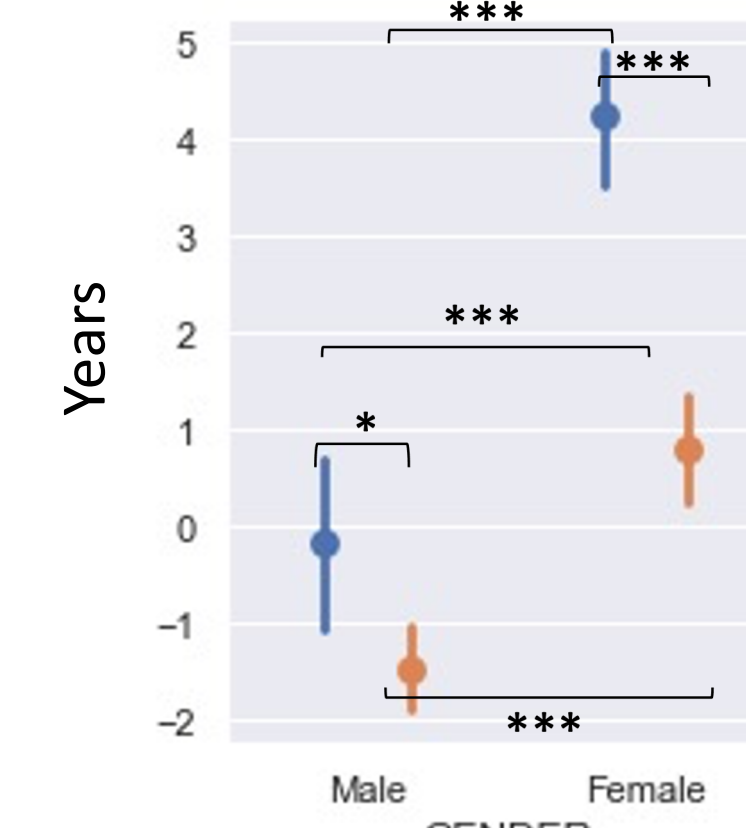
Endpoints	Spinal Male	Bulbar Male	Spinal Female	Bulbar Female	Interaction p-value	Subgroup relations
Age at baseline (y)	53.9 ± 11.8	55.7 ± 11.5	56.8 ± 11.1	60.5 ± 9.6	7.5e-03	SM<(BM,SF)<BF
Follow up (y)	1.0 ± 0.5	0.9 ± 0.4	0.9 ± 0.5	1.0 ± 0.4	1.3e-01	
Number of visits	10.6 ± 5.9	10.6 ± 4.7	10.4 ± 5.5	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	

Legend:

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

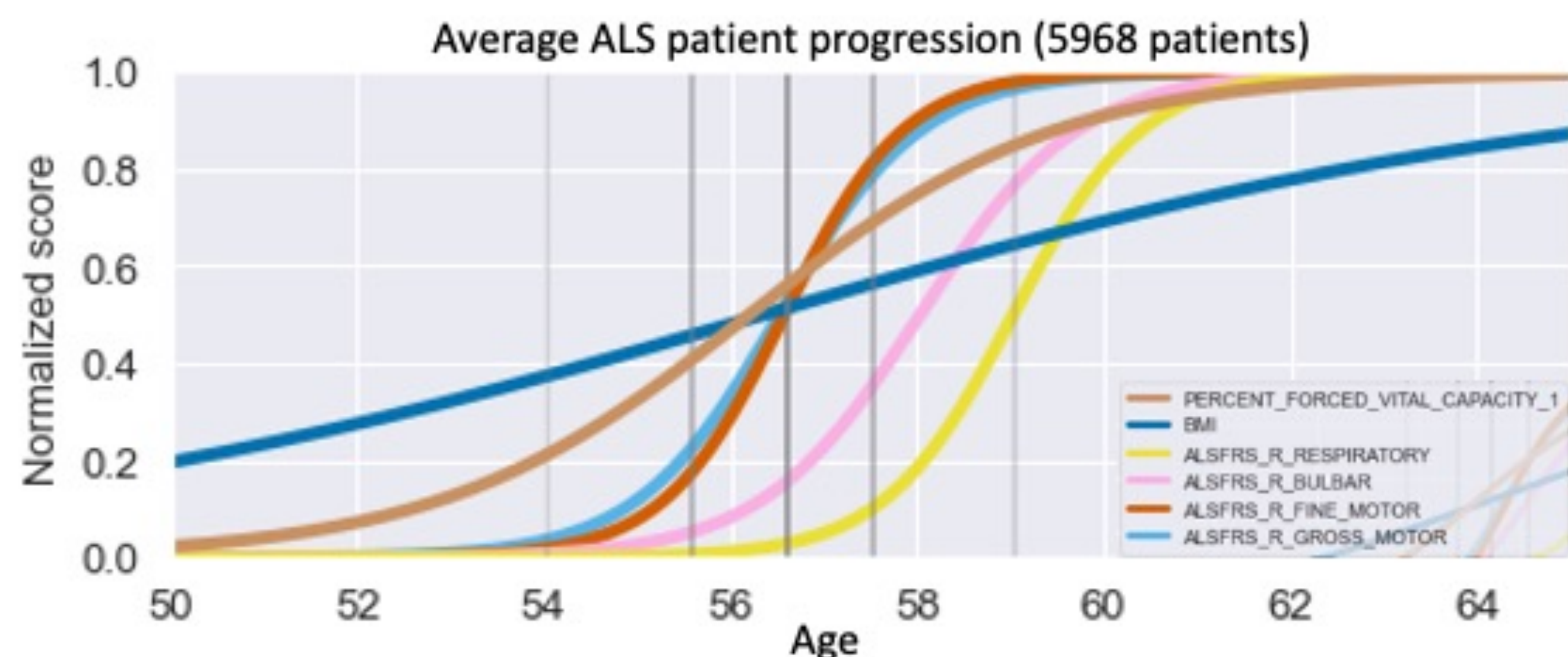
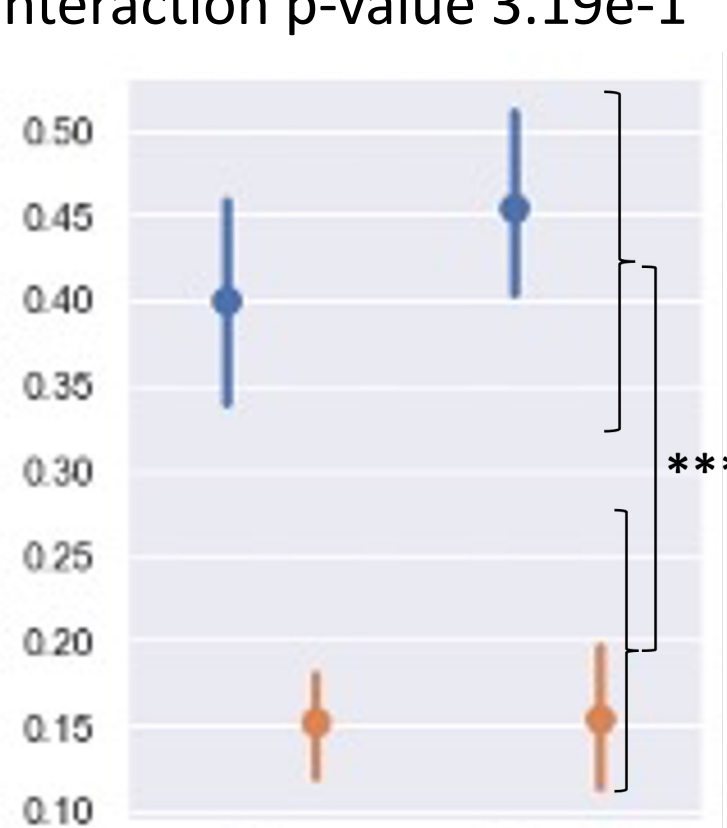
Time-shift distributions

Interaction p-value 2.9e-3

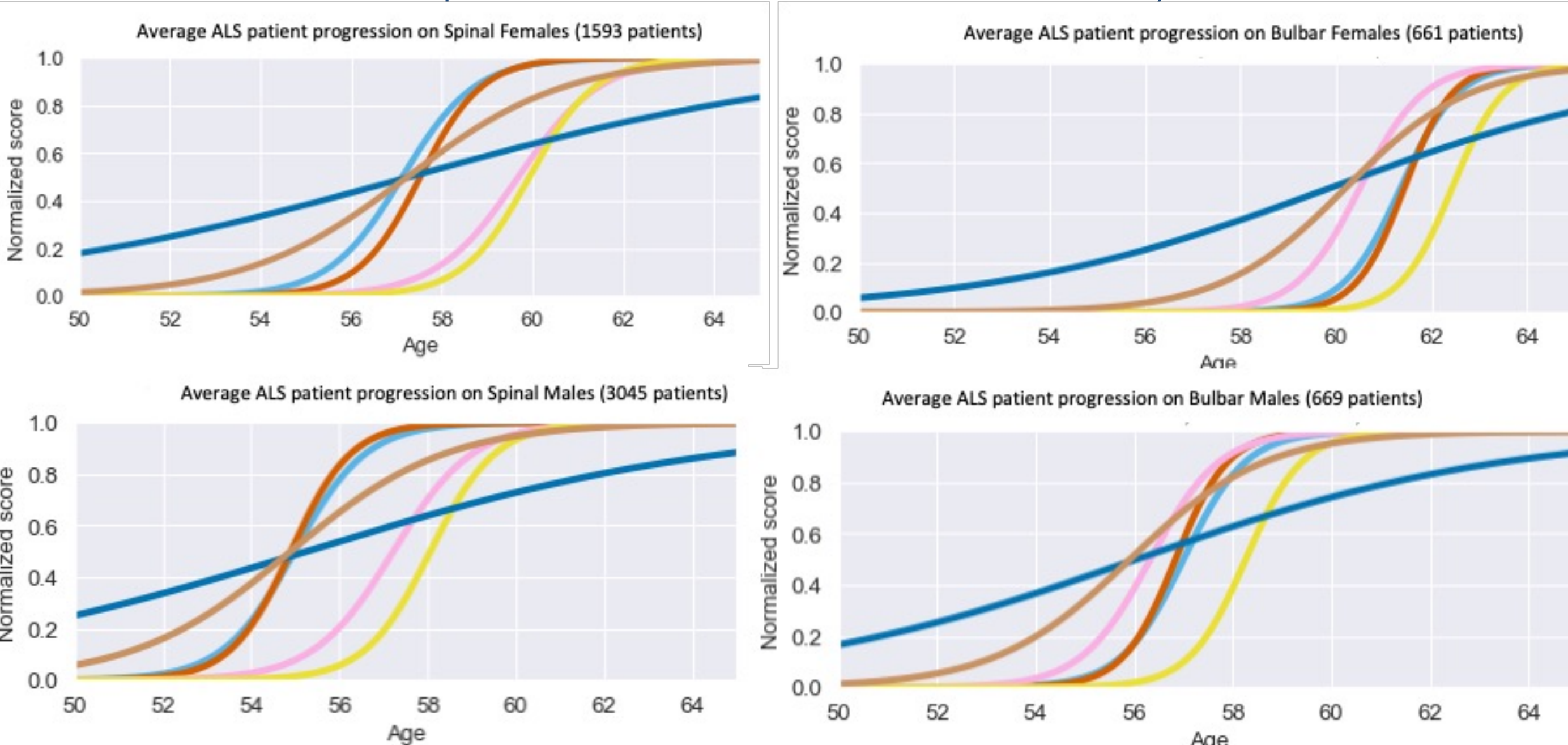


Log acceleration factor distributions

Interaction p-value 3.19e-1

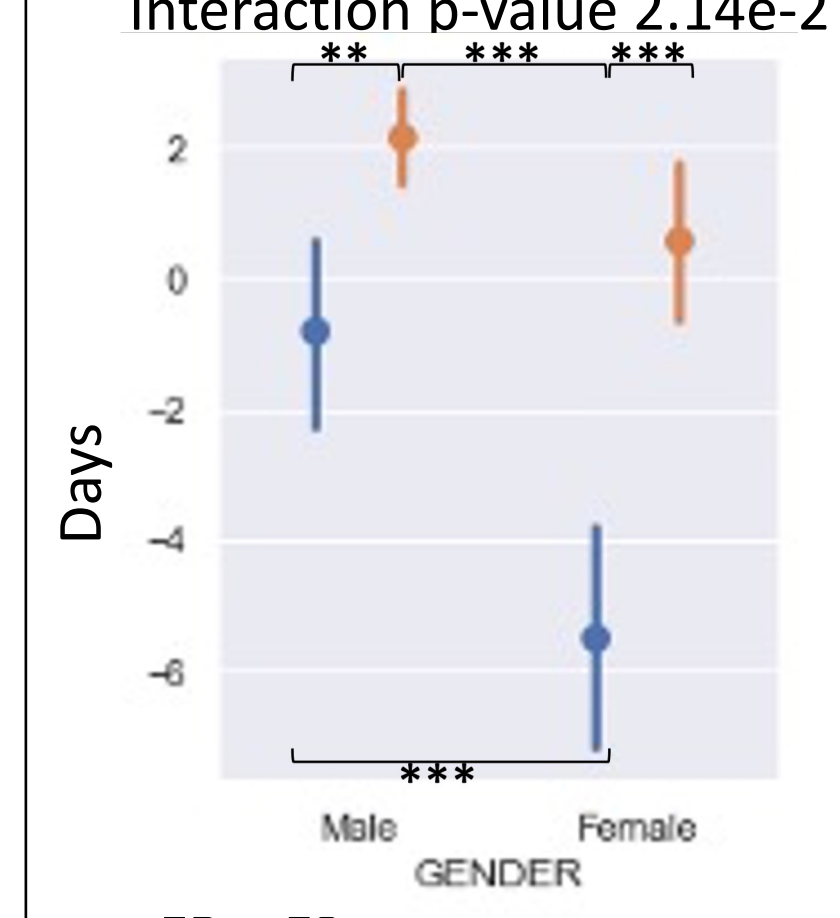


disease progression of the typical patient: Symptoms develop between the age of 55 and 75. Slope at inflection point is in line with Jacobsen et al. Muscle Nerve. 2019



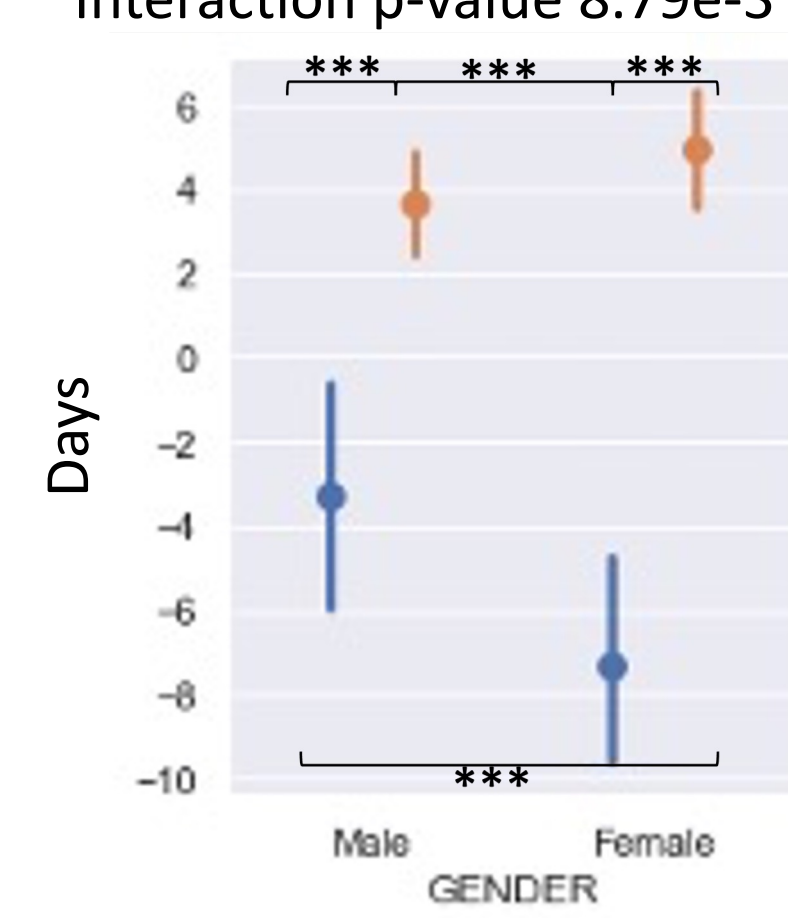
BMI inter-marker spacing distributions

Interaction p-value 2.14e-2



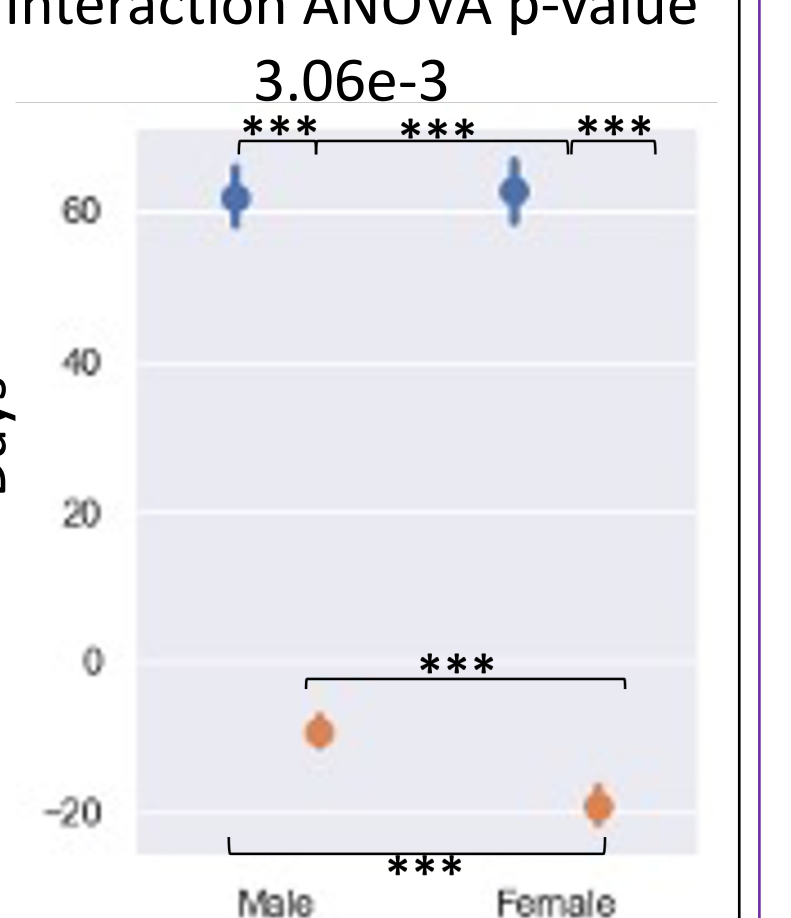
PFVC inter-marker spacing distributions

Interaction p-value 8.79e-3



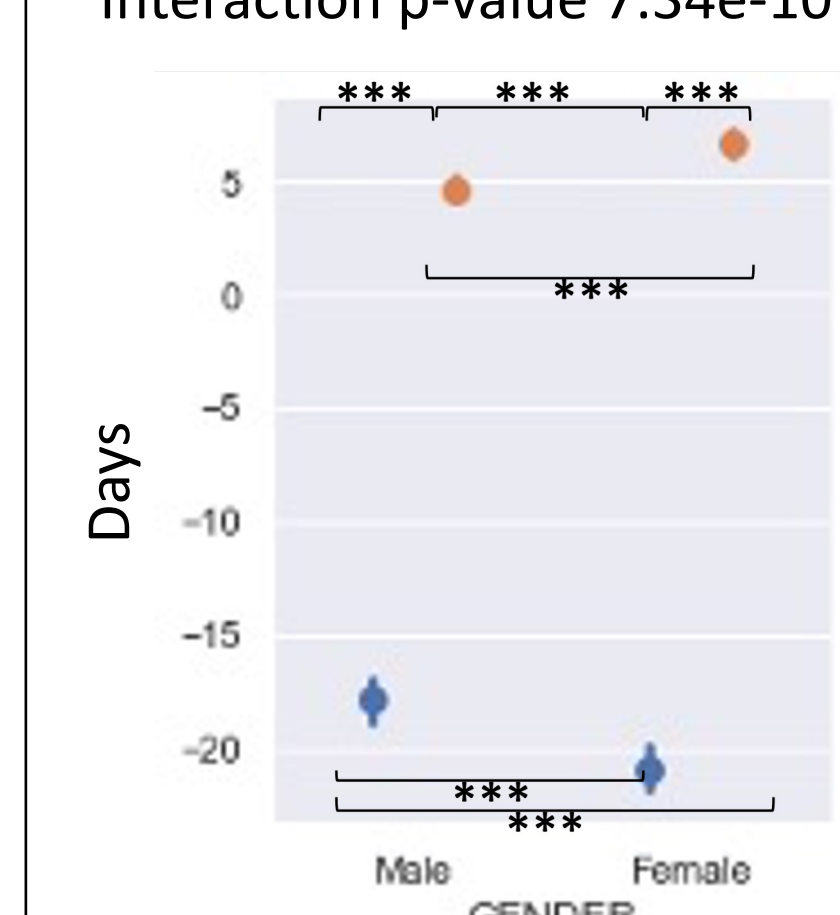
ALSFRS-R gross motor inter-marker spacing distributions

Interaction ANOVA p-value 3.06e-3



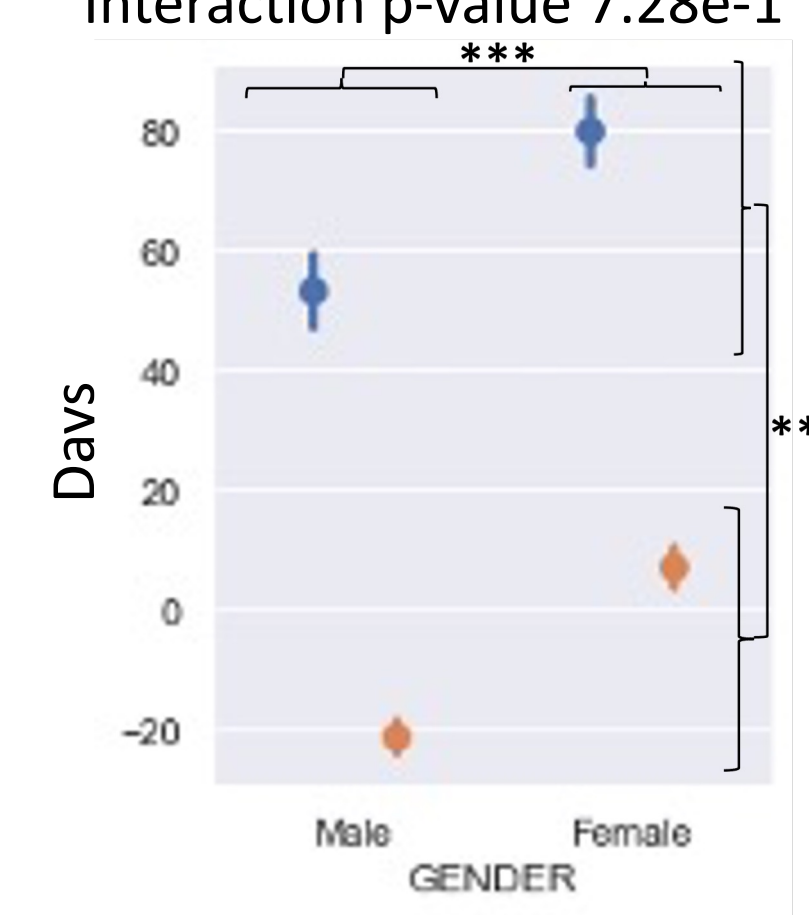
ALSFRS-R bulbar inter-marker spacing distributions

Interaction p-value 7.34e-10



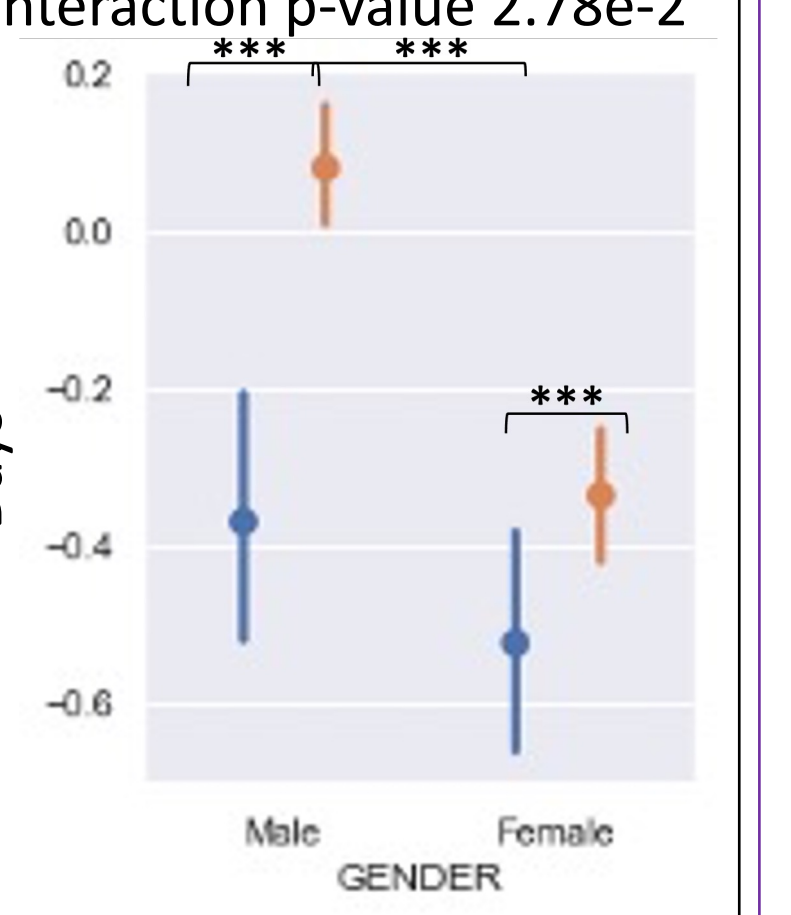
ALSFRS-R Fine motor inter-marker spacing distributions

Interaction p-value 7.28e-1



ALSFRS-R Respiratory inter-marker spacing distributions

Interaction p-value 2.78e-2



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 Trosjii, 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.