

# **Association of Flexibility of Fast Brain Dynamics With Disease Severity in Patients With Amyotrophic Lateral Sclerosis**

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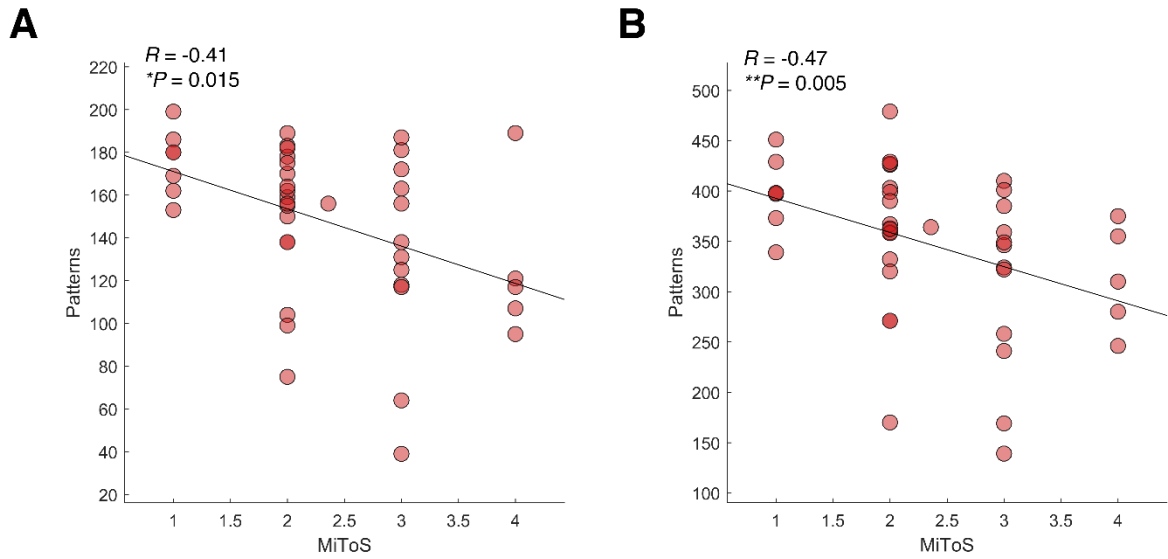
## **Supplementary Table and Figures**

**eTable 1.** Differences in the size of the functional repertoire in the cohort, with different binnings and thresholds, in both the delta and the theta frequency bands.

Parameter	ALS patients (n = 42), mean ( $\pm$ SD)	HC (n = 42), mean ( $\pm$ SD)	P-values
<b><i>Binning (Delta)</i></b>			
No bin	144.93 ( $\pm$ 45.25)	171.43 ( $\pm$ 45.73)	0.01
Bin 2	146.93 ( $\pm$ 37.32)	171.00 ( $\pm$ 45.57)	0.01
Bin 3	146.43 ( $\pm$ 37.13)	170.36 ( $\pm$ 45.39)	0.01
Bin 4	145.90 ( $\pm$ 36.90)	169.43 ( $\pm$ 44.84)	0.01
Bin 5	145.69 ( $\pm$ 36.90)	168.69 ( $\pm$ 44.52)	0.01
<b><i>Binning (Theta)</i></b>			
No bin	338.05 ( $\pm$ 92.82)	397.21 ( $\pm$ 94.91)	0.01
Bin 2	345.19 ( $\pm$ 75.97)	393.86 ( $\pm$ 93.26)	0.01
Bin 3	343.88 ( $\pm$ 75.67)	391.12 ( $\pm$ 92.25)	0.01
Bin 4	343.21 ( $\pm$ 75.59)	388.10 ( $\pm$ 91.25)	0.02
Bin 5	340.93 ( $\pm$ 74.88)	385.07 ( $\pm$ 90.47)	0.02
<b><i>Threshold (Delta)</i></b>			
2.5	188.83 ( $\pm$ 54.27)	218.86 ( $\pm$ 68.41)	0.03
3.5	70.24 ( $\pm$ 22.23)	87.45 ( $\pm$ 32.23)	< 0.01
<b><i>Threshold (Theta)</i></b>			
2.5	452.71 ( $\pm$ 100.44)	505.43 ( $\pm$ 118.31)	0.03
3.5	162.93 ( $\pm$ 51.57)	203.74 ( $\pm$ 79.37)	< 0.01

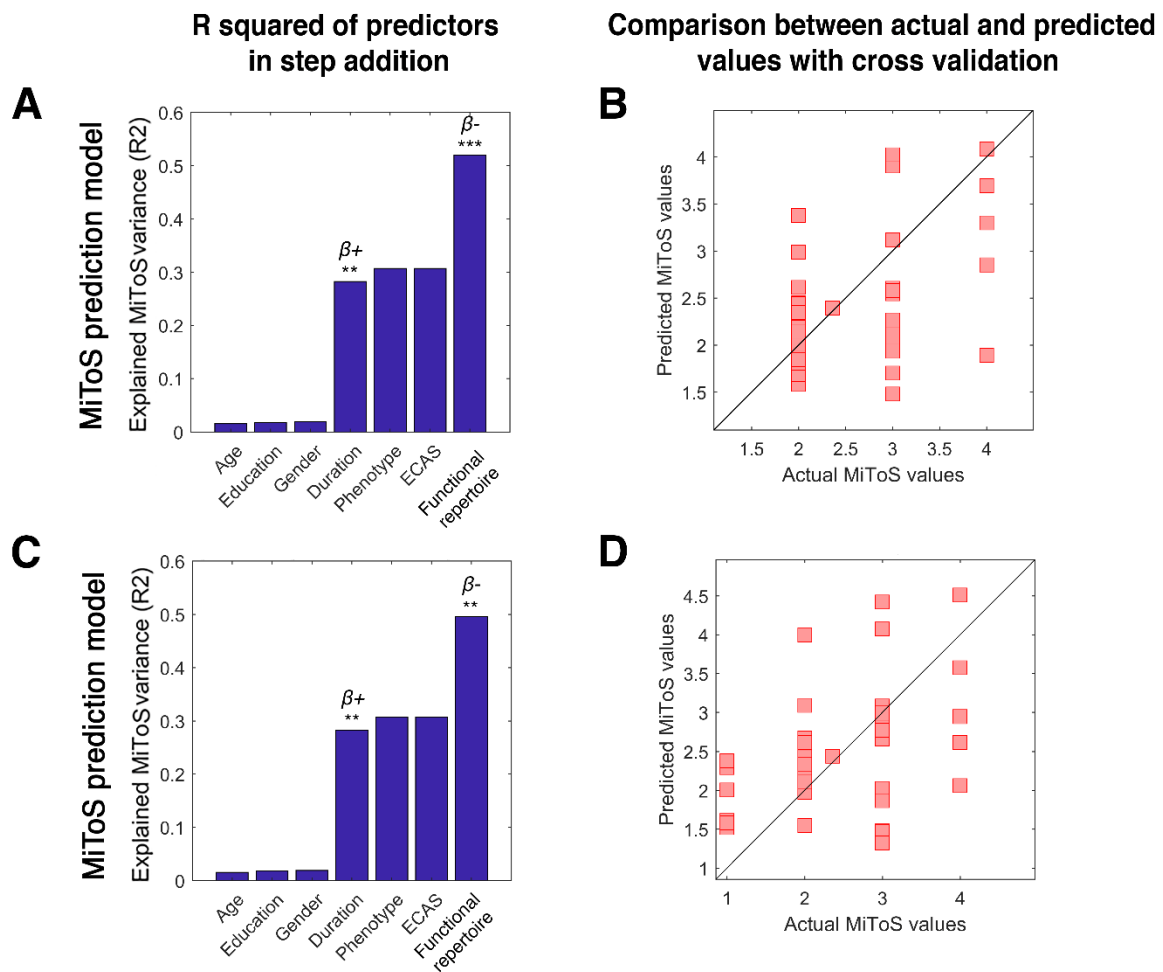
ALS = Amyotrophic Lateral Sclerosis; HC = Healthy Controls; SD = Standard Deviation.

**eFigure 1. The relationship between brain dynamics and clinical features in the ALS group in the delta (A) and the theta (B) frequency bands.** Negative correlation between the size of the functional repertoire and the MiToS clinical staging system in both the delta (A) ( $R = -0.41$ ,  $P = 0.015$ ) and the theta (B) ( $R = -0.47$ ,  $P = 0.005$ ) frequency bands. Spearman's correlation coefficient was used and results were corrected by False Discovery Rate (FDR) correction. Significance P-values:  $*P < 0.05$ ,  $**P < 0.01$ . The figure was made using Matlab 2019a.



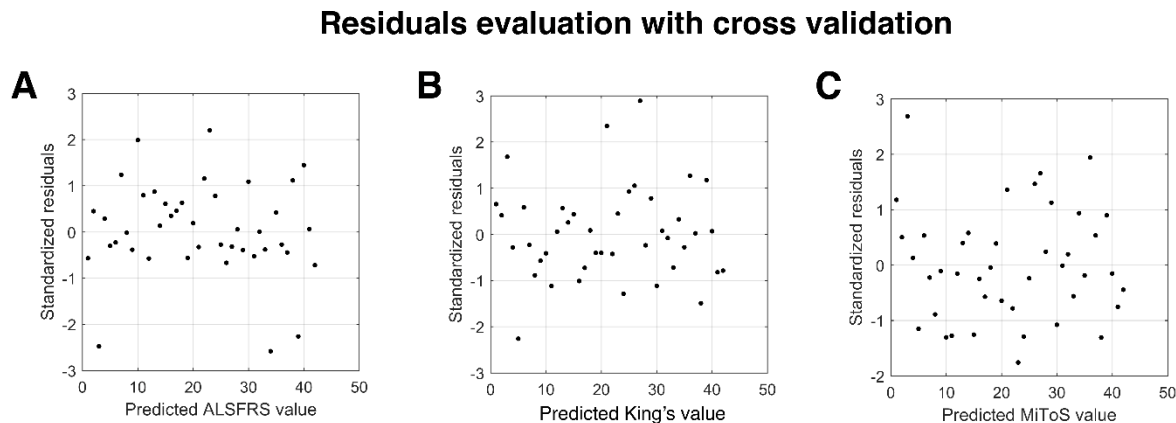
**eFigure 2. Multilinear model with k-fold cross-validation in the delta (A, B) and the theta (C, D) frequency bands.** Using as predictors age, education, gender, disease duration, ALS phenotype, ECAS and size of the functional repertoire, the model predicts the MiToS clinical staging system in both the delta (A, B) (disease duration:  $P < 0.01$ ,  $\beta = 0.01$ ; functional repertoire:  $P < 0.001$ ,  $\beta = -0.01$ ) and the theta (C, D) (disease duration:  $P < 0.01$ ,  $\beta = 0.01$ ; functional repertoire:  $P < 0.01$ ,  $\beta = -0.01$ ) frequency bands.

In the panels A, C, the explained variance of the variable to be predicted as a function of the predictors is illustrated. Significant predictors are indicated by asterisks; positive and negative coefficients are illustrated with  $\beta+$  and  $\beta-$ , respectively; significance  $P$ -values:  $**P < 0.01$ ,  $***P < 0.001$ . In the panels B, D, scatter plots of the comparison between actual and predicted values are reported. The figure was made using Matlab 2019a.



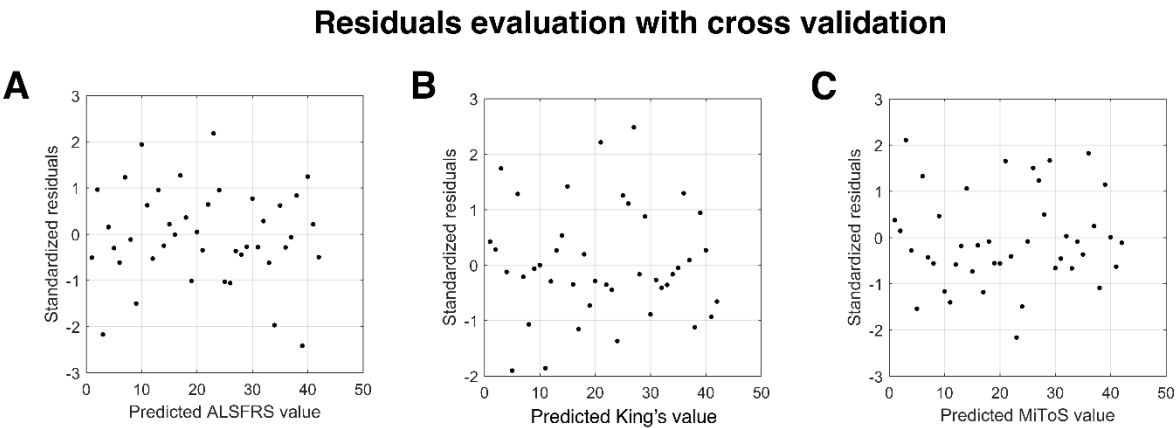
**eFigure 3. Residuals evaluation with k-fold cross-validation in the delta frequency band.**

The standardized residuals (standardization of the difference between observed and predicted values) are shown for the ALSFRS-R (A) and both the King’s (B) and the MiToS (C) clinical staging systems, in the delta frequency band.



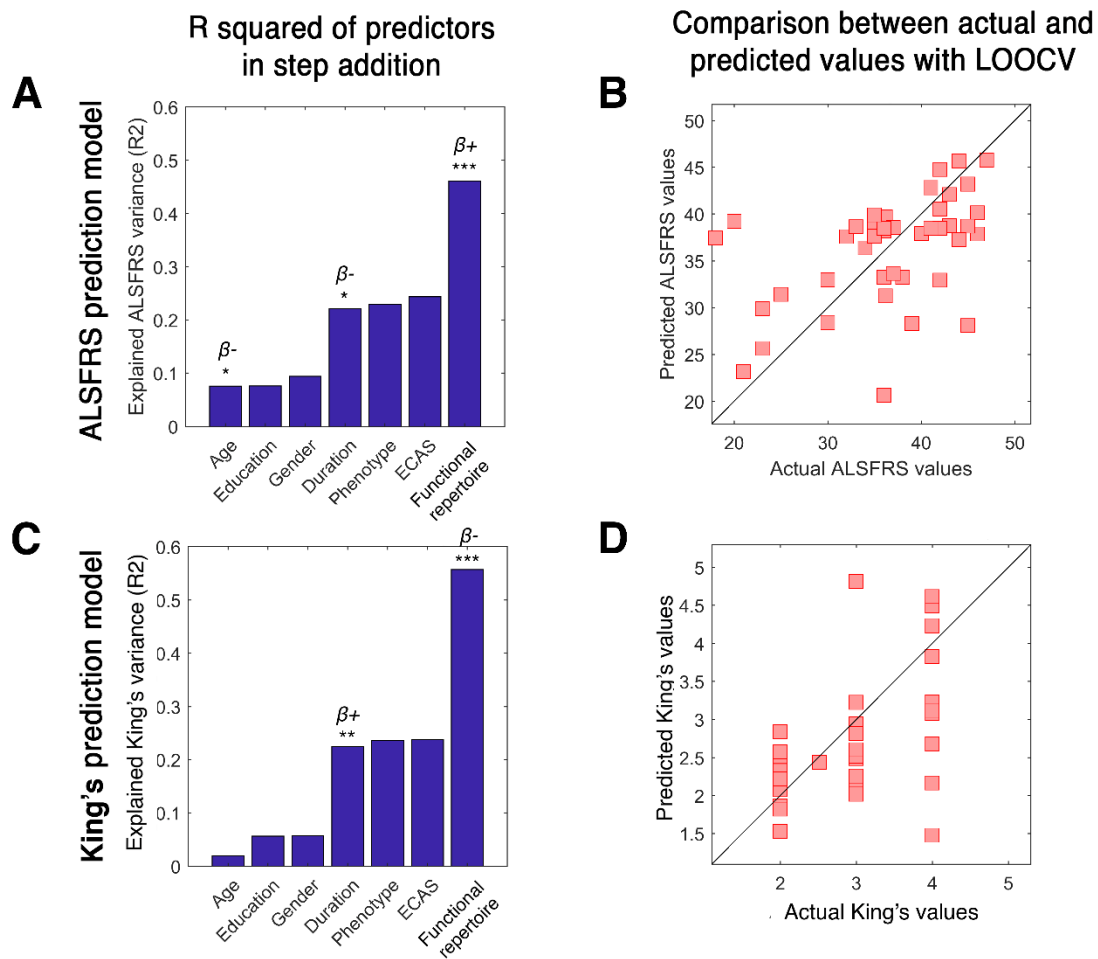
**eFigure 4. Residuals evaluation with k-fold cross-validation in the theta frequency band.**

The standardized residuals (standardization of the difference between observed and predicted values) are shown for the ALSFRS-R (A) and both the King’s (B) and the MiToS (C) clinical staging systems, in the theta frequency band.



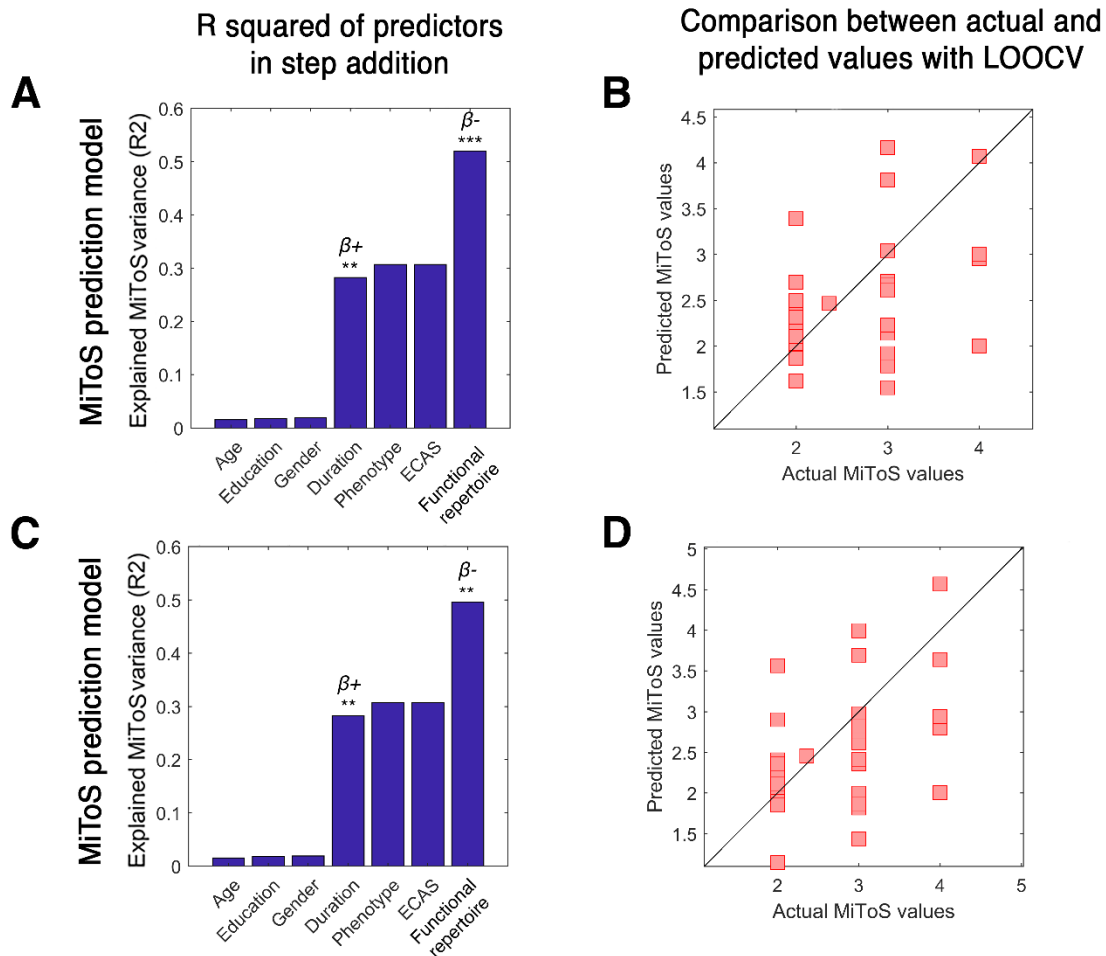
**eFigure 5. Multilinear model with leave-one-out cross-validation (LOOCV) in the delta frequency band.** Using as predictors age, education, gender, disease duration, ALS phenotype, ECAS and size of the functional repertoire, the model predicts: **(A)** the ALSFRS-R (age:  $P = 0.038$ ,  $\beta = -0.23$ ; disease duration:  $P = 0.020$ ,  $\beta = -0.05$ ; functional repertoire:  $P < 0.001$ ,  $\beta = 0.11$ ); **(B)** the King's clinical staging system (disease duration:  $P < 0.01$ ,  $\beta = 0.01$ ; functional repertoire:  $P < 0.001$ ,  $\beta = -0.02$ ).

In the panels **A, C**, the explained variance of the variable to be predicted as a function of the predictors is illustrated. Significant predictors are indicated by asterisks; positive and negative coefficients are illustrated with  $\beta+$  and  $\beta-$ , respectively; significance  $P$ -values:  $*P < 0.05$ ,  $**P < 0.01$ ,  $***P < 0.001$ . In the panels **B, D**, scatter plots of the comparison between actual and predicted values are reported. The figure was made using Matlab 2019a.



**eFigure 6. Multilinear model with leave-one-out cross-validation (LOOCV) in the delta (A, B) and the theta (C, D) frequency bands.** Using as predictors age, education, gender, disease duration, ALS phenotype, ECAS and size of the functional repertoire, the model predicts the MiToS clinical staging system in both the delta (A, B) (disease duration:  $P < 0.01$ ,  $\beta = 0.01$ ; functional repertoire:  $P < 0.001$ ,  $\beta = -0.01$ ) and the theta (C, D) (disease duration:  $P < 0.01$ ,  $\beta = 0.01$ ; functional repertoire:  $P < 0.01$ ,  $\beta = -0.01$ ) frequency bands.

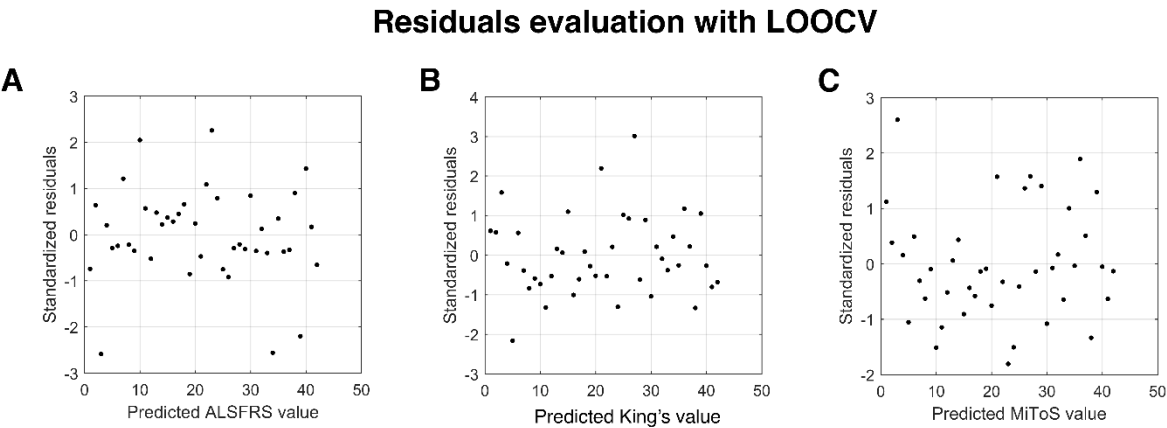
In the panels A, C, the explained variance of the variable to be predicted as a function of the predictors is illustrated. Significant predictors are indicated by asterisks; positive and negative coefficients are illustrated with  $\beta+$  and  $\beta-$ , respectively; significance  $P$ -values:  $**P < 0.01$ ,  $***P < 0.001$ . In the panels B, D, scatter plots of the comparison between actual and predicted values are reported. The figure was made using Matlab 2019a.





**eFigure 7. Residuals evaluation with leave-one-out cross-validation (LOOCV) in the delta frequency band.**

The standardized residuals (standardization of the difference between observed and predicted values) are shown for the ALSFRS-R (A) and both the King’s (B) and the MiToS (C) clinical staging systems, in the delta frequency band.





**eFigure 9. Residuals evaluation with leave-one-out cross-validation (LOOCV) in the theta frequency band.**

The standardized residuals (standardization of the difference between observed and predicted values) are shown for the ALSFRS-R (A) and both the King’s (B) and the MiToS (C) clinical staging systems, in the theta frequency band.

