A mixed-effects model with time reparametrization for longitudinal univariate manifold-valued data

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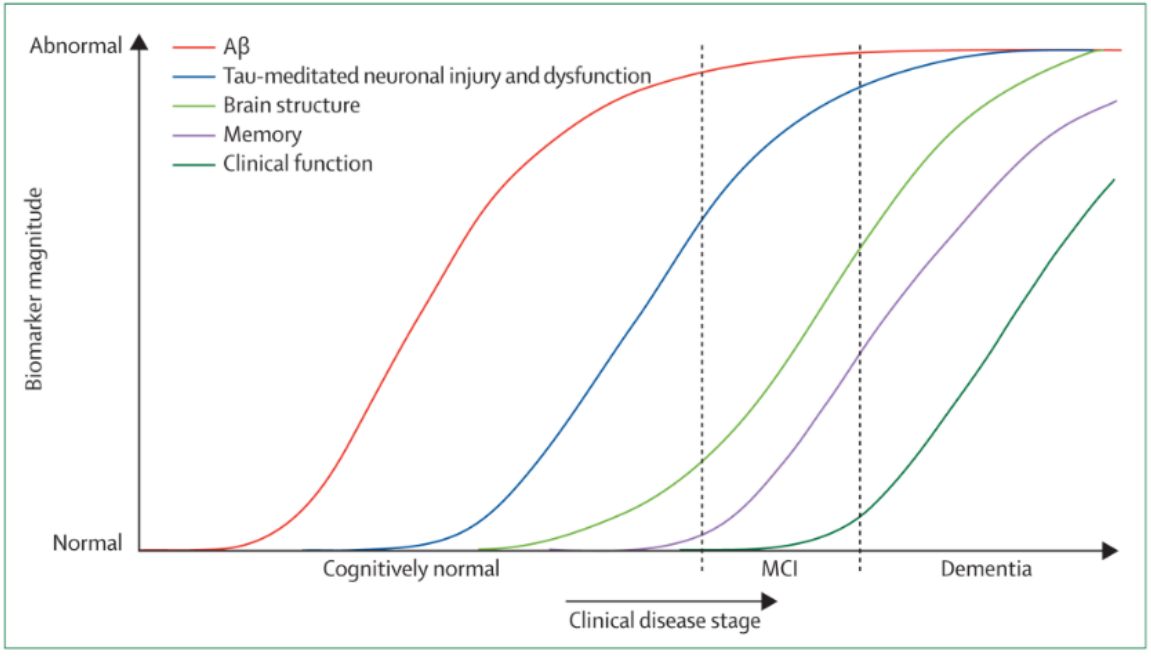
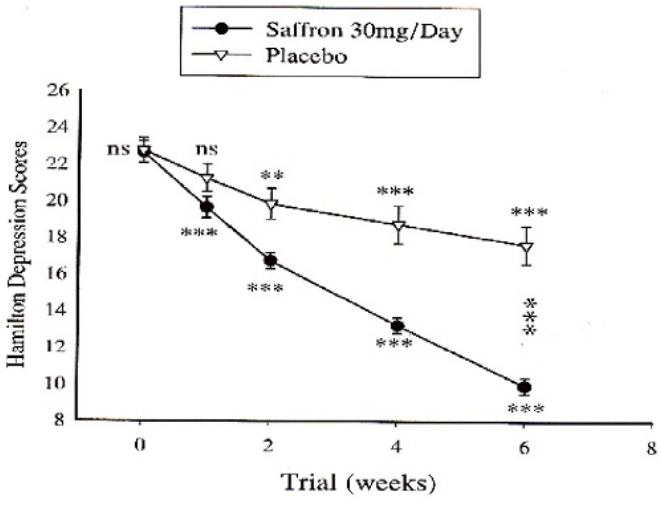
Overview - Disease Progression Models

Aims:

- understand the progression of the disease
- accurately stage subjects in clinical trials
- prognosis





Timeline of disease progression models

Model	Trajectory shape	Subject staging	Main limitation
Comparison of symptomatic stages	not modelled at all	very coarse	biased categories
Event-based Model	step-functions	discreete stages	no notion of time
Differential Equation Models	non-parametric	both onset and speed	trajectories not aligned
Disease Progression Score	sigmoids	both onset and speed	sigmoidal assumption
Self-modelling regression	non-parametric	both onset and speed	-
Manifold Model	sigmoids	both onset and speed	sigmoids have the same shape

What is a manifold

- An N-dimensional space that generalises the Euclidean space
- Equipped with an inner product and distance metric

The model

- The model is a non-linear mixed effects model placed in a Riemannian manifold setting
- Each subject i has an associated:
  - time shift τ_i
  - progression speed α_i
- Fixed effects are:
  - time shift t_0
  - progression speed v_0
  - observation point on the manifold t_0
- The biomarker trajectory γ_{p_0,t_0,v_0}

$$y_{i,j} = \gamma_{p_0,t_0,v_0}(\alpha_i v_0(t_{i,j} - t_0 - \tau_i)) + \epsilon_{i,j} \tag{1}$$

where

$$\begin{cases} \alpha_i = exp(\nu_i) \\ \nu_i \sim \bigotimes_{i=1}^{p} N(0, \sigma_\nu^2) \\ \tau_i \sim \bigotimes_{i=1}^{p} N(0, \sigma_\tau^2) \\ \epsilon_{i,j} \sim \bigotimes_{i,j} N(0, \sigma^2) \end{cases} \tag{2}$$

Results - time shifts

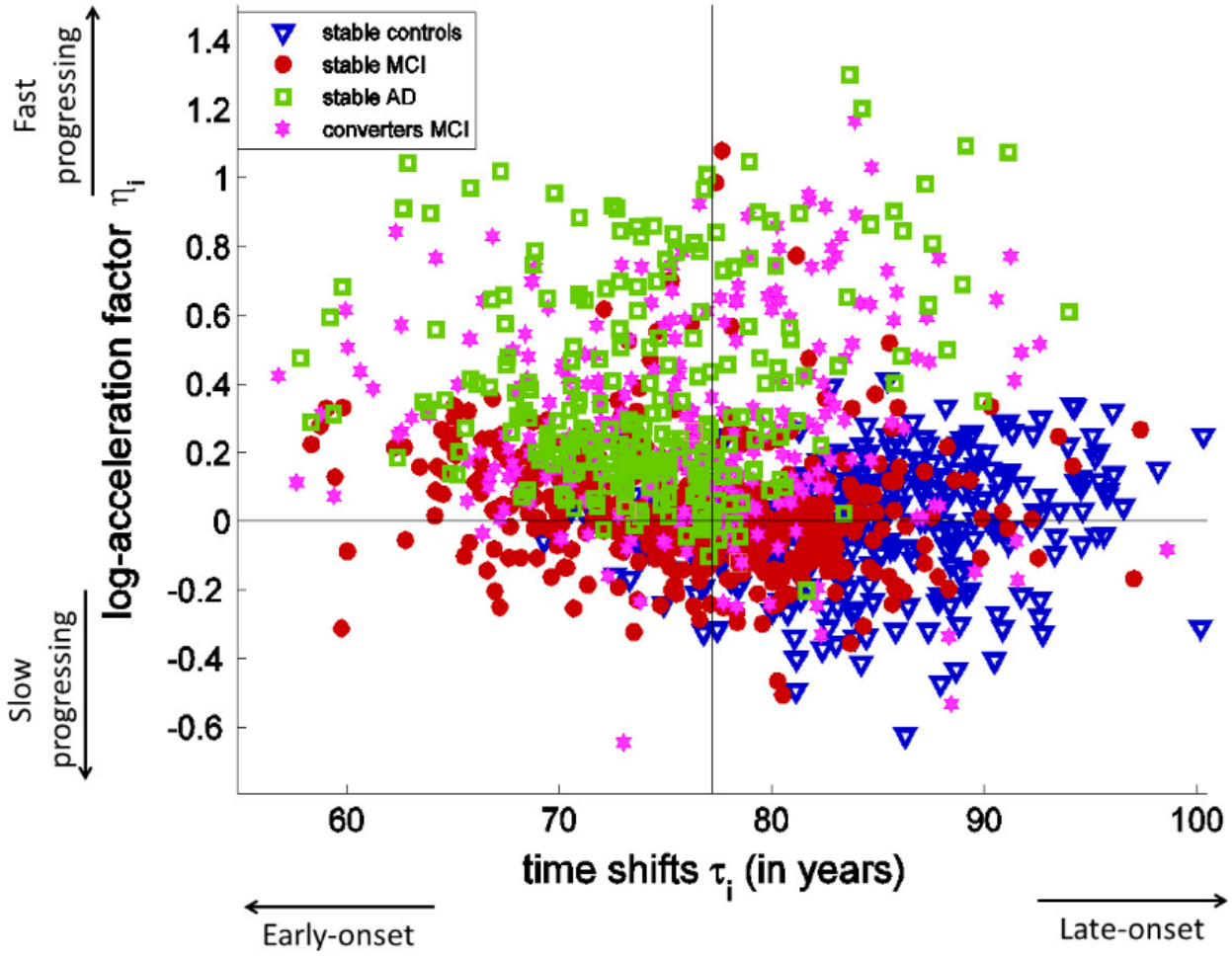


Fig. 1. Log-acceleration factors η_i plotted against the time shifts τ_i for the 1391 individuals with ADAS-Cog measurements. An horizontal line was plotted at the level $\eta_i = 0$ (no change in speed with respect to the average trajectory) and at $\tau_i = t_0 = 77.17$ (the estimated reference time t_0).

Results - AD vs stable controls

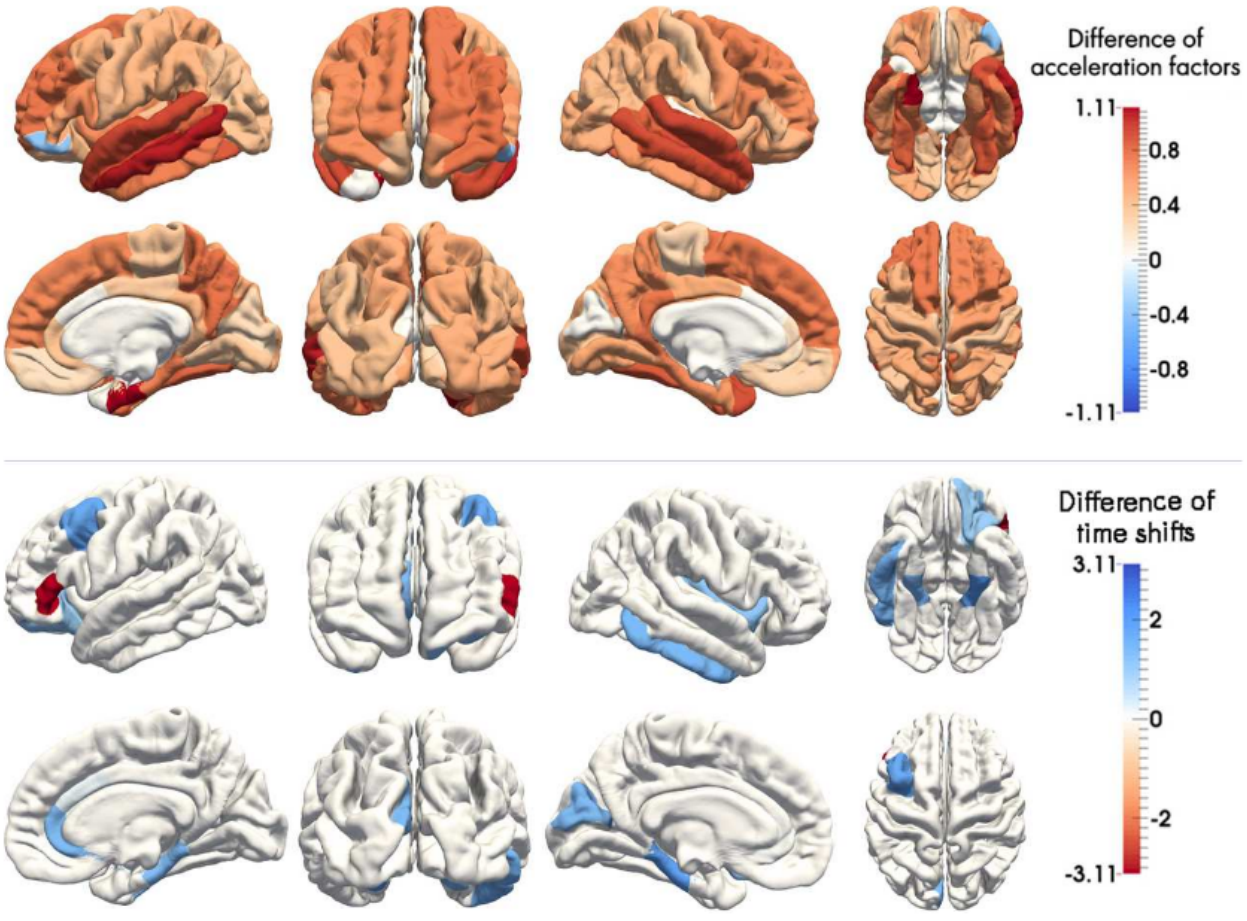


Fig. 2. At the top (respectively bottom) : the difference in averaged acceleration factors (respectively time shifts) between AD patients and stable controls is displayed on the cortex. Acceleration factors (and respectively time shifts) were averaged per regions of interest. Only regions where the difference was statistically significant ($p < 0.05$, corrected for multiple comparisons) were colored.

Results - MCI converters vs MCI stable

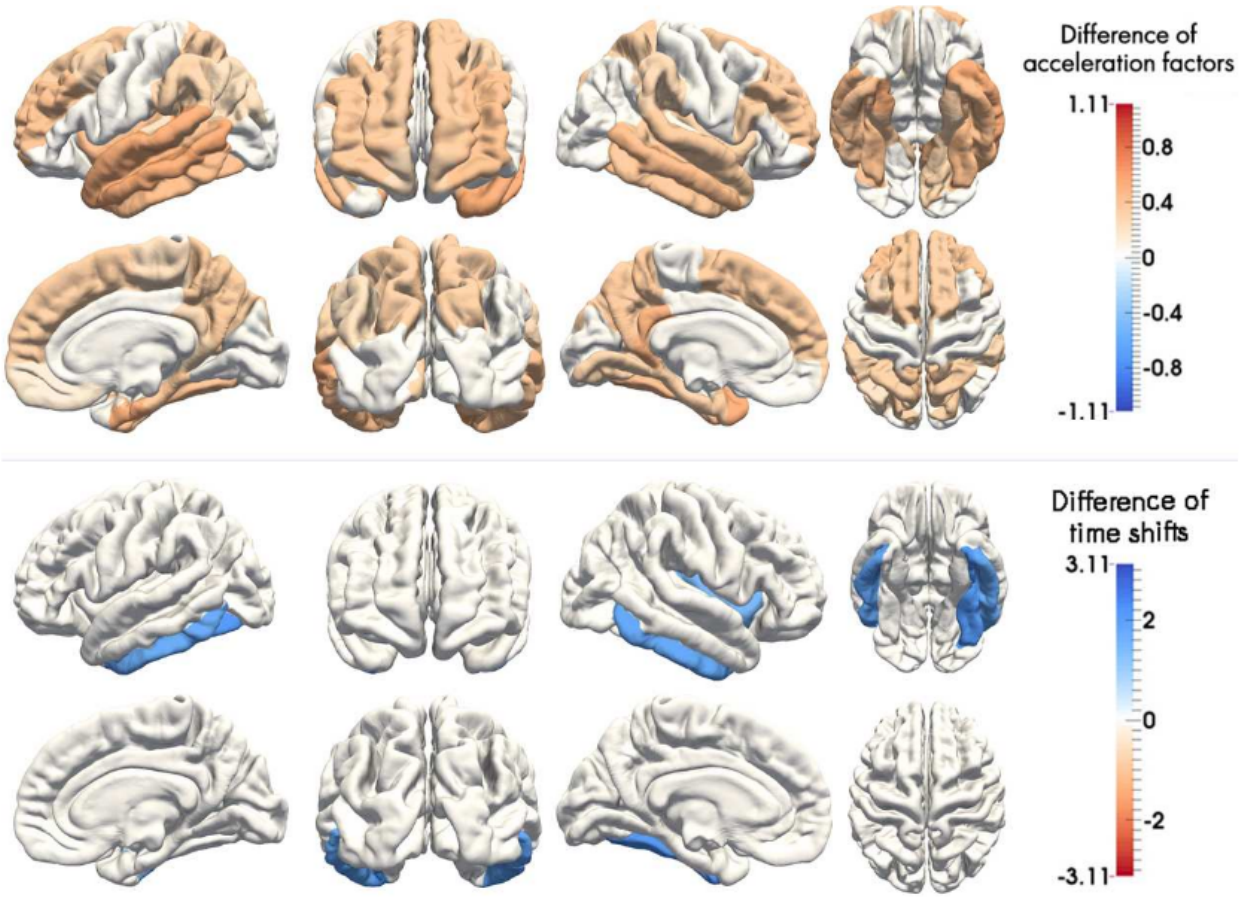


Fig. 3. At the top (respectively bottom) : the difference in averaged acceleration factors (respectively time shifts) between converters MCI and stable MCI is displayed on the cortex. Acceleration factors (and respectively time shifts) were averaged per regions of interest. Only regions where the difference was statistically significant ($p < 0.05$, corrected for multiple comparisons) were colored.