



# “Complexity of cardiovascular control in amyotrophic lateral sclerosis patients is related to disease duration”

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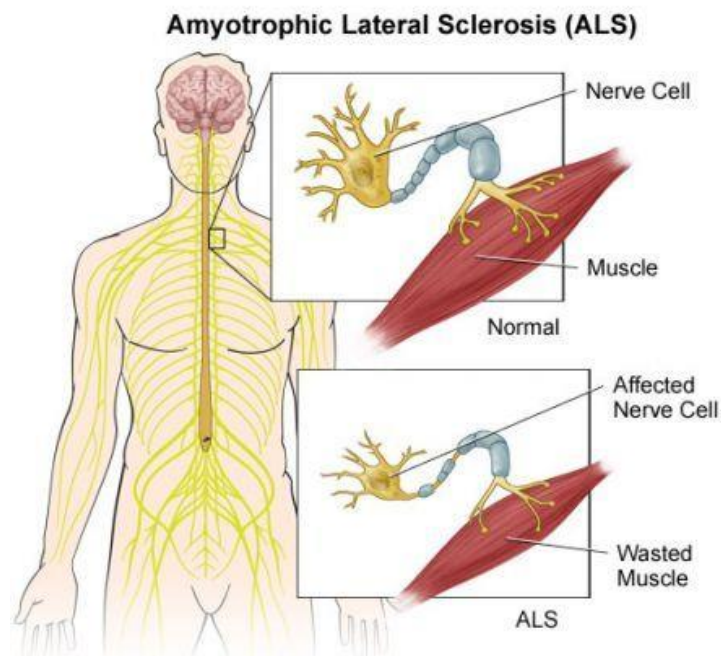
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## Amyotrophic Lateral Sclerosis (ALS):

- ✓ Neurodegenerative disease, compromising upper and lower motorneurons
  - Progressive motor weakness
  - Limitations of voluntary movements
- ✓ Rapid and unpredictable course
- ✓ Main cause of death: respiratory failure





## Multisystem disease:

### **autonomic nervous system involvement**

- ✓ **Reduced baroreceptor sensitivity**  
(Pavlovic et al., Amyotroph Lateral Scler, 2010)
- ✓ **Abnormal sympathetic skin response and sudomotor function**  
(Shindo et al., J Neurol Sci, 1995)
- ✓ **Blunted response to orthostasis**  
(Dalla Vecchia et al, Physiol Meas, 2015)
- ✓ **Patients' groups with different autonomic profiles**  
(De Maria et al., Proceeding EMBC, 2015)



## ANS impairment in ALS patients may reduce quality and expectancy of life of patients:

- Sudden cardiac arrest due to sympathetic hyperactivity  
(Shimizu et al., J Neurol Sci, 1994)
- Sudden death  
(Pinto et al., 2012)
- Hypertensive crisis  
(Hecht et al., J Neurol Sci, 2003)



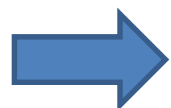
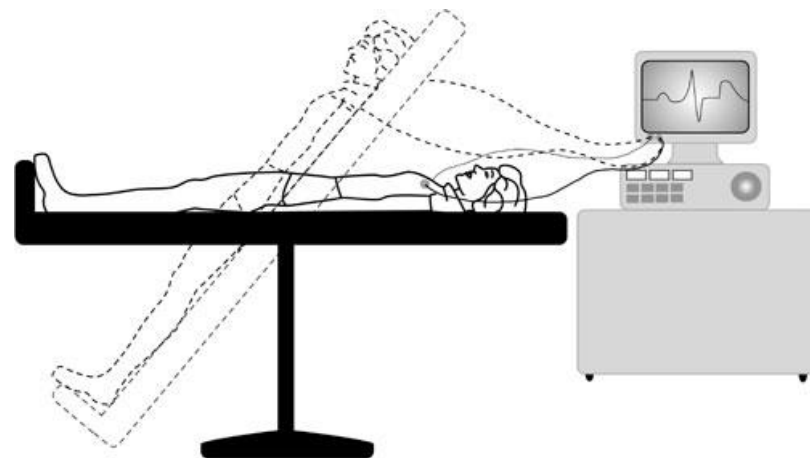
- To correlate power spectral and complexity indices derived from heart period (HP) and systolic arterial pressure (SAP) series with ALS patients' clinical markers describing the disease and its rate of progression

**Population:** 52 ALS patients (28 m, 24 f; age  $61.79 \pm 11.47$ )

## Experimental protocol:

➤ 10 minute REST

➤ 10 minute head up TILT TEST at  $75^\circ$



### Signals:

- Electrocardiographic signal (ECG)
- Arterial blood pressure signal (AP)  
Pletismographic device

$f_s$ : 250 Hz

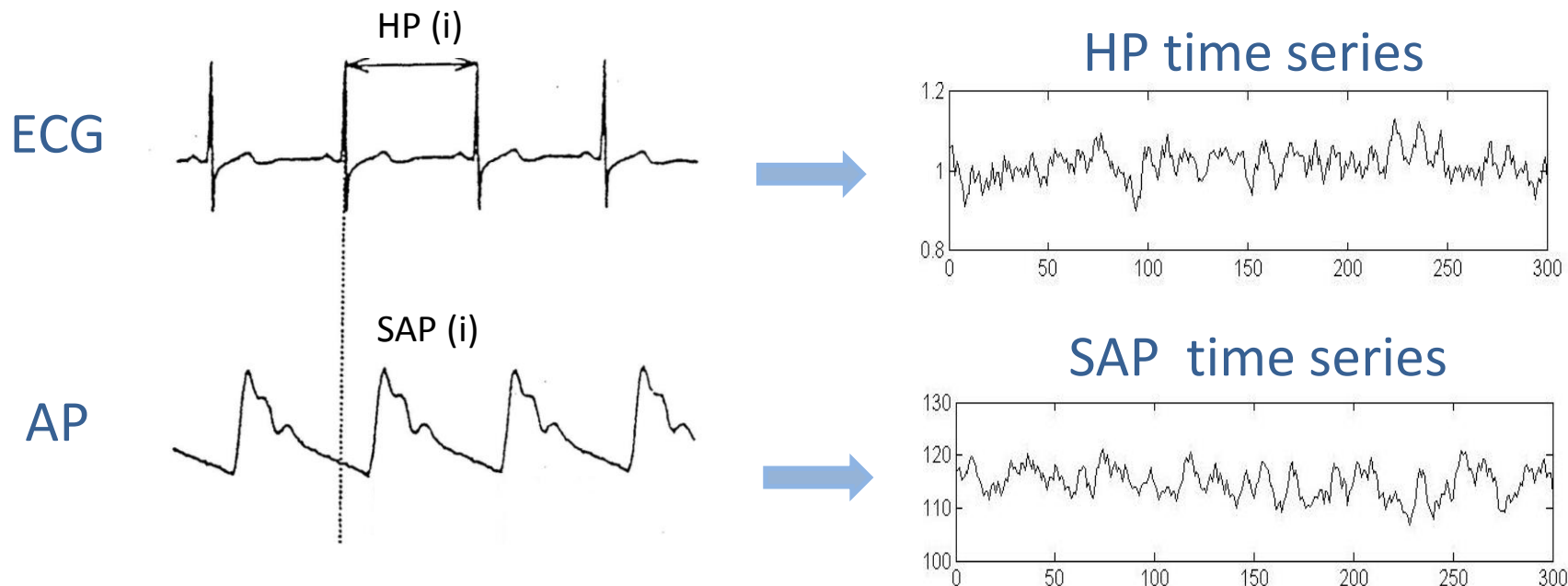


## Clinical evaluation of ALS patients:

- **Disease duration (DD):** time from the beginning of the symptoms and the day of evaluation
- **Functional status:** Revised ALS Functional Rating Scale (ALSFRS-R), ranging from 48 (normal) to 0 (vegetative)
- **Bulbar involvement:** ALSFRS-R bulbar subscore (ALSFRS-R BS), ranging from 12 (normal) to 0 (vegetative)
- **Rate of disease progression (RDP):** difference between two ALSFRS-R scores at two different evaluation times divided by the months between the two evaluations



## Beat-to-beat time series extraction:



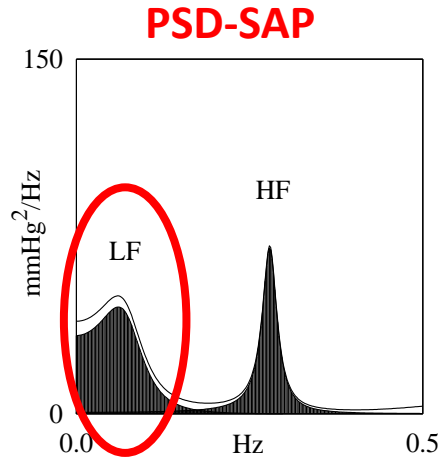
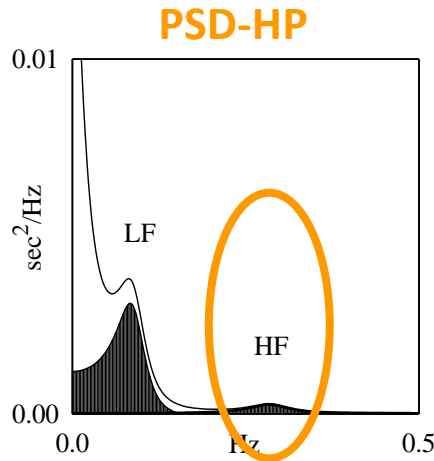
**Short term analysis:** 256 consecutive and stationary beats

- Time domain indices:**
- Mean of HP and SAP series,  $\mu_{HP}$  and  $\mu_{SAP}$
  - Variance of HP and SAP series,  $\sigma^2_{HP}$  and  $\sigma^2_{SAP}$



# Methods: power spectral analysis

**Parametric power spectral analysis on HP and SAP series:**  
autoregressive model, order according to Akaike information criterion



Akselrod S et al, Science, 213:220-223, 1981  
Pagani M et al, Circ Res.;59(2):178-93, 1986

- $HF_{a,HP}$ : absolute power of HP series in high frequency band (HF: 0.15-0.5Hz) → markers of **vagal modulation directed to the sinus node**
- $HF_{nu,HP} = \frac{HF_{a,HP}}{\sigma_{HP}^2 - VLF_{a,HP}} \cdot 100$  Very low frequency band (VLF < 0.04 Hz)
- $LF_{a,SAP}$ : absolute power in LF (LF: 0.04-0.15Hz) of SAP series → index of **sympathetic modulation directed to the vessels**



## Complexity analysis of HP and SAP series:

- Highest complexity: null predictability of the series
- Lowest complexity: maximum predictability of the series

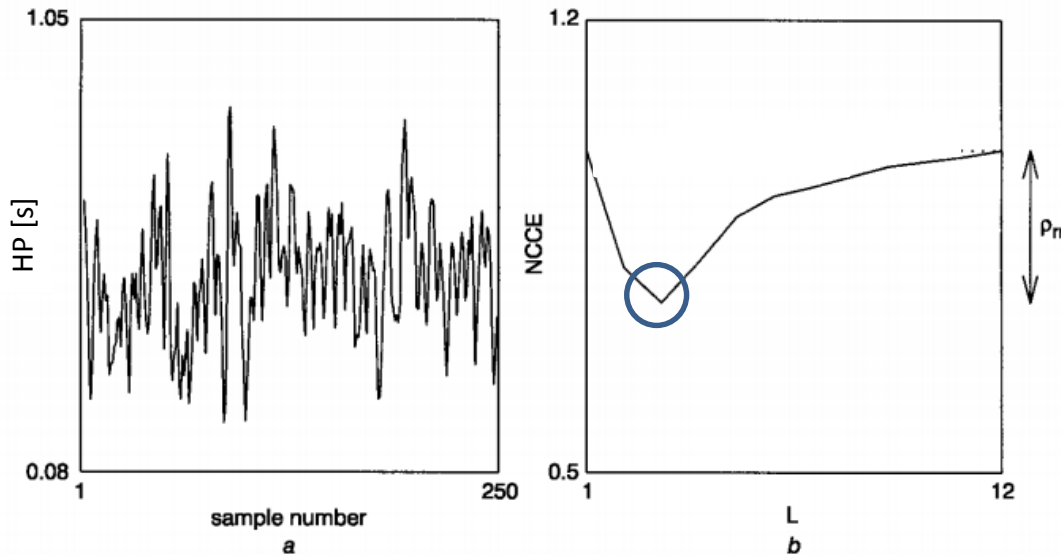
## Corrected Conditional Entropy

(Porta A et al., Biol Cybern, 1998)



amount of information carried by the most recent sample of the series when L-1 past samples are given

# Methods: complexity analysis



CCE ranges from 0 to the Shannon Entropy (maximum amount of information carried by the series, without conditioning of past samples)

- Complexity index of HP and SAP series:  $CI_{HP}$  and  $CI_{SAP}$   
Minimum of the CCE with respect to past conditioning samples  $L$
- Normalized Complexity Index of HP and SAP series:  $NCI_{HP}$  and  $NCI_{SAP}$

$$NCI_{HP} = \frac{CI_{HP}}{SE_{HP}}$$

$$NCI_{SAP} = \frac{CI_{SAP}}{SE_{SAP}}$$



## Statistical analysis:

- Linear correlation analysis: association between ALS clinical features and the indices extracted from HP and SAP series; Pearson correlation coefficient was computed;  $p < 0.05$  significant

# Results: power spectral analysis

Correlation between power spectral indices at REST and patients' clinical features

Index	REST							
	ALSFRS-R		RDP		DD		ALSFRS-R BS	
	r	p	r	p	r	p	r	p
$\mu_{HP}$ [ms]	0.194	0.168	-0.16	0.273	0.092	0.517	0.229	0.102
$\sigma^2_{HP}$ [ms <sup>2</sup> ]	0.036	0.802	0.144	0.307	0.004	0.979	0.146	0.303
$HF_{a,HP}$ [ms <sup>2</sup> ]	0.077	0.588	0.071	0.618	-0.01	0.94	0.219	0.12
$HF_{nu,HP}$ [nu]	-0.02	0.884	-0.15	0.307	0.05	0.723	0.042	0.769
$\mu_{SAP}$ [mmHg]	0.099	0.487	-0.11	0.431	0.157	0.267	-0.06	0.67
$\sigma^2_{SAP}$ [mmHg <sup>2</sup> ]	-0.02	0.9	-0.11	0.447	0.149	0.29	0.126	0.372
$LF_{a,SAP}$ [mmHg <sup>2</sup> ]	-0.07	0.682	0.315	0.023	0.027	0.851	-0.02	0.865

- RDP positively correlated with  $LF_{a,SAP}$  at REST

The higher the RDP, the higher the sympathetic modulation directed to the vessels

# Results: power spectral analysis

Correlation between power spectral indices during TILT and patients' clinical features

INDEX	TILT							
	ALSFRS-R		RDP		DD		ALSFRS-R BS	
	r	p	r	p	r	p	r	p
$\mu_{HP}$ [ms]	0.144	0.308	-0.257	0.066	0.155	0.273	0.174	0.216
$\sigma^2_{HP}$ [ms <sup>2</sup> ]	0.107	0.451	0.028	0.846	0.079	0.58	0.131	0.354
$HF_{a,HP}$ [ms <sup>2</sup> ]	0.069	0.626	-0.066	0.64	0.11	0.438	0.162	0.25
$HF_{nu,HP}$ [nu]	0.046	0.748	-0.291	0.036	0.137	0.332	0.034	0.811
$\mu_{SAP}$ [mmHg]	0.157	0.265	0.123	0.383	-0.003	0.982	0.098	0.49
$\sigma^2_{SAP}$ [mmHg <sup>2</sup> ]	0.119	0.4	-0.001	0.993	0.093	0.514	0.119	0.402
$LF_{a,SAP}$ [mmHg <sup>2</sup> ]	0.174	0.216	0.079	0.578	-0.069	0.626	0.158	0.263

- RDP negatively correlated with  $HF_{nu,HP}$  during TILT

Higher the RDP, lower the vagal cardiac modulation of ALS patients

# Results: complexity analysis

Correlation between complexity indices at REST and patients' clinical features

Index	REST							
	ALSFRS-R		RDP		DD		ALSFRS-R BS	
	r	p	r	p	r	p	r	p
CI <sub>HP</sub>	0.104	0.466	-0.0822	0.566	0.0539	0.707	0.11	0.444
NCI <sub>HP</sub>	0.104	0.468	0.0296	0.837	-0.0861	0.548	0.0587	0.682
CI <sub>SAP</sub>	-0.0802	0.576	0.166	0.243	-0.25	0.0768	-0.164	0.25
NCI <sub>SAP</sub>	-0.0202	0.888	0.177	0.213	-0.291	0.0383	-0.102	0.474

- NCI<sub>SAP</sub> negatively correlated to DD at REST

The higher the DD, the lower the complexity, the higher the sympathetic modulation directed to the vessels

## Correlation between complexity indices during TILT and patients' clinical features

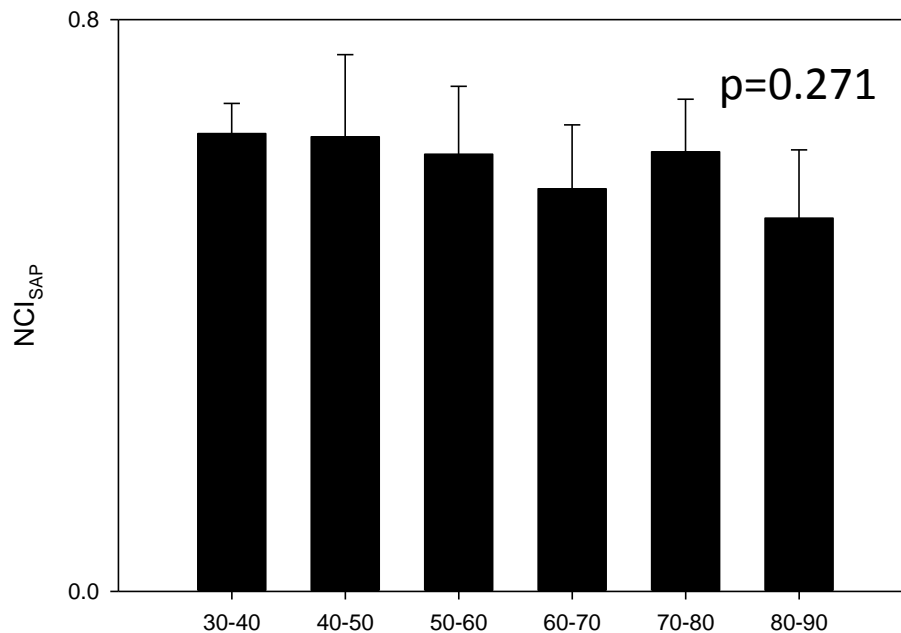
TILT								
Index	ALSFRS-R		RDP		DD		ALSFRS-R BS	
	r	p	r	p	r	p	r	p
$CI_{HP}$	0.0931	0.516	-0.171	0.23	0.085	0.553	0.163	0.253
$NCI_{HP}$	0.0785	0.584	-0.208	0.142	0.0865	0.546	0.139	0.33
$CI_{SAP}$	-0.0289	0.840	0.178	0.212	-0.274	0.0518	-0.126	0.38
$NCI_{SAP}$	0.0305	0.832	0.116	0.416	-0.206	0.147	-0.116	0.417



## Is observed reduction of $NCI_{SAP}$ with DD due to the effect of age?

Catai et al., Entropy, 2014

No difference between 30-40 and 80-90 groups



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The observed correlation is due to the effect of the disease on the cardiovascular control

# Conclusion: complexity analysis

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- Autonomic nervous system indexes in ALS are associated with the rate of disease progression suggesting that lower vagal and higher sympathetic modulations are linked to faster progression rates
- Complexity indexes of the vascular control are associated with the disease duration suggesting that lower complexity of vascular control is linked to longer disease durations regardless of the patients' age

# Conclusion: complexity analysis

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- Complexity indexes provided different information compared to spectral markers because they are associated to different clinical markers
- Complexity indexes provide a quantification of the progressive isolation of physiological systems and reduced level of integration among them. While spectral indexes could be utilized to distinguish groups characterized by different disease severities

# Thank you for your attention!

