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Neuroimagerie, neurologie et modèles numériques pour la maladie d'Alzheimer

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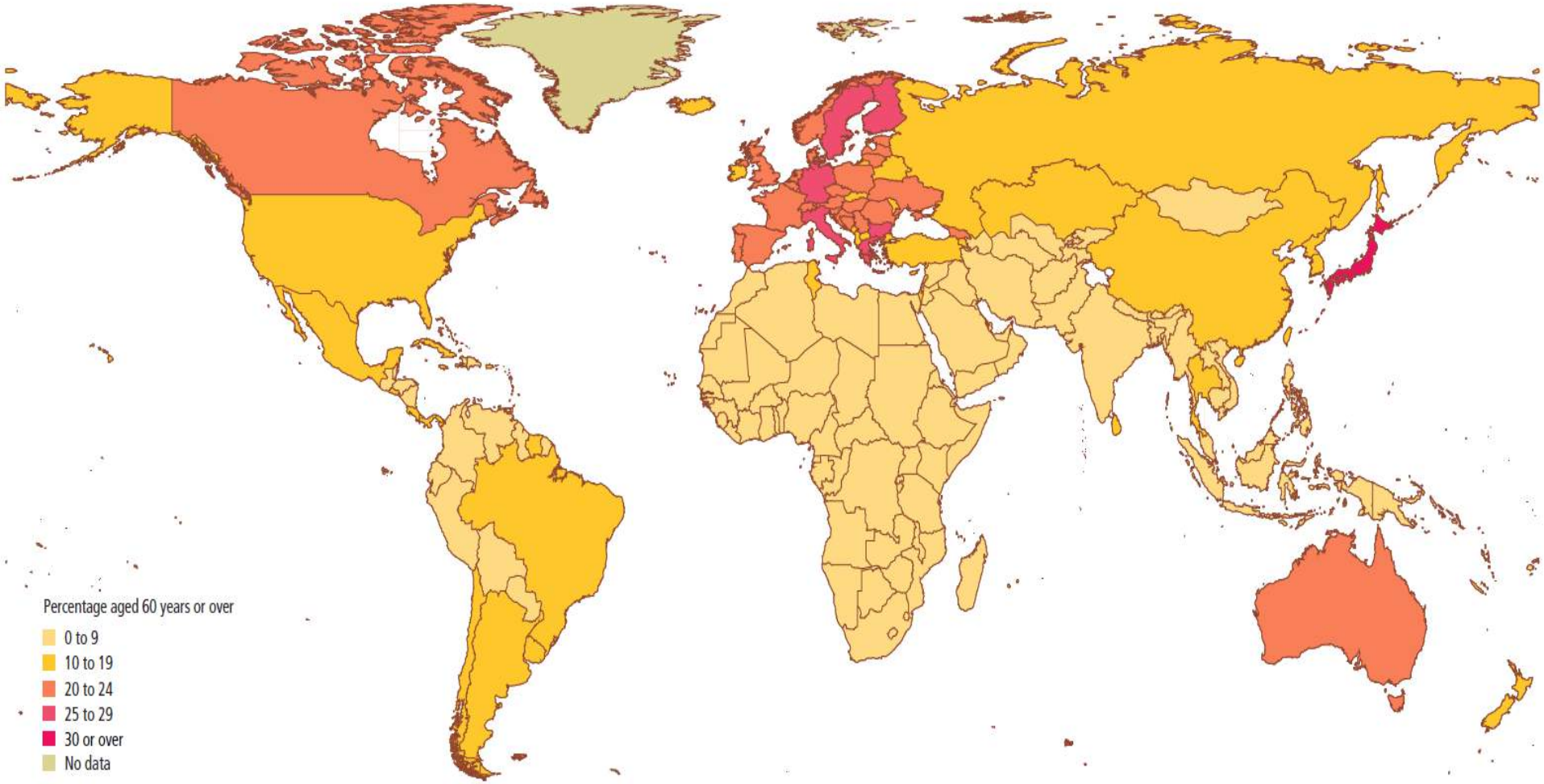
2012



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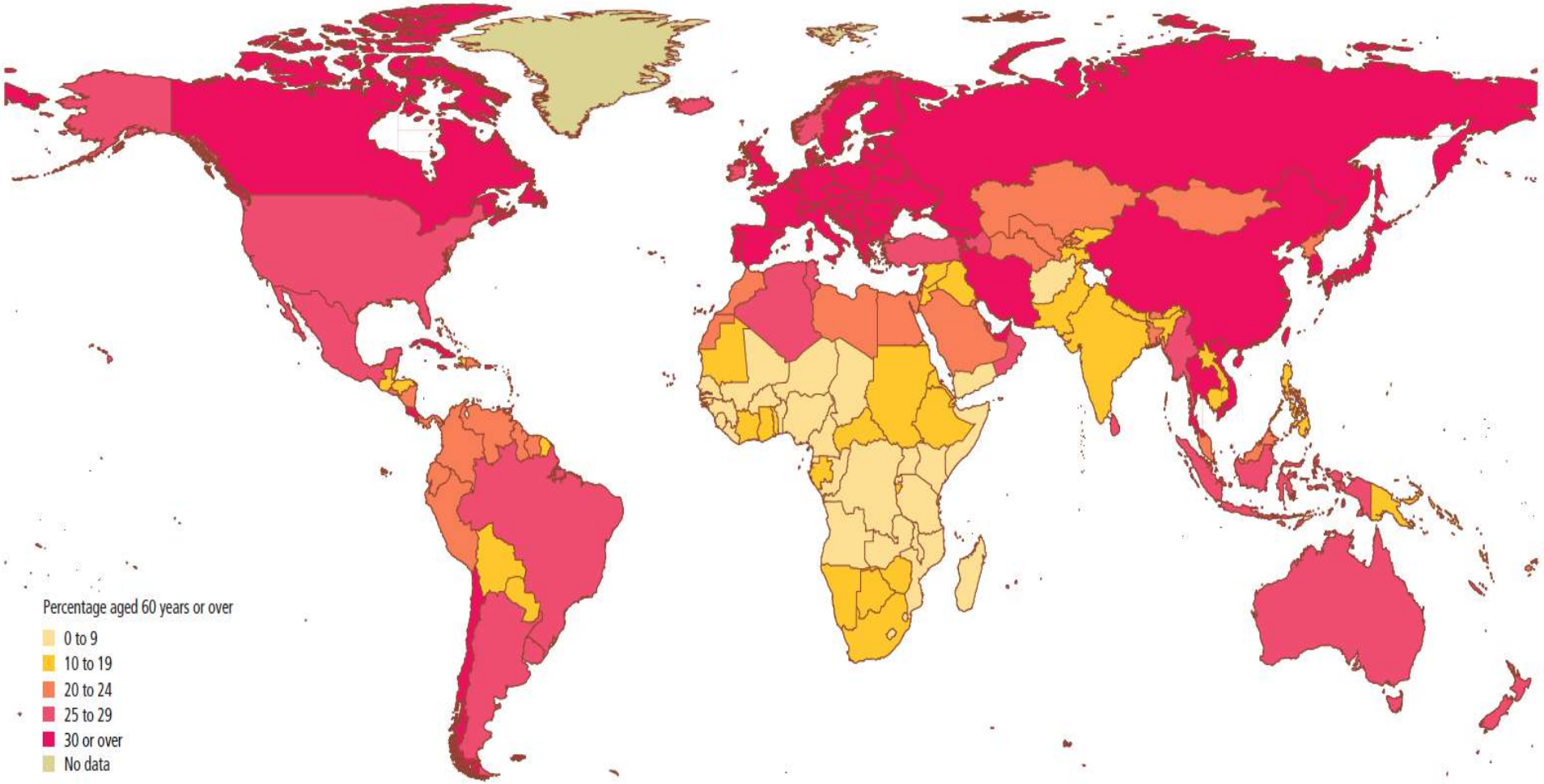
2050



Données Epidemiologiques

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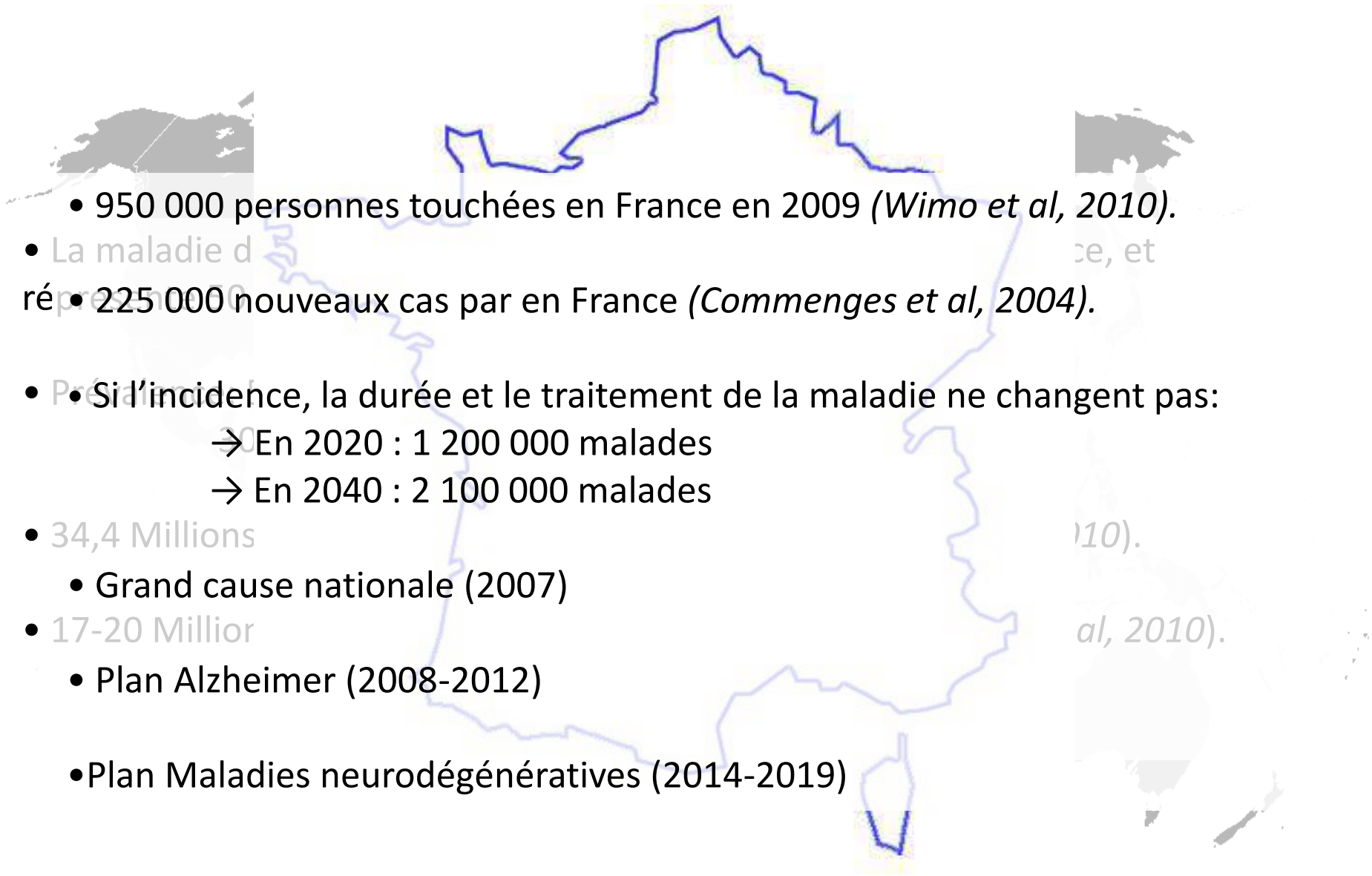
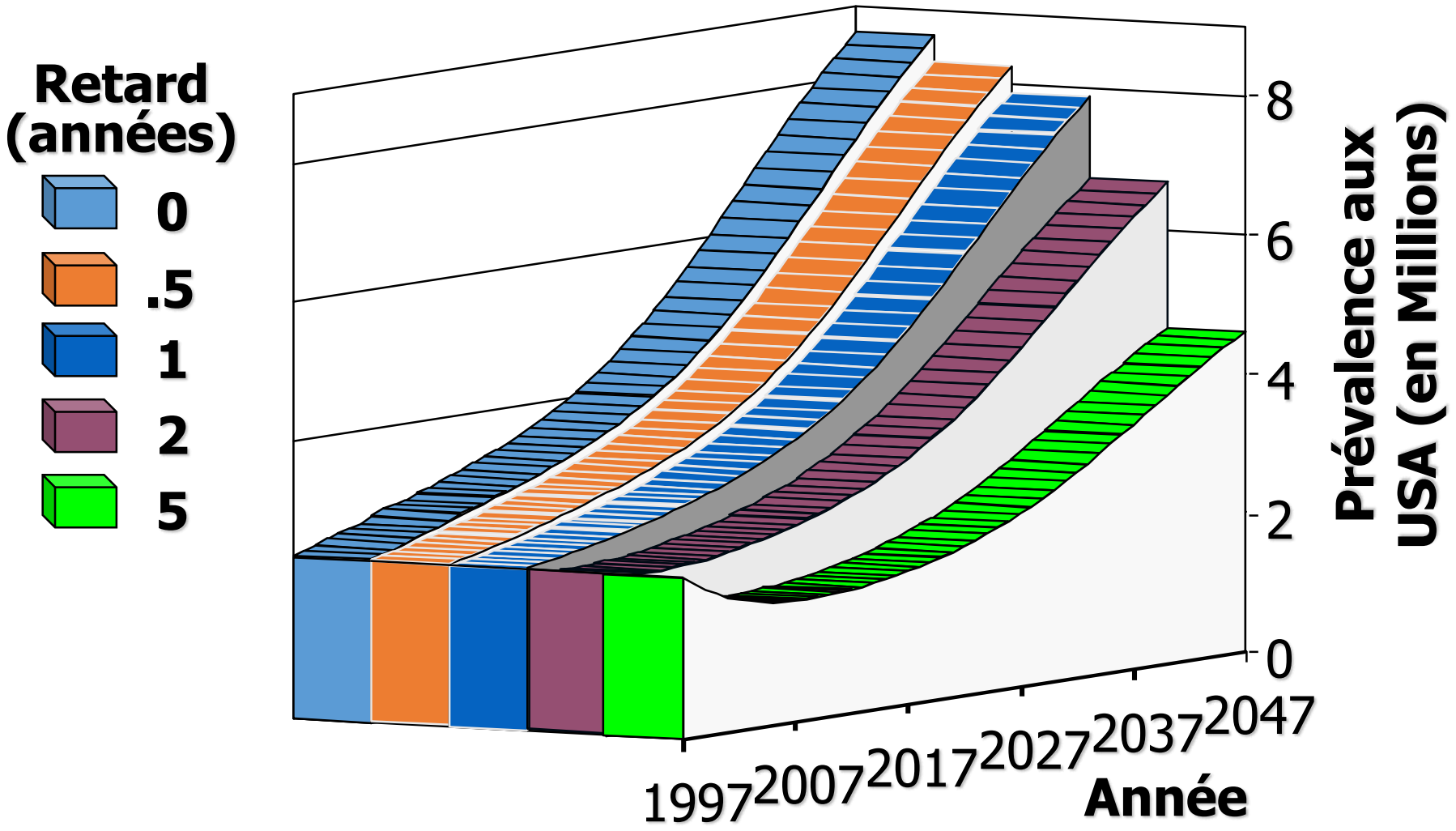


- 950 000 personnes touchées en France en 2009 *(Wimo et al, 2010).*
- La maladie d ce, et
ré • 225 000 nouveaux cas par en France *(Commenges et al, 2004).*

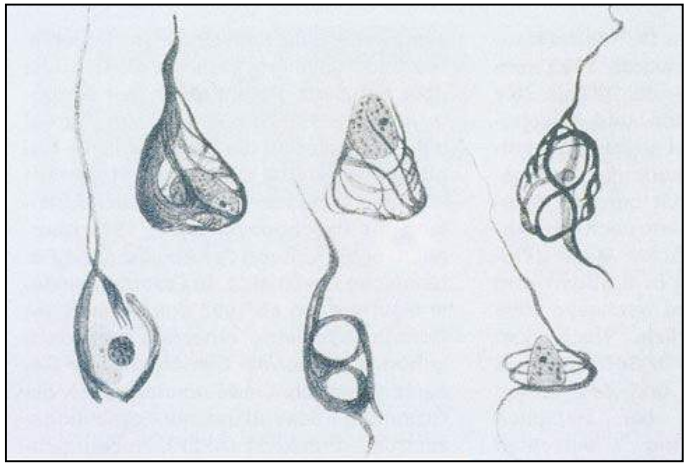
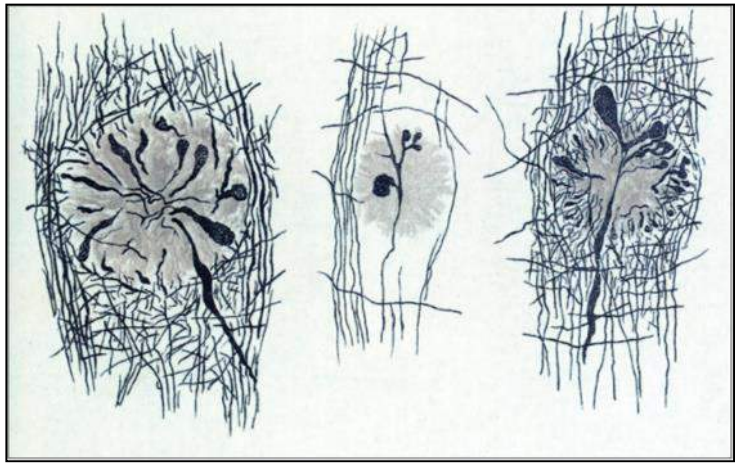
- Si l'incidence, la durée et le traitement de la maladie ne changent pas:
  - → En 2020 : 1 200 000 malades
  - → En 2040 : 2 100 000 malades
- 34,4 Millions *10*).
  - Grand cause nationale (2007)
- 17-20 Millior *al, 2010*).
  - Plan Alzheimer (2008-2012)

  - Plan Maladies neurodégénératives (2014-2019)

Si l'on retarde le début de la phase symptomatique de la maladie…



Brookheimer et al. *Am J Pub Health*. 1998;88:1337-1342.

(Alzheimer 1906, 1907, Fisher 1907)

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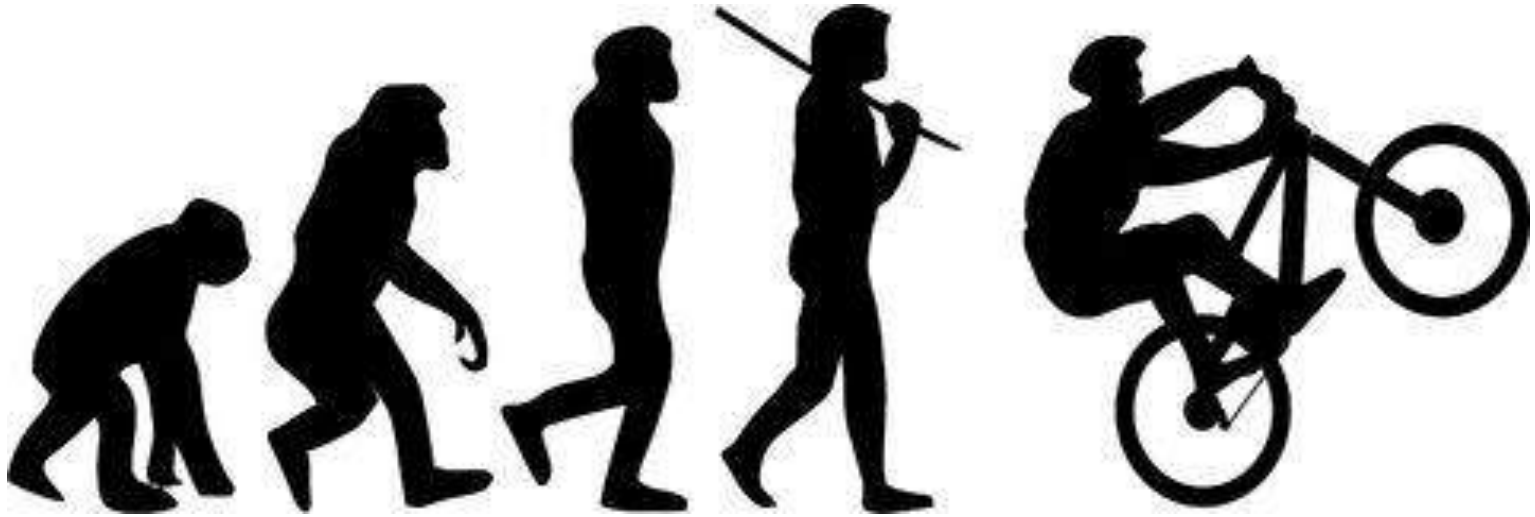
Évolution du concept de la maladie d'Alzheimer



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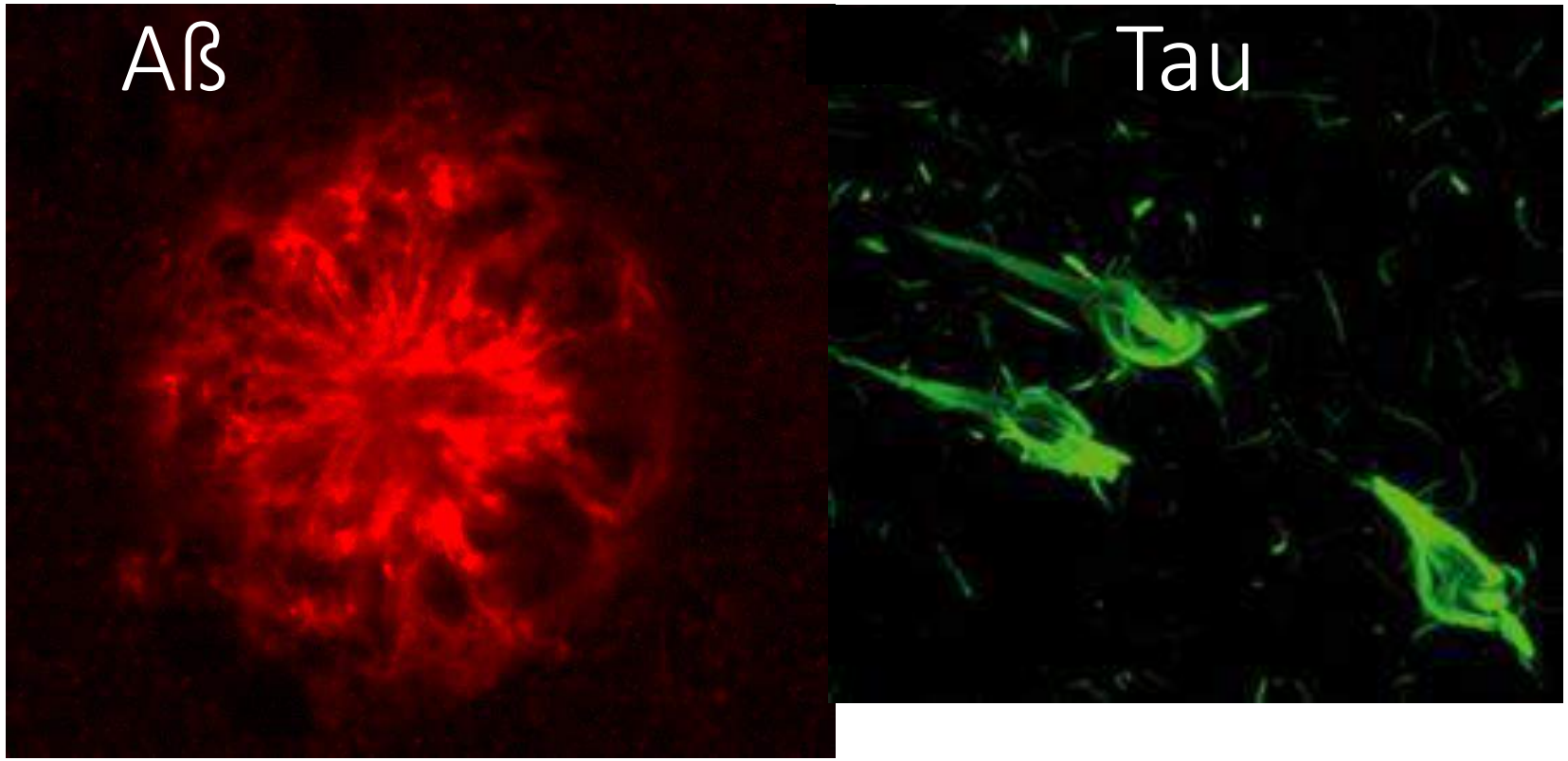
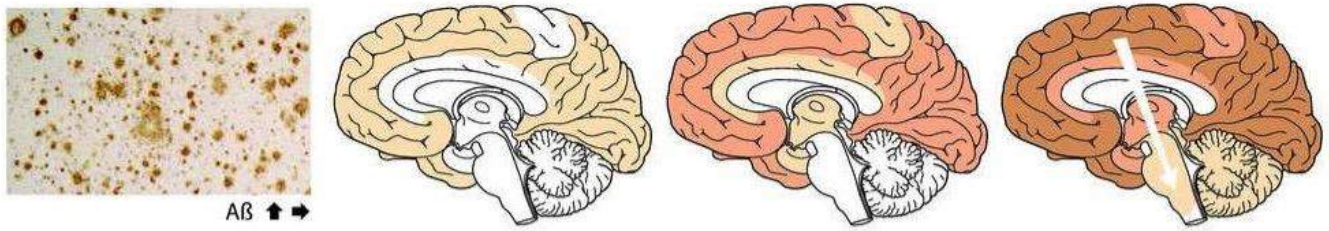
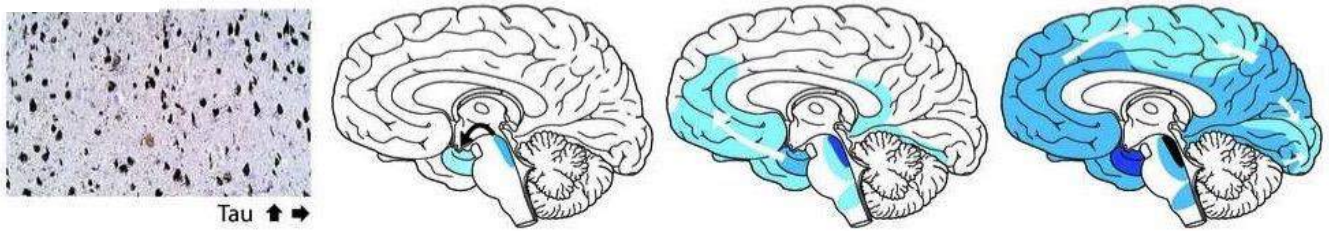


Progression de la maladie

Thal



Braak



(Braak et Braak 1991, Thal et al 2002)

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tests cognitifs :
Pas de pattern spécifique

CT or MRI:
proposé pour exclure des lésions vasculaires, tumorales…

Clinical diagnosis of Alzheimer's disease:

Report of the NINCDS-ADRDA Work Group* under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease

Guy McKhann, MD; David Drachman, MD; Marshall Folstein, MD; Robert Katzman, MD;
Donald Price, MD; and Emanuel M. Stadlan, MD

1984

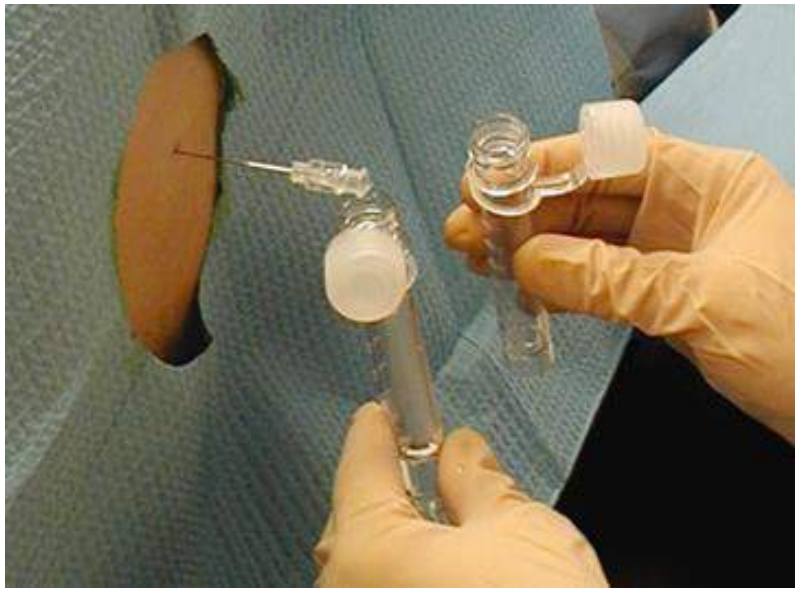
LCR:
proposé pour exclure une méningite

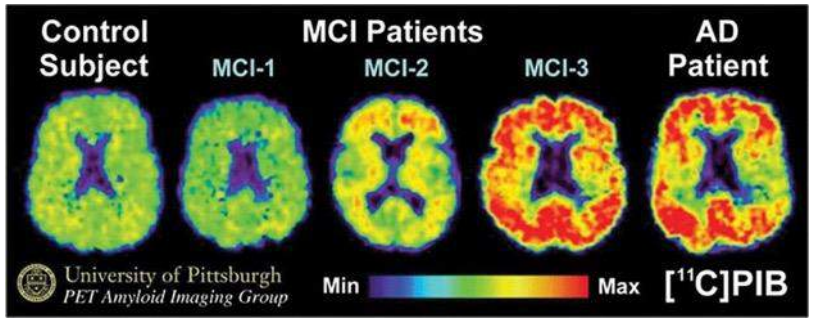
FDG-PET
non mentionné et
PET amyloïde inconnu

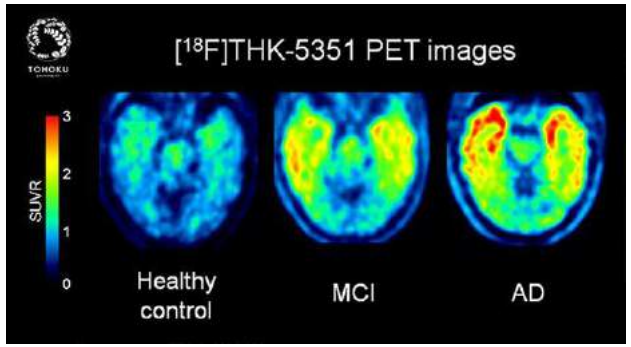
Critères révisés IWG-2 de la maladie d'Alzheimer à but de recherche

1. **Un phénotype clinique spécifique**:
   - Syndrome amnésique

2. **Un marqueur d'état physiopathologique de MA:**







Dubois et al. 2007, 2010, 2014

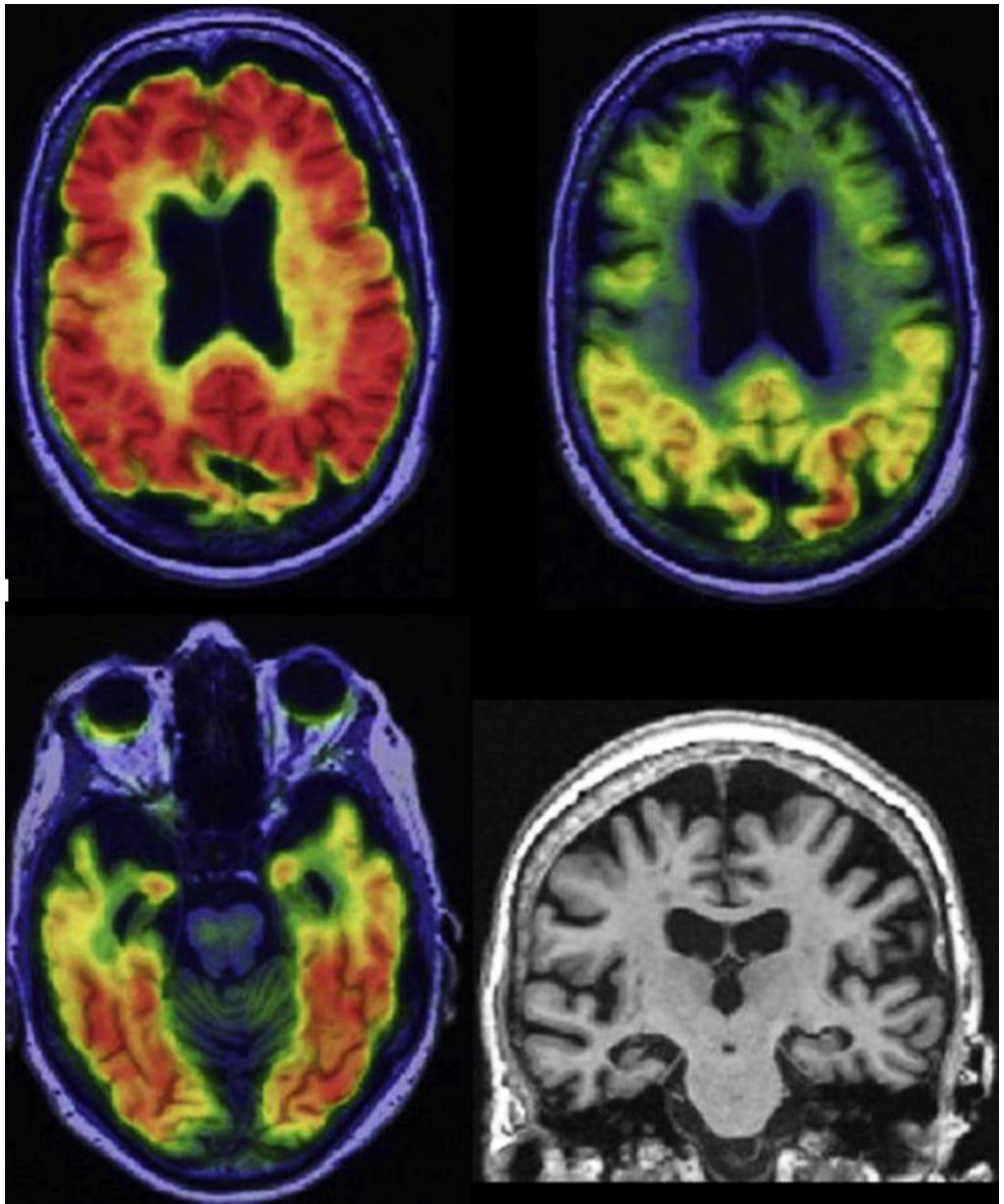
Critères NIA AA de la maladie d'Alzheimer (Avril 2018)

Alzheimer's & Dementia 14 (2018) 535-562

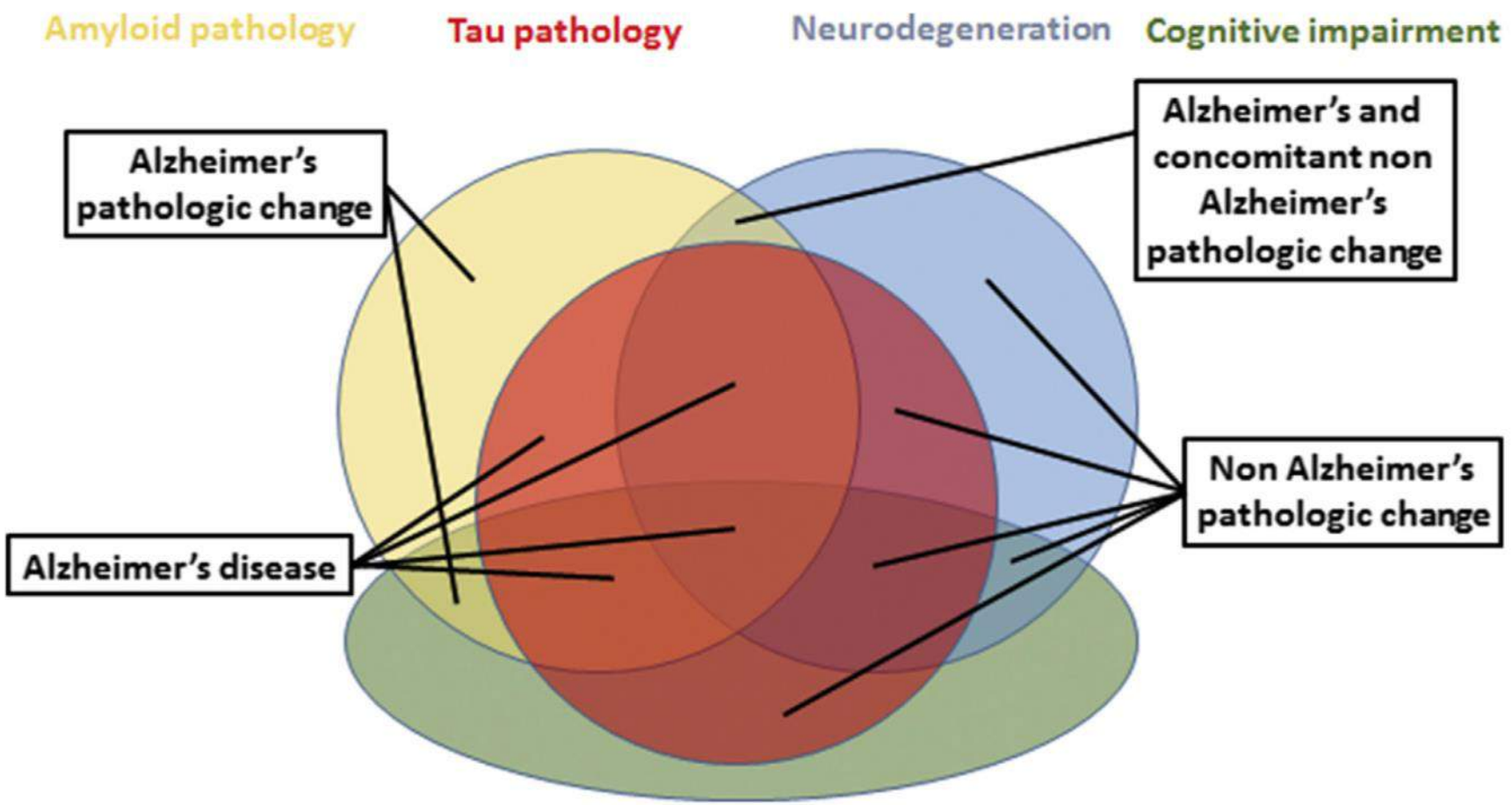
2018 National Institute on Aging—Alzheimer's Association (NIA-AA) Research Framework

NIA-AA Research Framework: Toward a biological definition of Alzheimer's disease

Clifford R. Jack, Jr.,[a,*], David A. Bennett[b], Kaj Blennow[c], Maria C. Carrillo[d], Billy Dunn[e], Samantha Budd Haeberlein[f], David M. Holtzman[g], William Jagust[h], Frank Jessen[i], Jason Karlawish[j], Enchi Liu[k], Jose Luis Molinuevo[l], Thomas Montine[m], Creighton Phelps[n], Katherine P. Rankin[o], Christopher C. Rowe[p], Philip Scheltens[q], Eric Siemers[r], Heather M. Snyder[d], Reisa Sperling[s]



En réalité la situation est beaucoup plus complexe…



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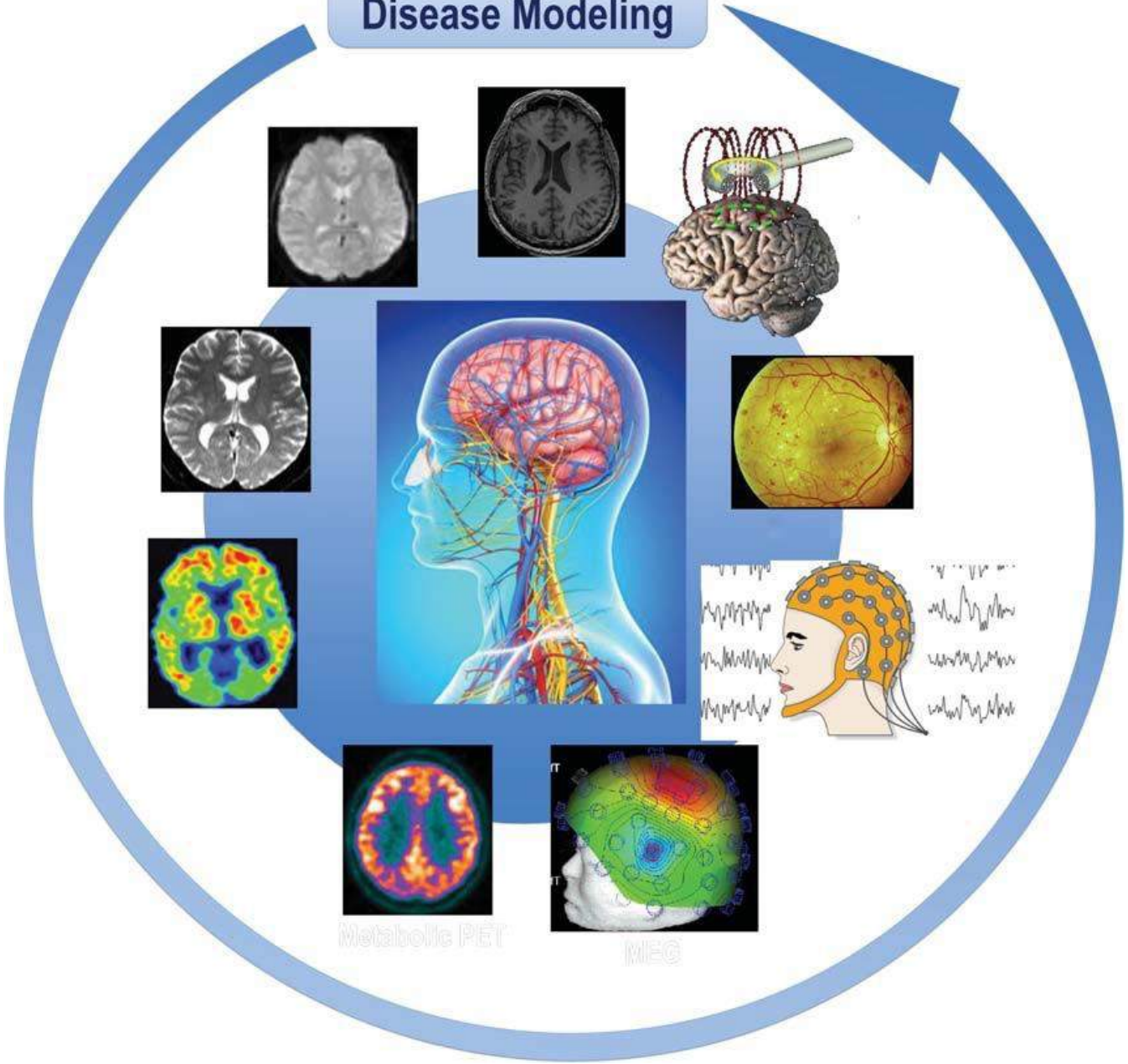
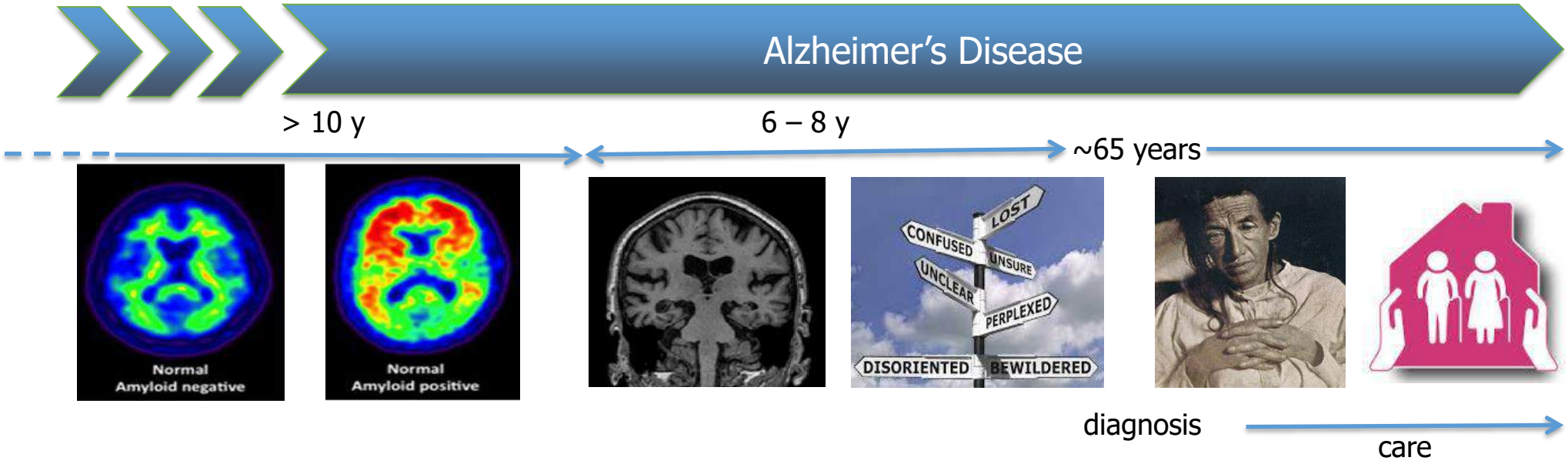
Integrative Disease Modeling





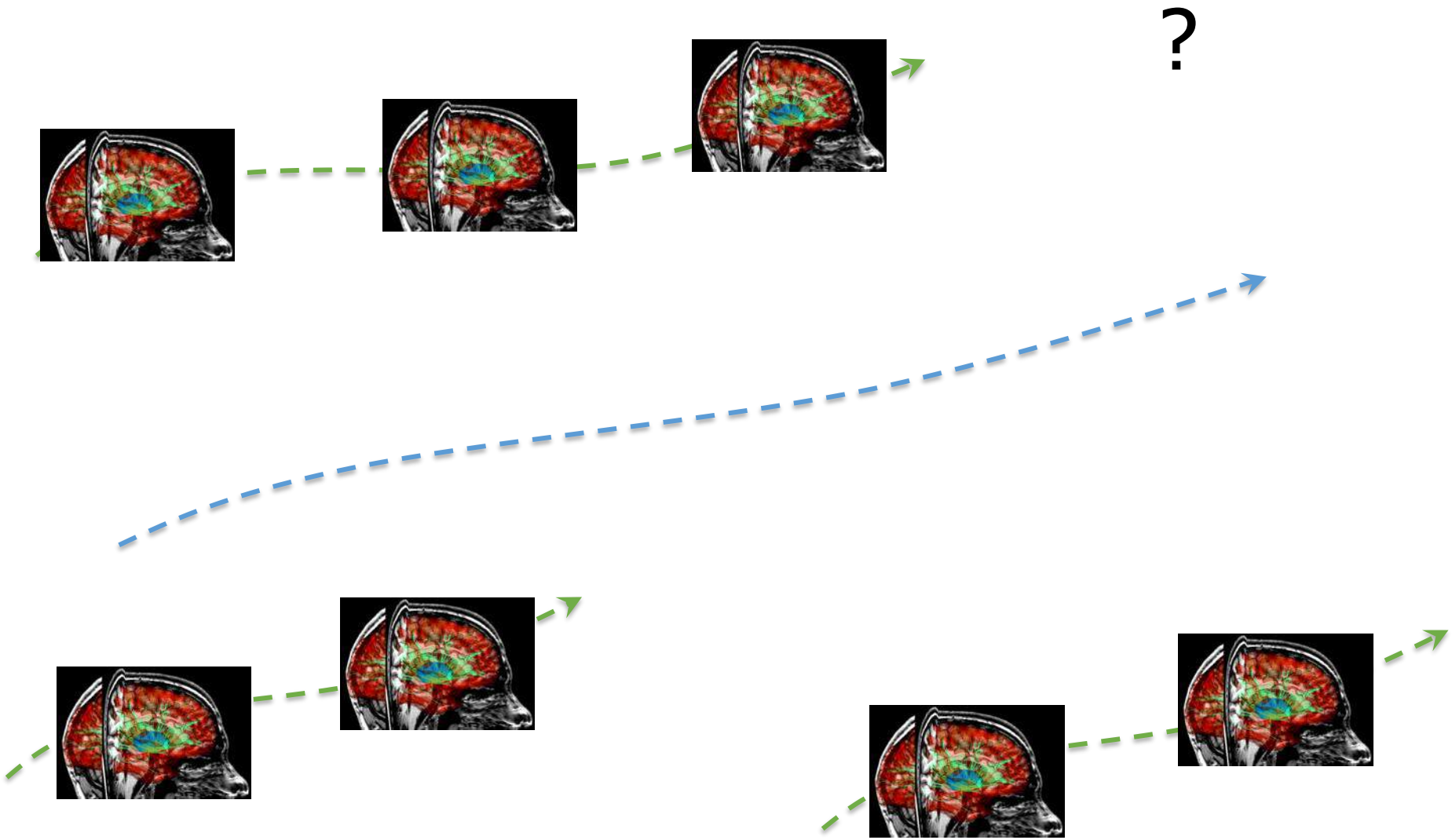
Build digital model of brain aging

from clinical and imaging data

Understand
effects of the disease on the brain and their heterogeneity at the individual level

Predict
disease onset

Digital Models of Disease Progression



Hierarchical model

Population level

Average trajectory :

$$\gamma_0(\cdot) = \gamma_{p_0,t_0,v_0}(\cdot)$$

→ Geodesic on a Riemannian manifold $\mathbb{M}$

Individual level $(1 \leq i \leq p)$

Individual trajectory $\gamma_i(\cdot) = \eta^{w_i}(\gamma_0, \psi_i(\cdot))$

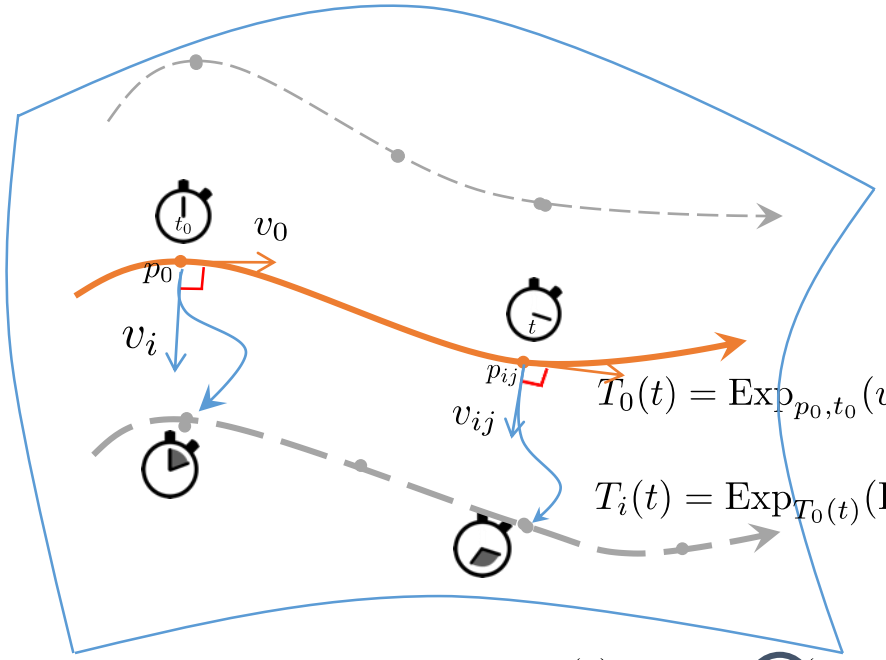
→ Spatiotemporal transform of trajectory

Observations

$$y_{i,j} = \gamma_i(t_{i,j}) + \varepsilon_{i,j}$$

→ data point lying on a sub-Riemannian manifold

Spatiotemporal hierarchical model



$$T_0(t) = \mathrm{Exp}_{p_0,t_0}(v_0)(t)$$

$$T_i(t) = \mathrm{Exp}_{T_0(t)}(\mathrm{P}^{T_0}_{t_0,t}(v_i)) \quad y_{ij} = T_i(\psi_i(t)) + \varepsilon_{ij}$$

$$\psi_i(t) = t_0 + \alpha_i(t - t_0 - \tau_i)$$

Random effects:

Acceleration factor: $\alpha_i \sim log\,\mathcal{N}(0, \sigma_\alpha^2)$

Time-shift: $\tau_i \sim \mathcal{N}(0, \sigma_\tau^2)$

Space-shift: $v_i = (A_1|\ldots|A_K)\, s_i$, $A_k \perp v_0$

Fixed effects: (p_0, t_0, v_0)

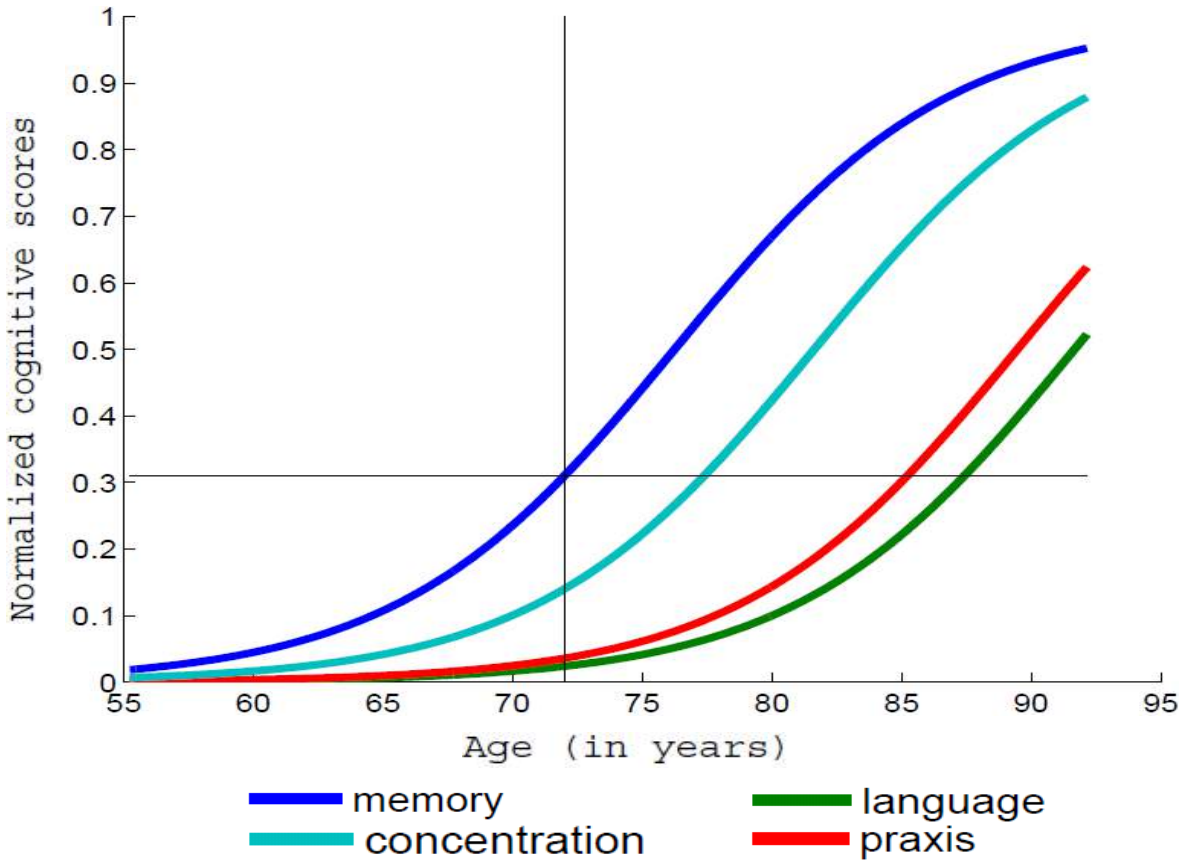
- A statistical model to estimate:
  - a **population average trajectory** of data changes
  - **Individual spatiotemporal variations** in:
    - measurement values
    - pace of measurement changes
- Orthogonality condition ensures unique space/time decomposition
- Time is not a covariate but a random variable
- Inference with stochastic optimization methods

[Schiratti et al. IPMI'15, NIPS'15, PhD'17, JMLR'17]

Model of cognitive decline in Alzheimer's Disease

- Neuropsychological tests ADAS-Gog from ADNI
- 248 subjects who converted from MCI to AD
- 6 time-points per subjects on average (min 3, max 11)
- Data points $y_{ij} \in]0,1[^4$ with propagation logistic model

The average trajectory of data changes

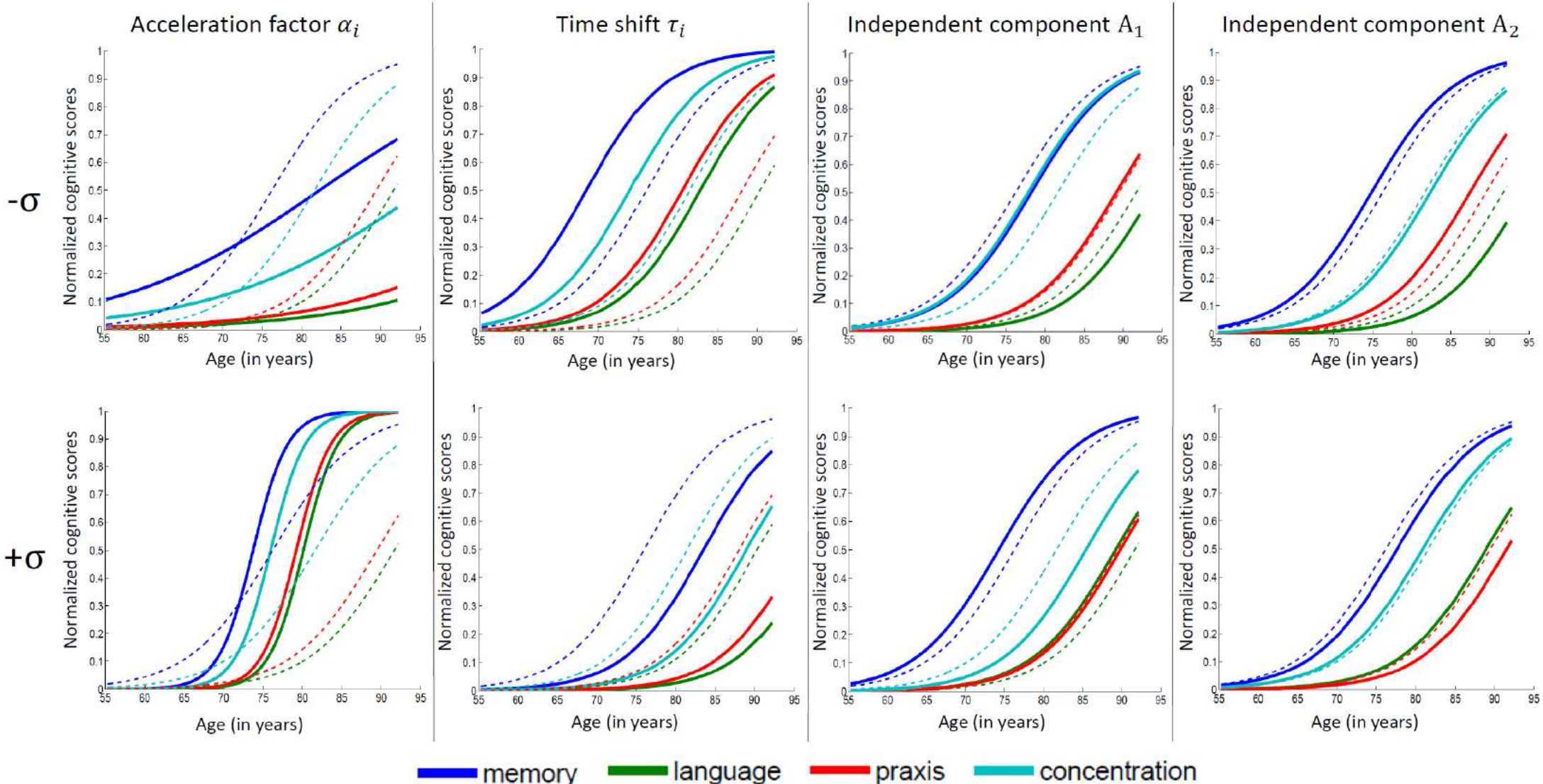


[Schiratti et al. IPMI'15, NIPS'15, PhD'17, JMLR'17]

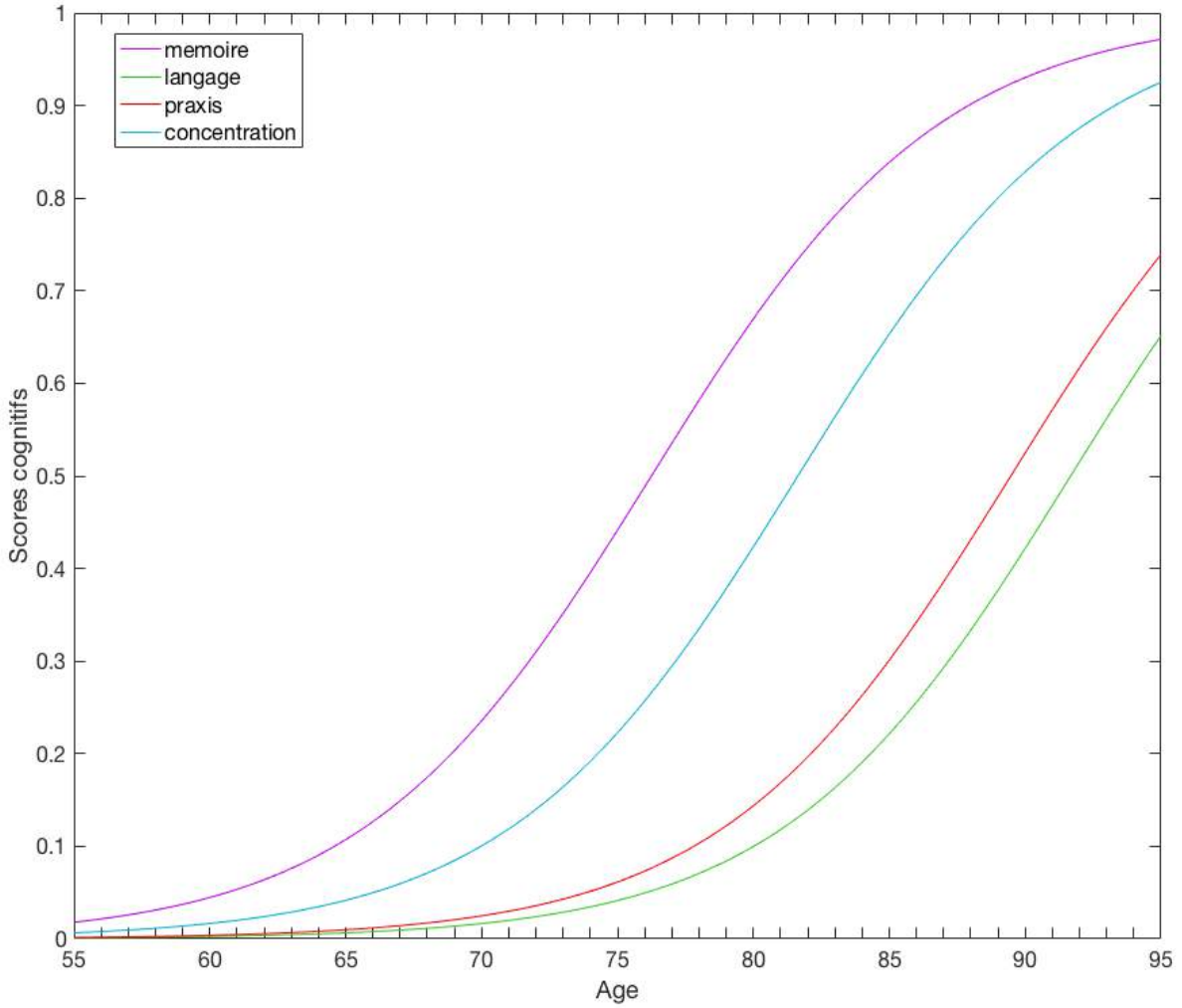
Distinguish **fast** vs. **slow** progressers

Distinguish **early** vs. **late** onset individuals

Variability in the **relative timing** and **ordering** of the events



Automatic prognosis system (patent pending)



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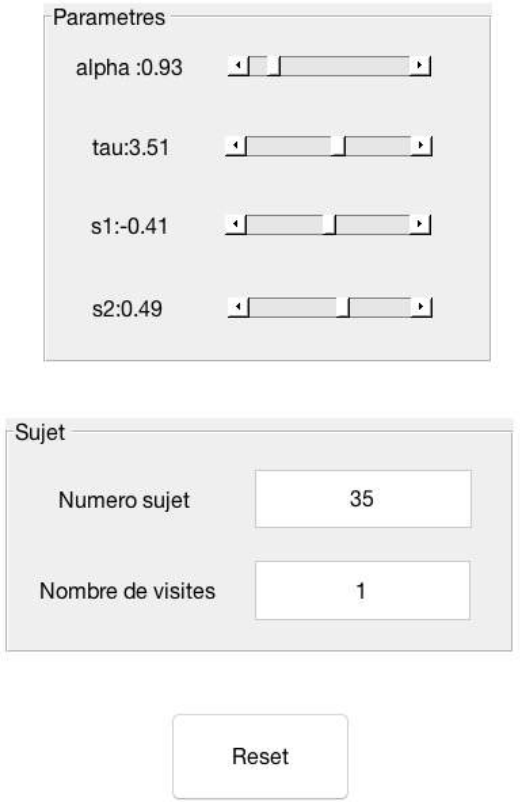
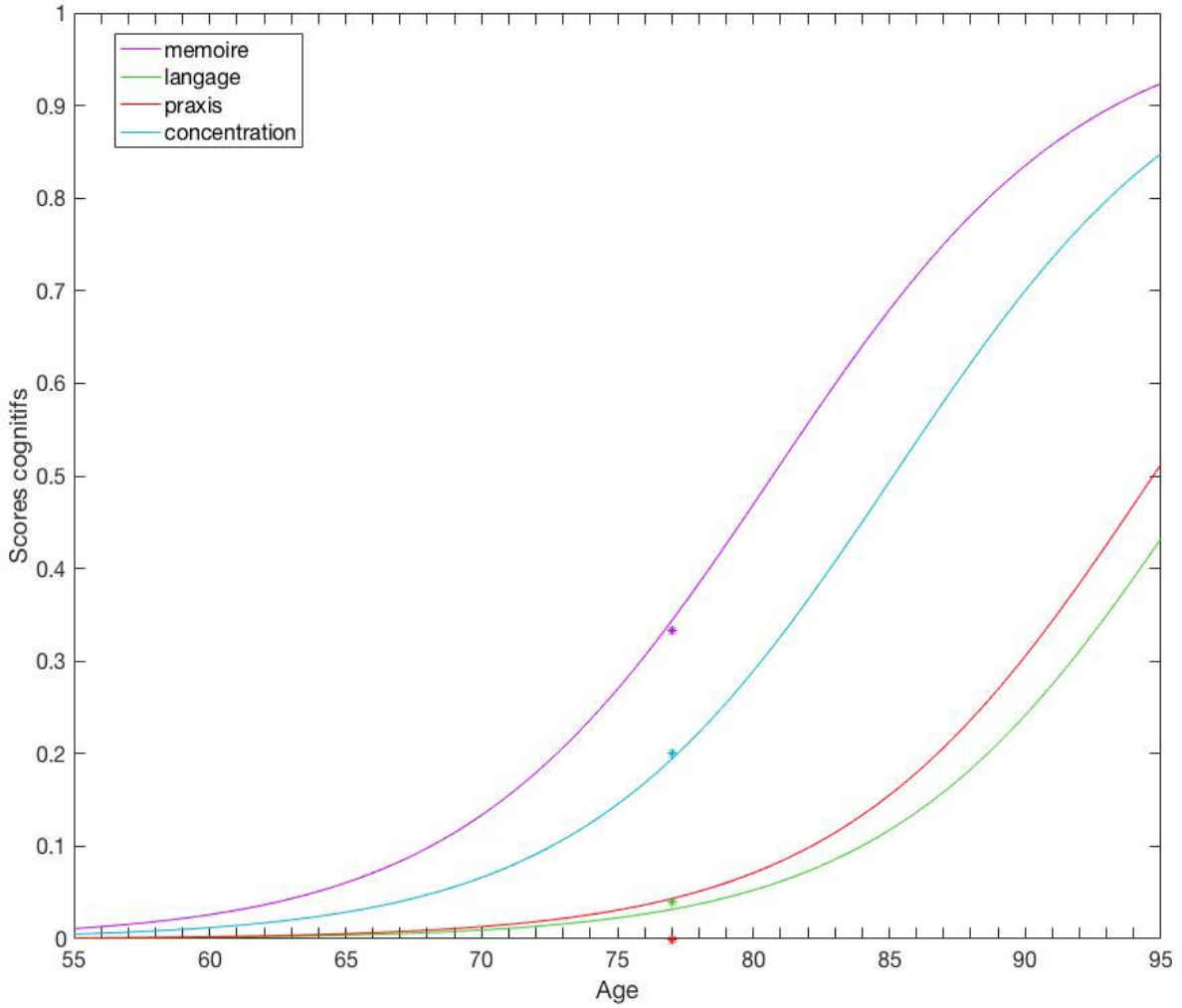
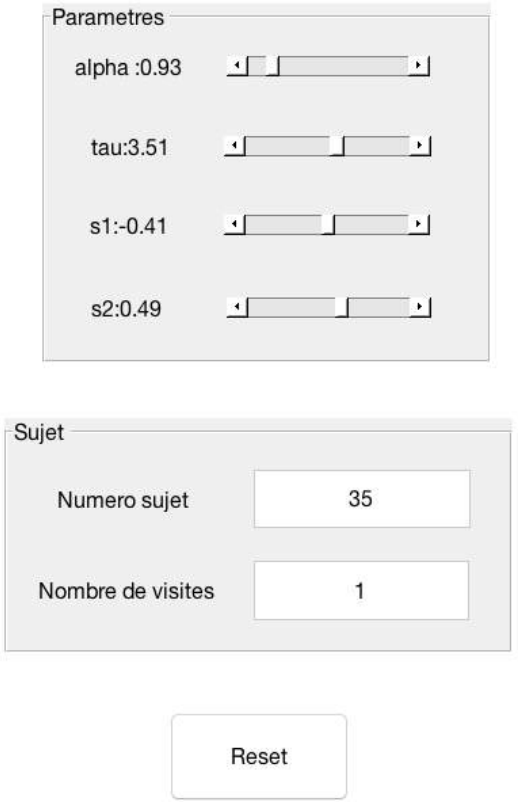
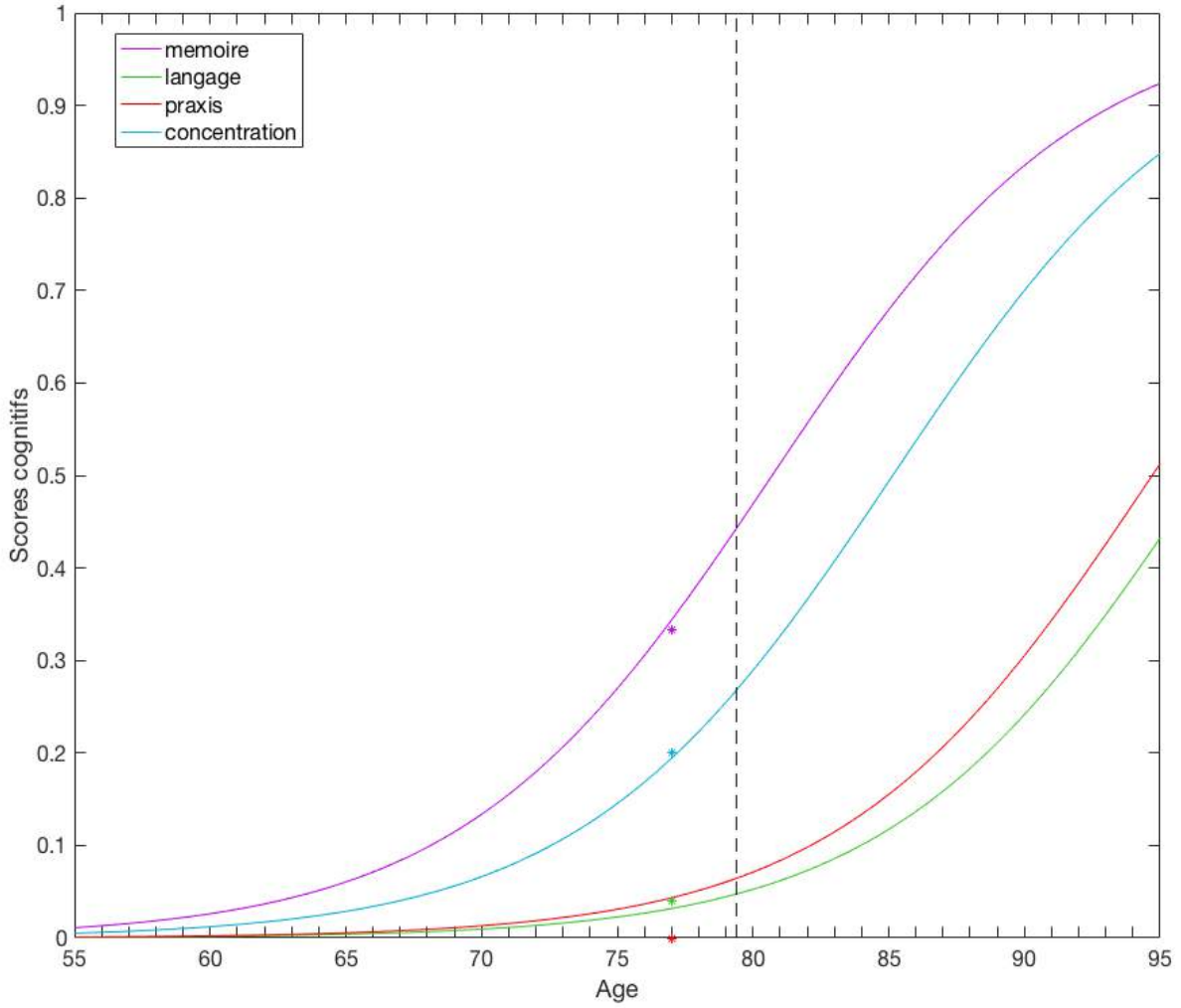




Automatic prognosis system (patent pending)





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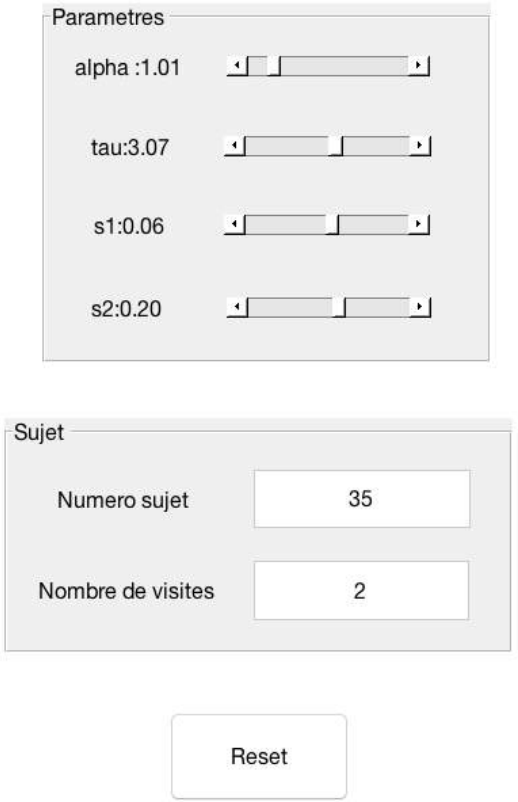

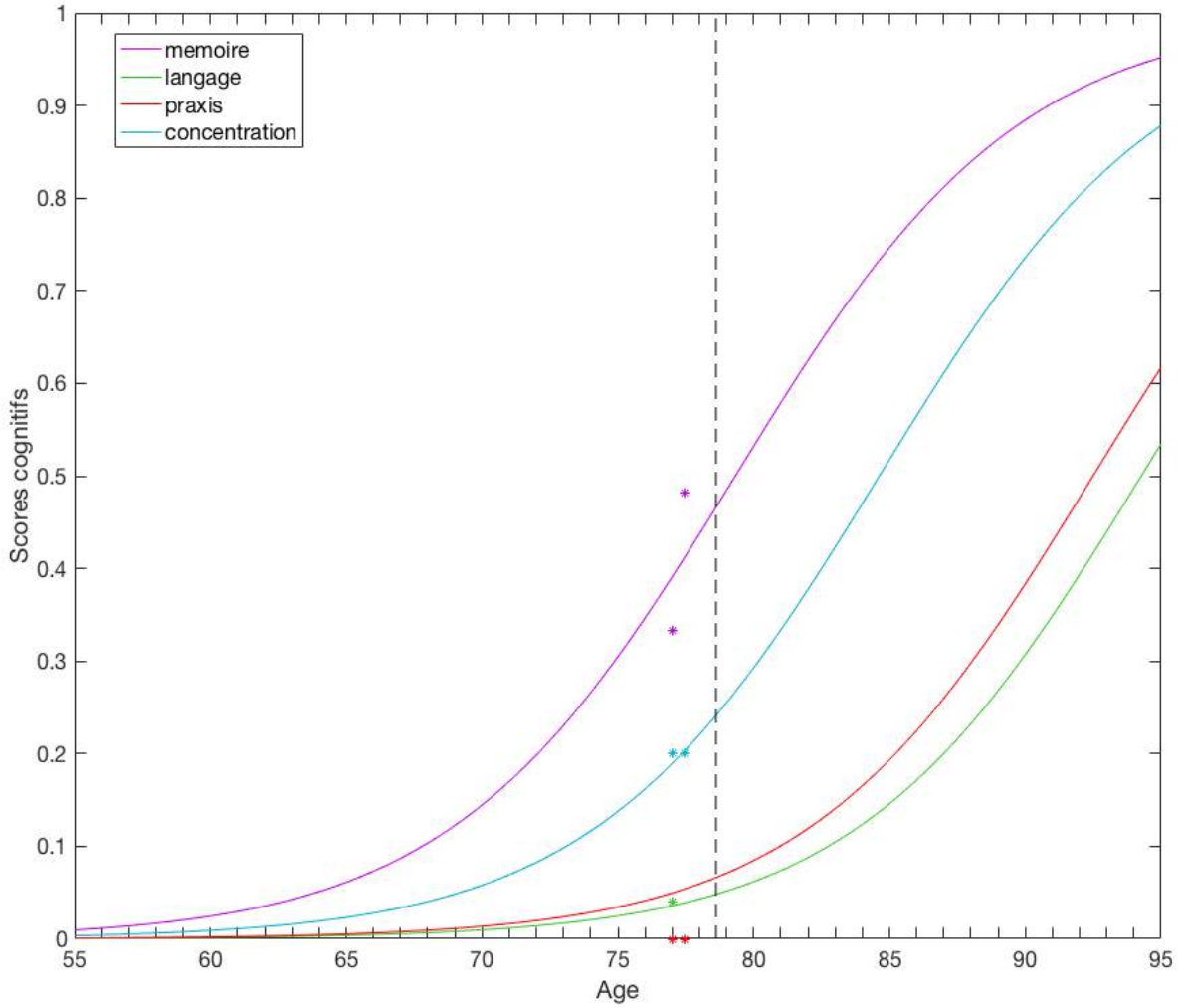

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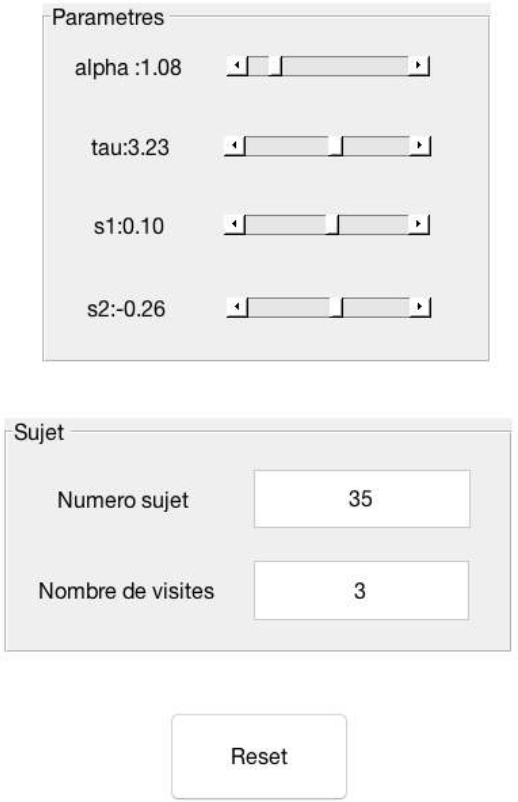
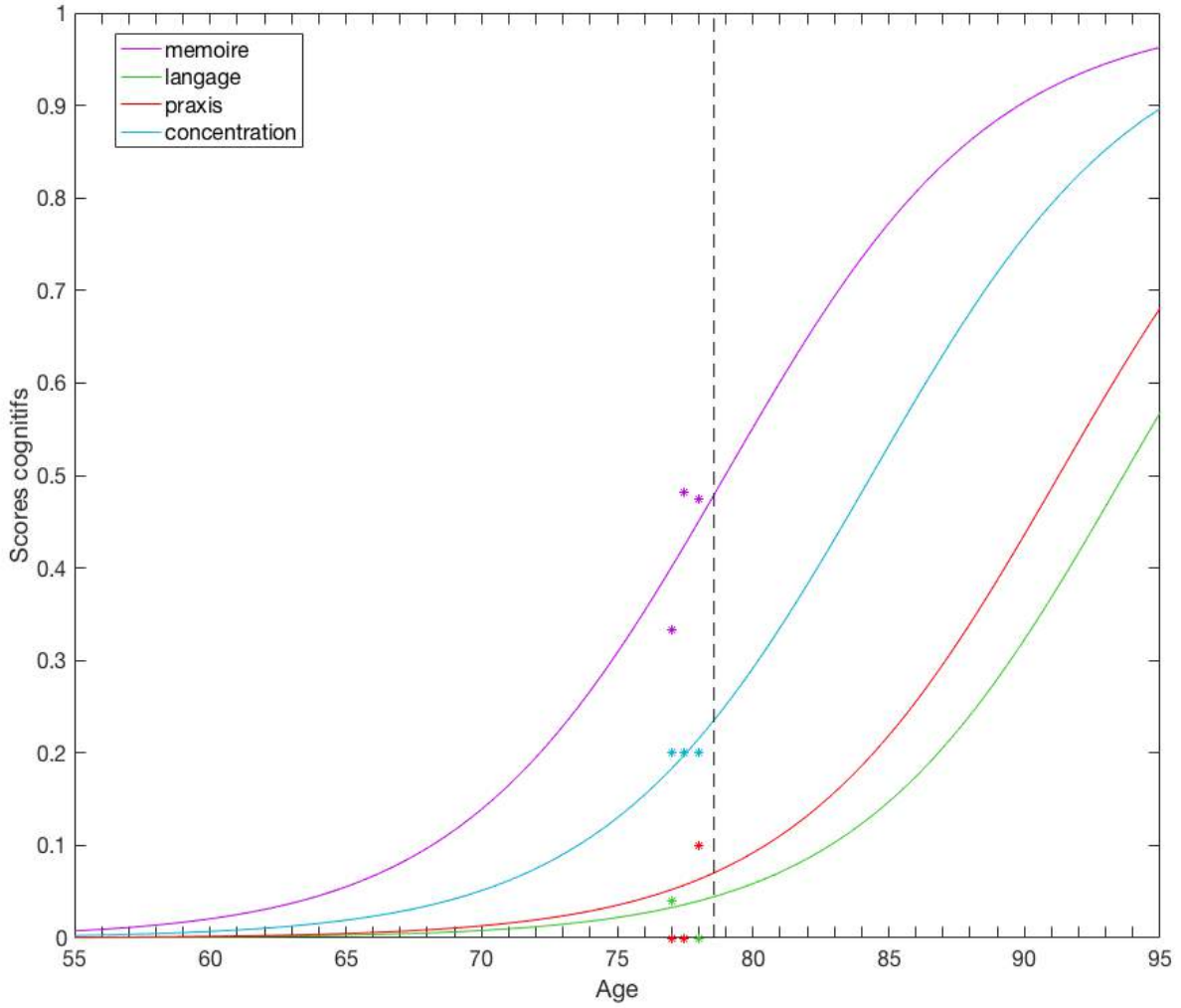
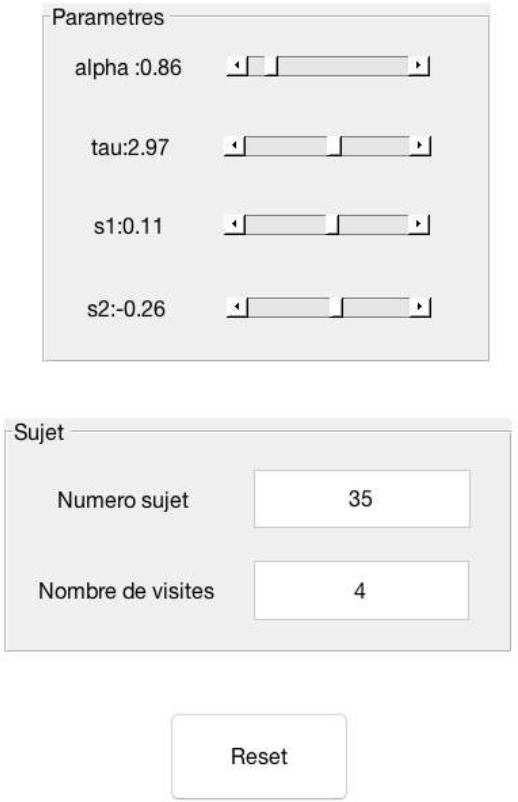
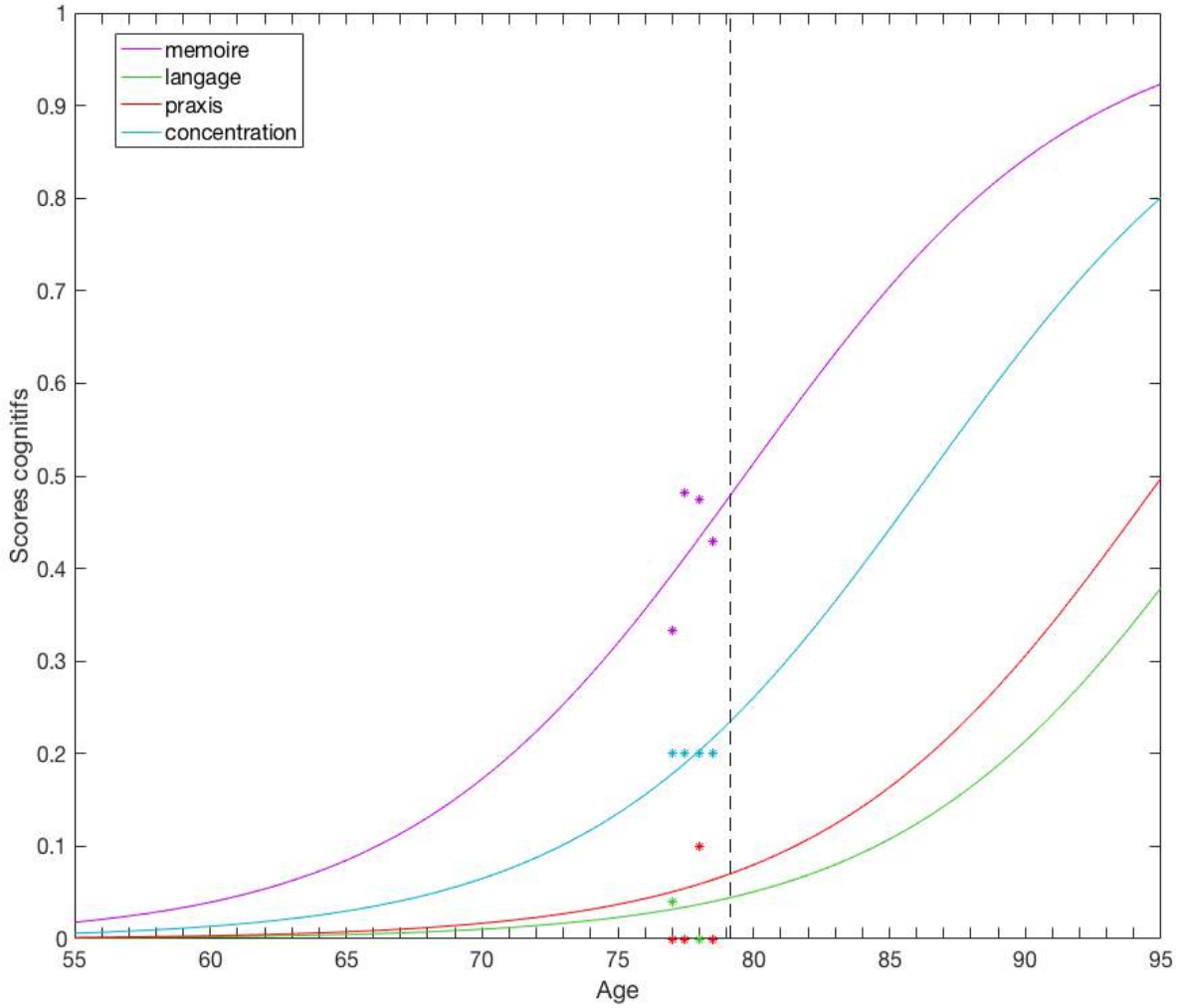


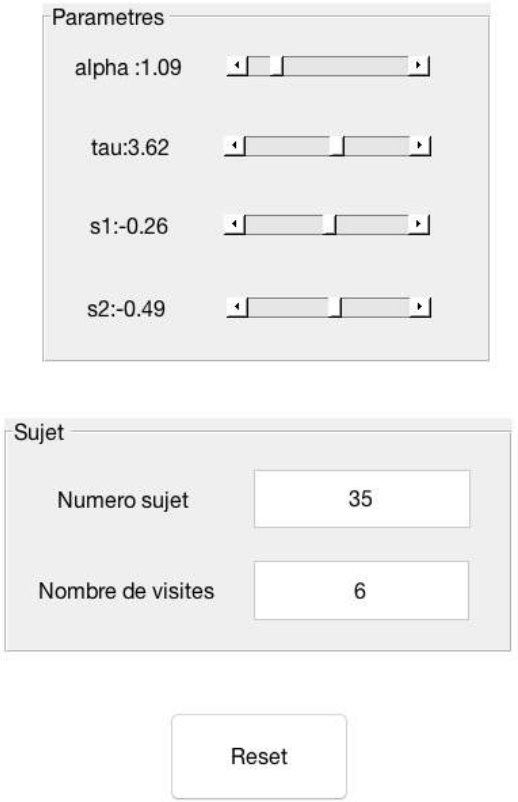


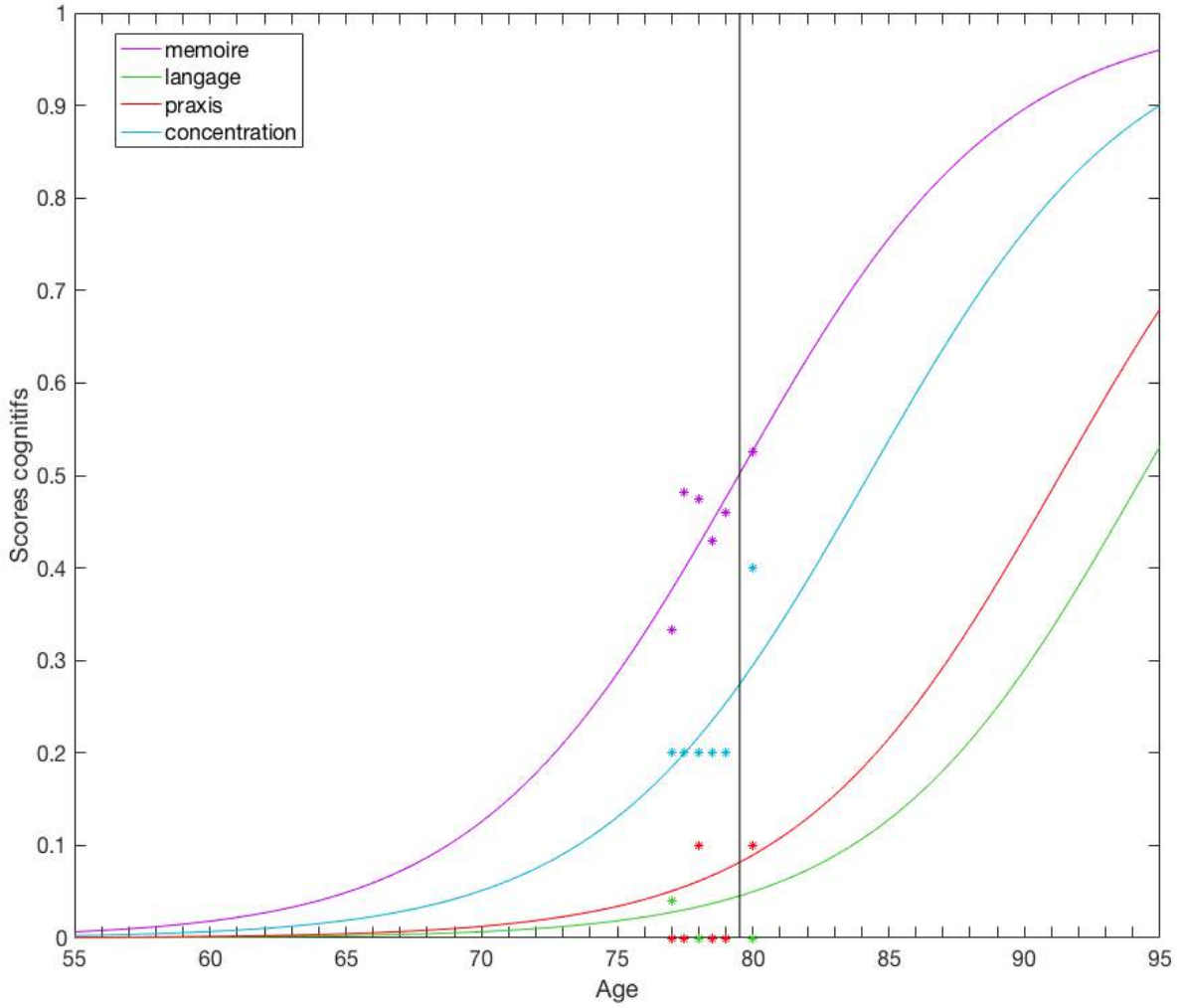
Automatic prognosis system (patent pending)





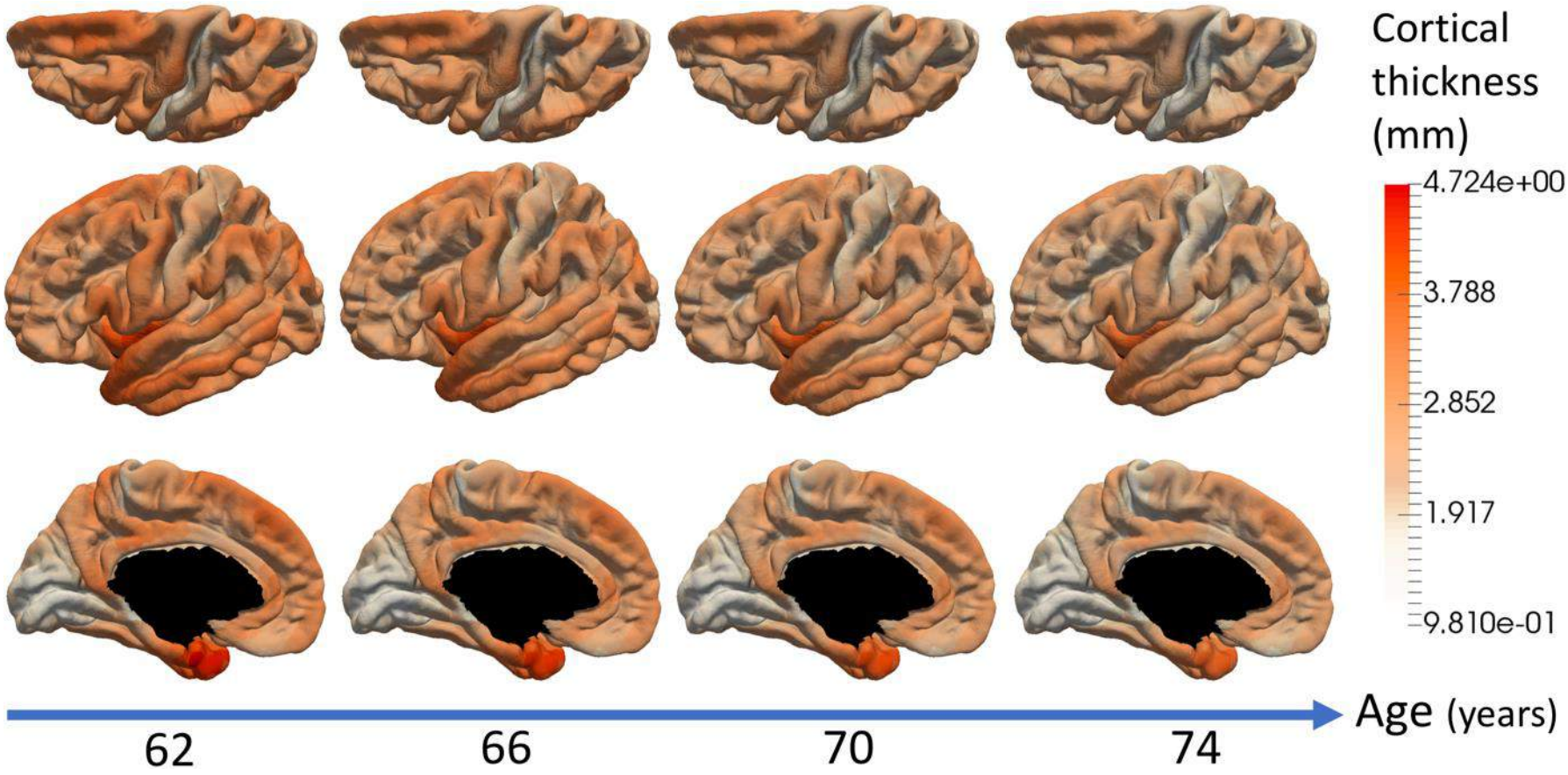
Automatic prognosis system (patent pending)





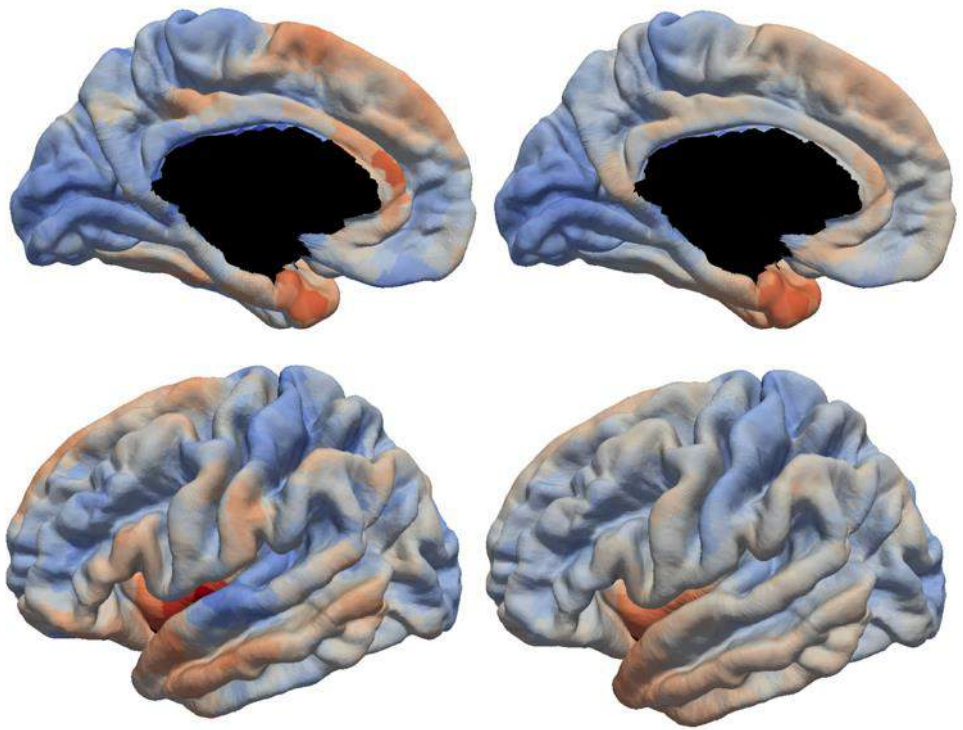
Model of cortical atrophy in Alzheimer's Disease

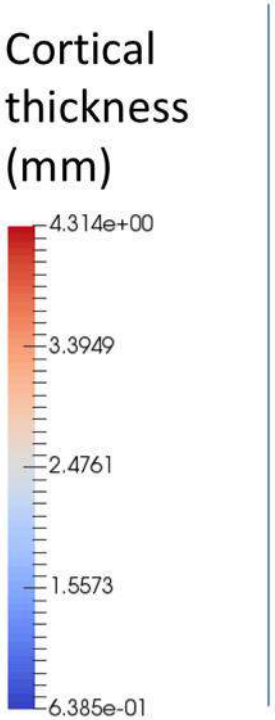
- Maps of cortical thickness
  - 1827 nodes (patches)
  - 258 control nodes
- 248 subjects who converted from MCI to AD
- 6 time-points per subjects on average (min 3, max 11)

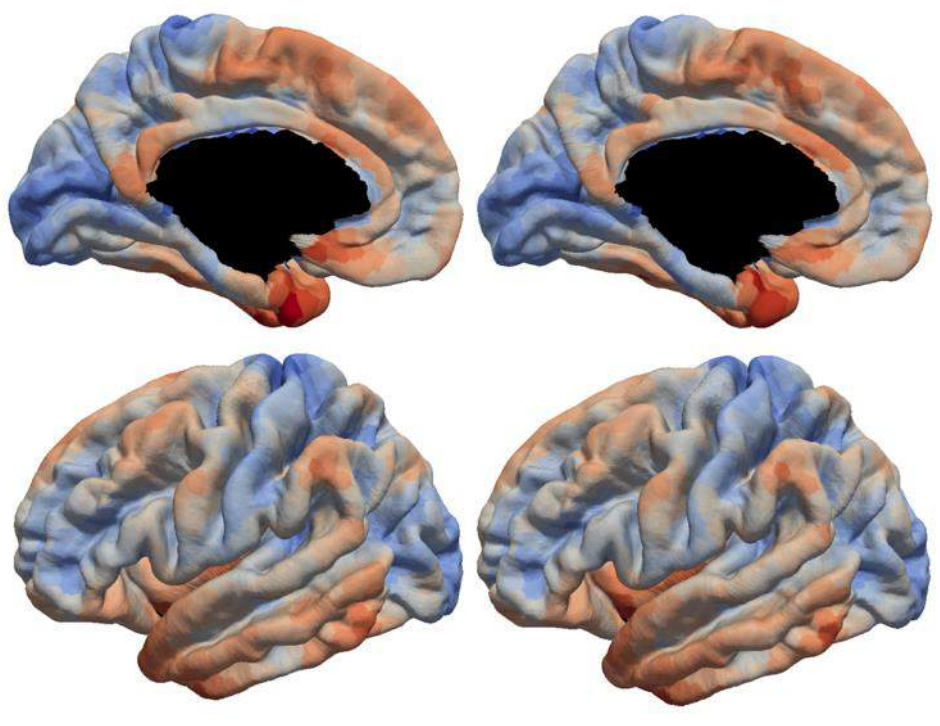


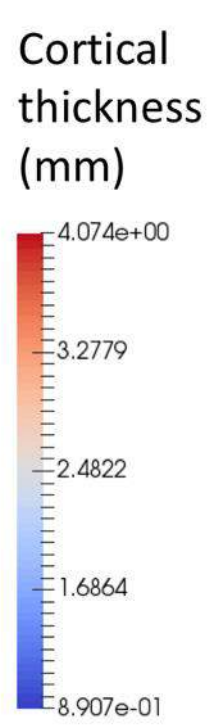
[Koval et al.MICCAI'17, Frontiers'17 (in revision)]

Reconstruction of individual observations by model personalization





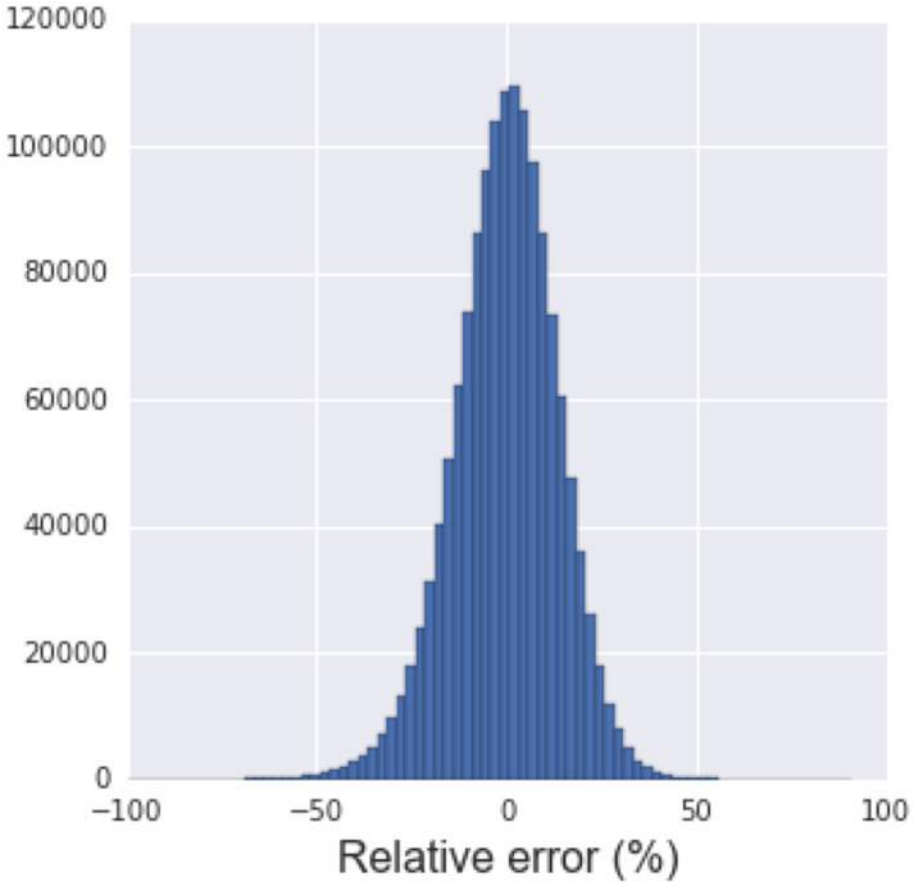


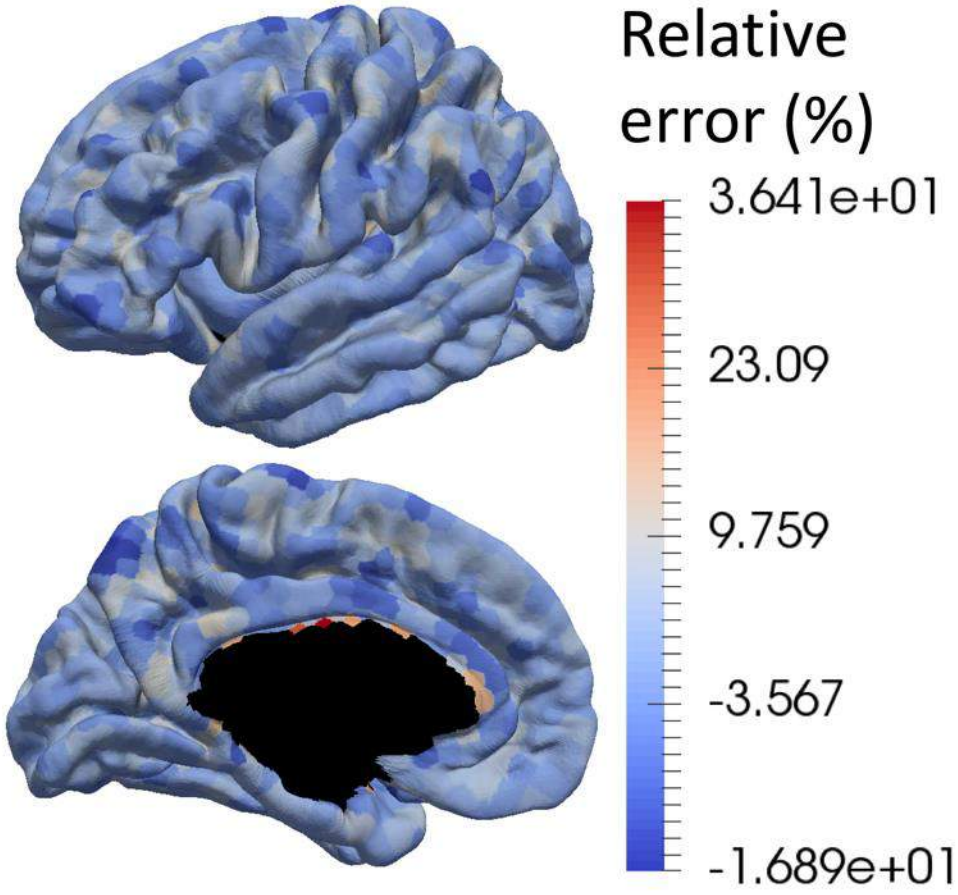


[Koval et al.MICCAI'17, Frontiers'17 (in revision)]

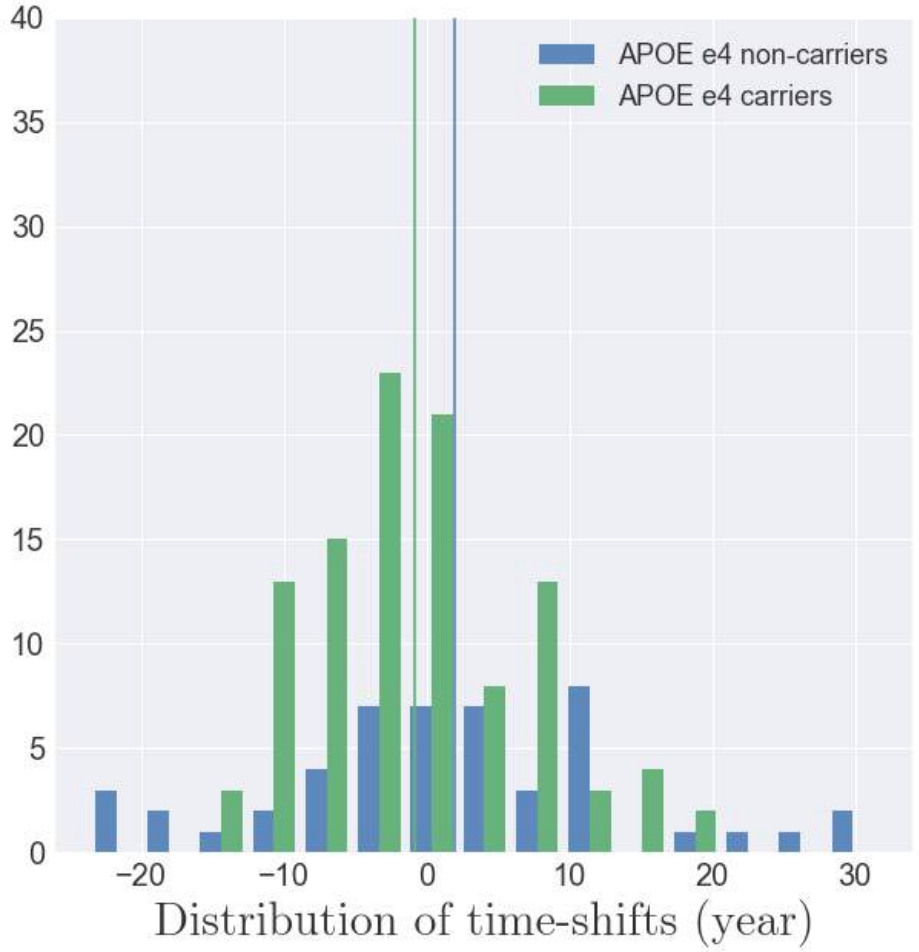
Reconstruction error at the individual vertex level

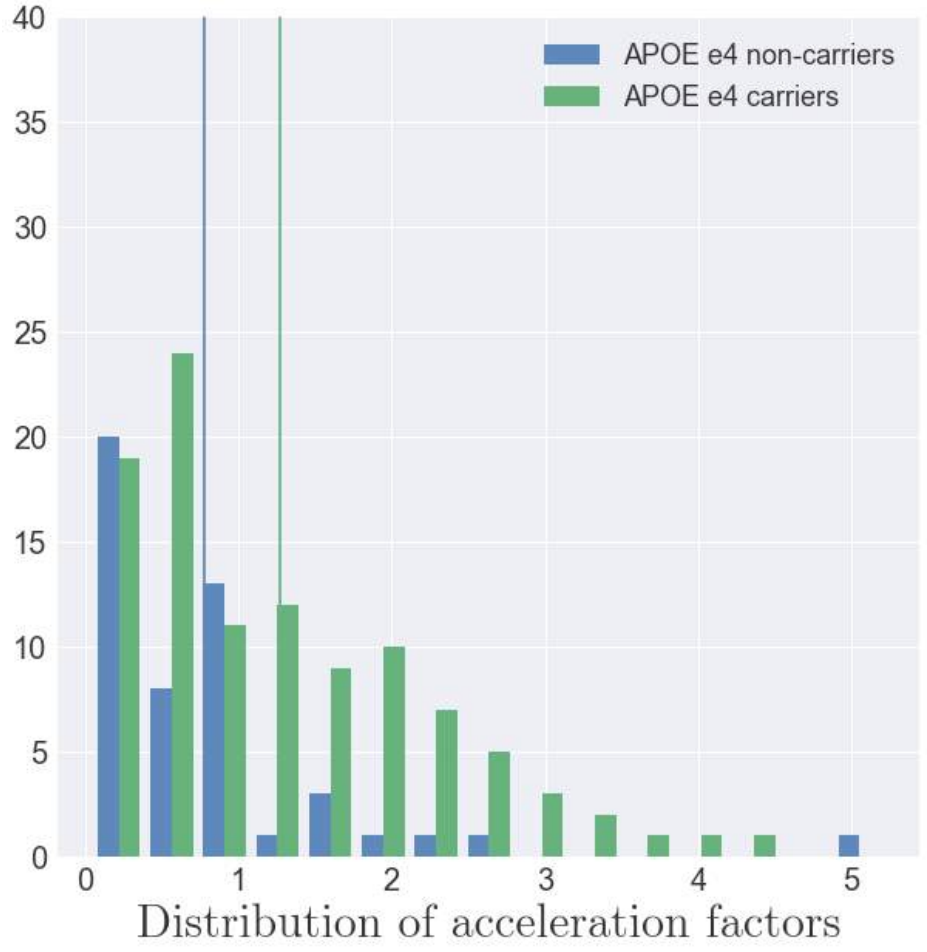
(1.5 millions of patches in 787 meshes from 154 individuals)





Model of cortical atrophy in Alzheimer's Disease

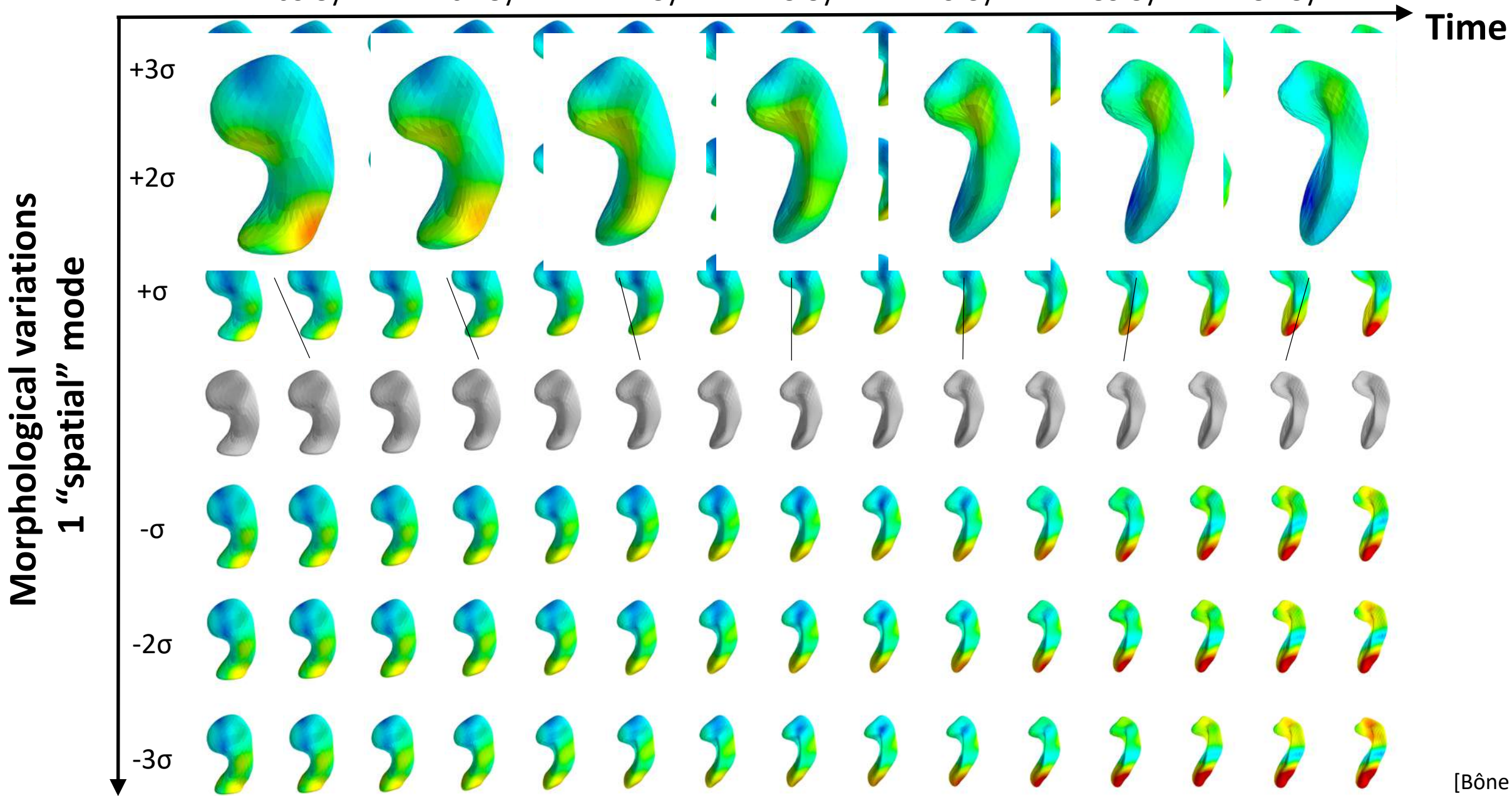




APOE e4 carriers have an earlier onset and faster cortical atrophy than others ($p<0.05$)

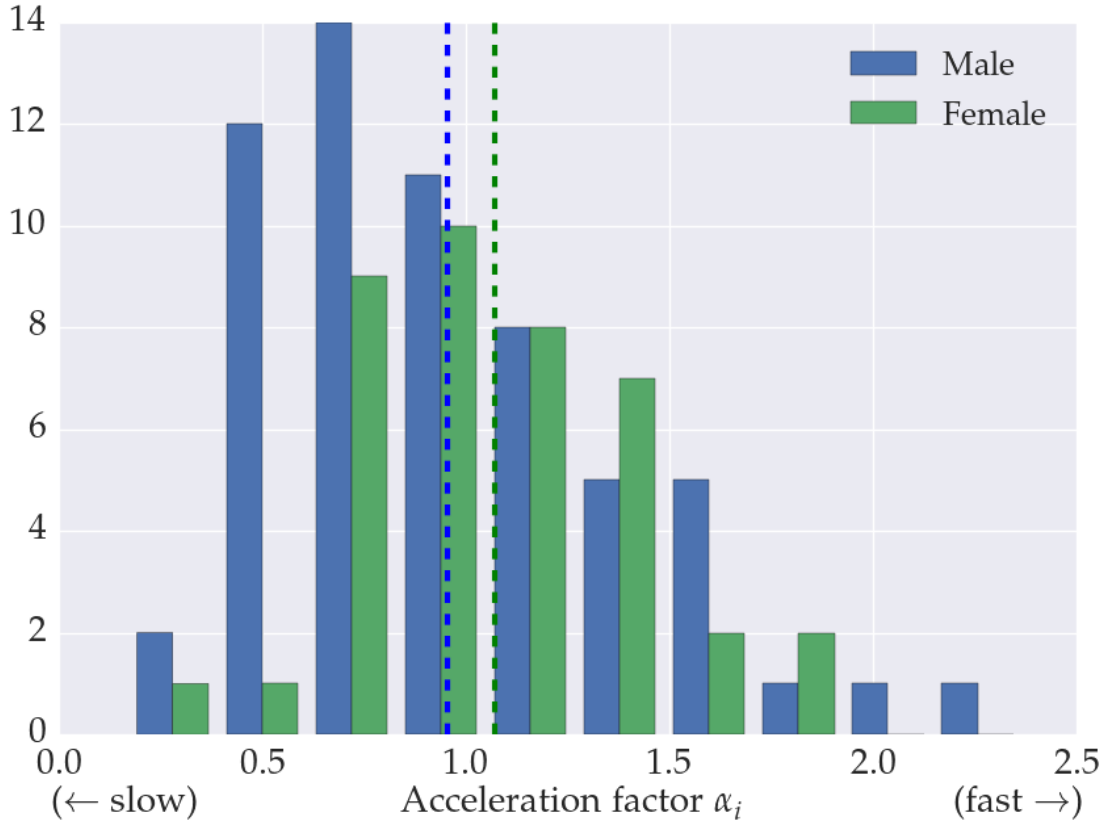
[Koval et al.MICCAI'17, Frontiers'17 (in revision)]

Digital Models of Disease Progression

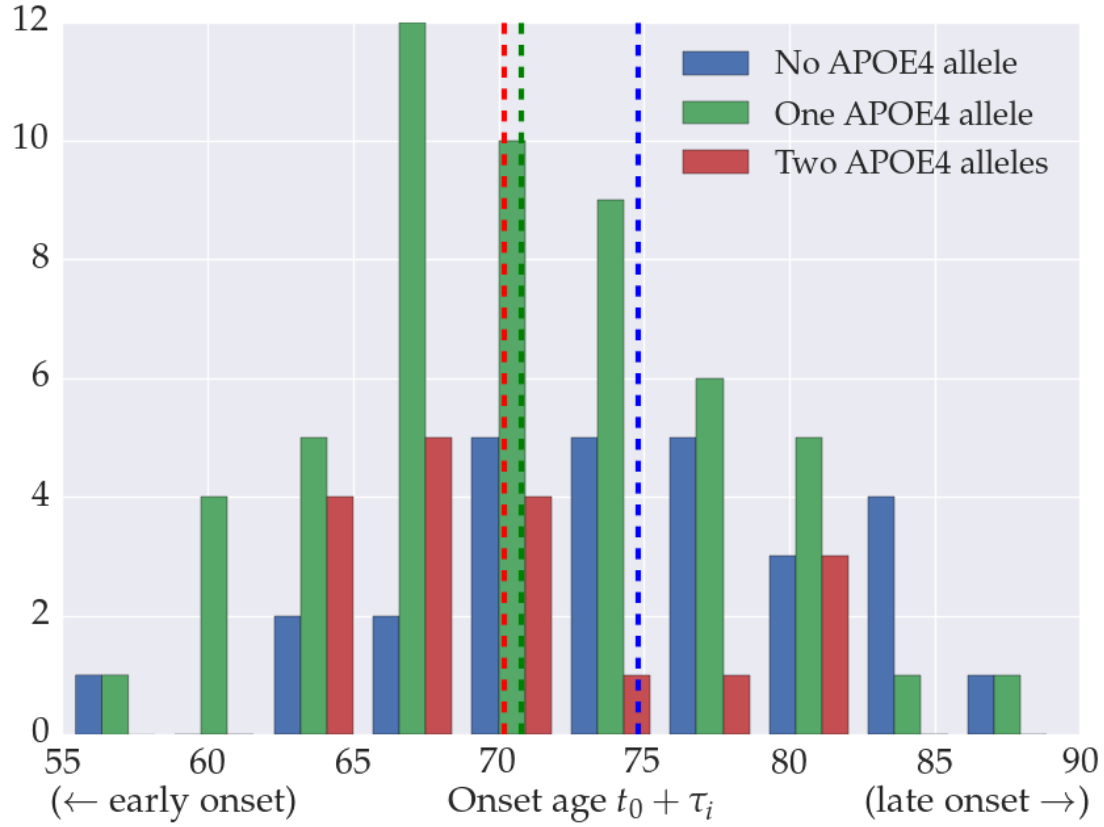


[Bône et al'17]

Dynamical model of hippocampal atrophy in Alzheimer's Disease



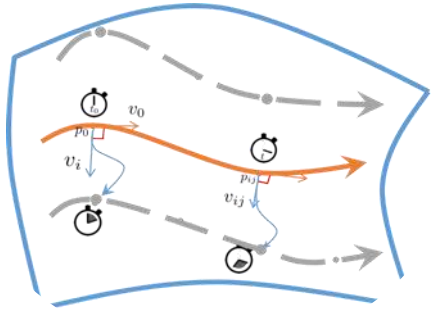
Female have a faster hippocampal atrophy than male ($p<0.05$)



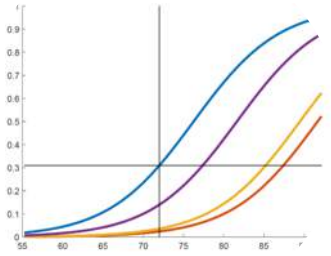
APOE carriers have an earlier hippocampal atrophy than non-carriers ($p<0.05$)

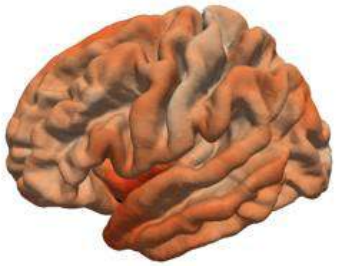
[Bône et al'17]

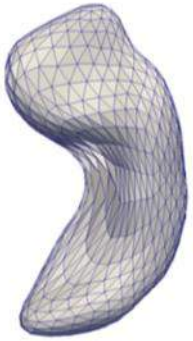
- A generic Bayesian mixed-effect model for longitudinal data
  - Concept of time-warp for temporal variablily
  - Condition for spatial-temporal identifiability
  - Individual effects allow personalization and prediction



- Personalized models of
  - cognitive decline
  - cortical atrophy
  - hippocampal atrophy
  - → association with dynamical parameters only?







- Evaluate the predictive power of the model
  - Model Personalization to assess predictive power
  - Computer-aided diagnosis and prognosis systems