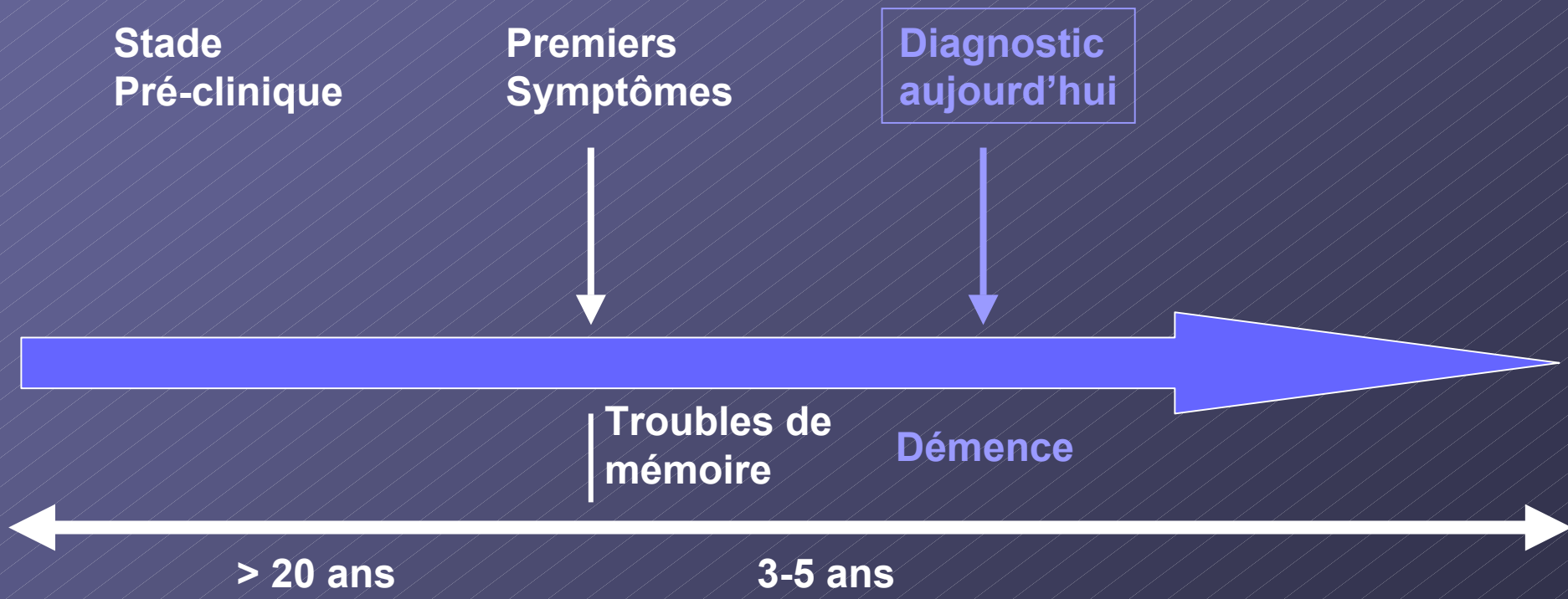
GIENS 2009

Table Ronde N°3

Maladie d'Alzheimer: biomarqueurs, nouveaux schémas d'étude, phases précoces

Zeina Antoun, Olivier Arnaud, Claude Bidaut-Mazel, Olivier Blin,
Régis Bordet, Antoine Coquerel, Jean-François Dartigues, Catherine Deguines,
Philippe Derambure, Patrice Dosquet, Bruno Dubois
Jean-Pierre Duffet, Jean-Marie Goehrs, Sylvia Goni, Philippe Gustovic,
Marie Lang et son bébé, Marie-Laure Laroche, Antoine Pariente,
Florence Pasquier, Jean-Jacques Pere, Odile Regnier, Franck Semah,
Philippe Truffinet, Laura Vernoux,

Maladie d'Alzheimer = une évolution insidieuse…



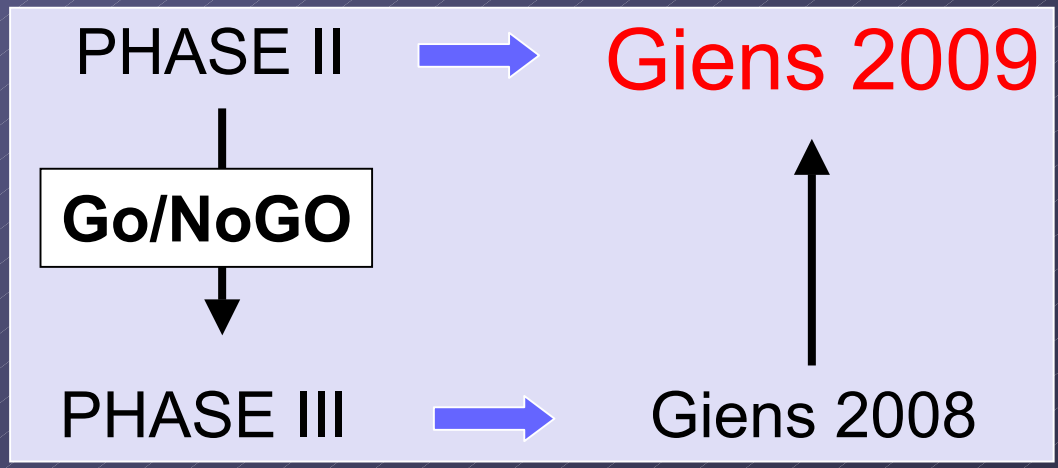
Disease-modifying drug :

- modification du cours évolutif
- effet sur la cascade physiopathologique

Un diagnostic plus précoce pourrait permettre de mieux étudier l'efficacité des traitements « Disease-modifying »

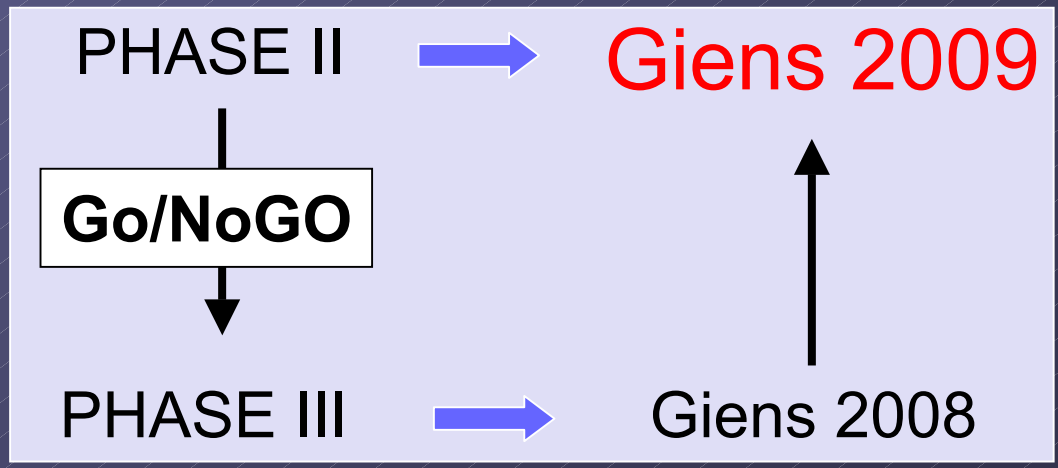
Giens 2008 ➔ Giens 2009
Le Bilan des Industriels

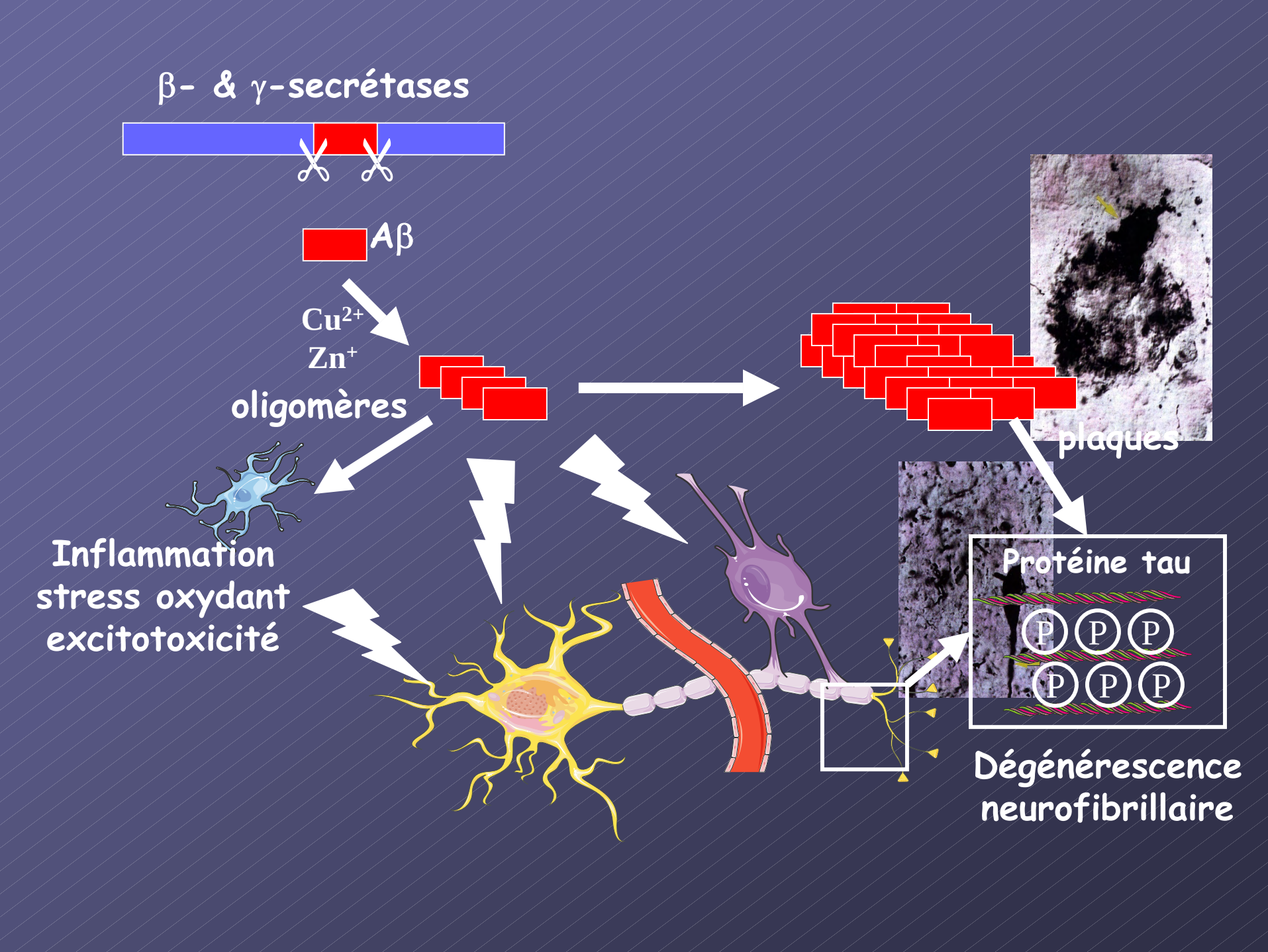
- Les nombreux échecs en termes de développement (tarenflurbil, tramiprosate, AN1792, semagestat, solanezumab, lithium, rosiglitazone, xaliproden)
- Un lourd investissement…



Giens 2008 → Giens 2009
Les attentes des Industriels

- Redéfinir la place du biomarqueur dans la stratégie de développement
- Pour les phases précoces du développement
- Proposer un algorithme de choix du ou des biomarqueurs à chaque étape du protocole




β- & γ-secrétases
Aβ
Cu2+
Zn+
oligomères
plaques
Inflammation
stress oxydant
excitotoxicité
Protéine tau
P
Dégénérescence
neurofibrillaire

Strategies étiopathogéniques

« Mécanismes non spécifiques »

- Excitotoxicité
- Flux ioniques
- Homéostasie Redox
- Neuro-inflammation
- Voies de transduction du signal
- Apoptose

- Facteurs neurotrophiques
- Neurogénèse

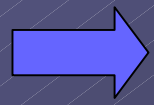
« Mécanismes Spécifiques »

Anomalies protéiques

- β-amyloïdogénèse
- Hyperphosphorylation Tau

Types de Biomarqueurs :

- biologiques
- génétiques
- imagerie
- neurophysiologique
- cognitif

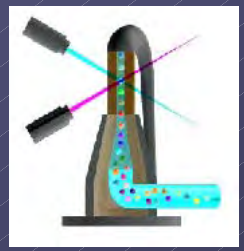


Types d'utilisation :

- diagnostic
- enrichissement
- stratification
- évaluation
- mécanisme
- sécurité d'emploi

Detection of AD: CSF biomarker signature in MCI → AD converters

	Threshold value	MCI → AD conversion time	
		12-24 months (n=37)	Baseline-12 months (n=32)
tTau	93 pg/ml	59.4%	55.0%
Aβ 1-42	192 pg/ml	90.6%	89.9%
pTau 181P	23 pg/ml	81.2%	84.0%
tTau/Aβ 1-42	0.39	84.4%	88.4%
pTau/Aβ 1-42	0.10	90.6%	92.8%



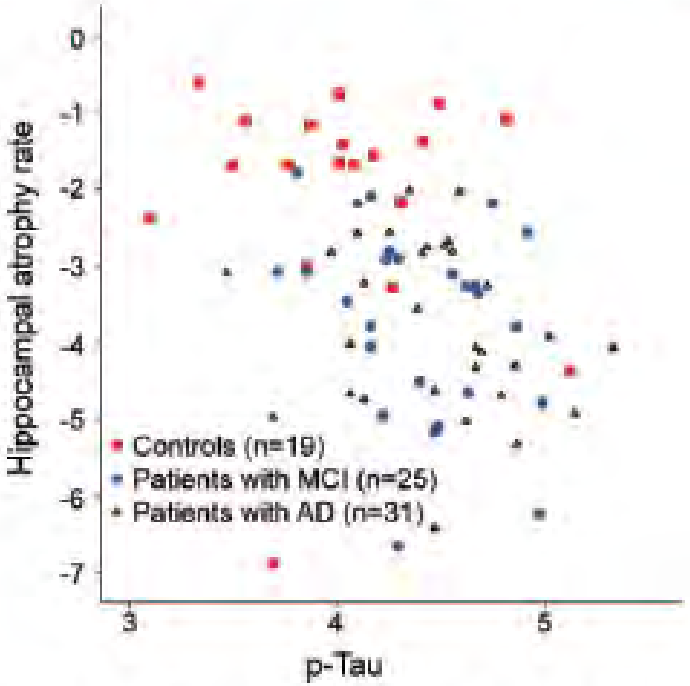
xMap® technology

Method: INNOBIA AlzBio3

ADNI Data Presentations Meeting · April 26, 2009 · 8:00 AM – 5:00PM,
ADNI Biomarker Core Report, Shaw L, Trojanowski JQ

Henneman et al, Neurology, 2009 VUmc Amsterdam

Figure p-Tau vs hippocampal atrophy rate



Scatterplot of hippocampal atrophy rate (percentage/year) by log-transformed (natural logarithm) levels of tau phosphorylated at threonine 181 (p-tau). MCI = mild cognitive impairment; AD = Alzheimer disease.

Baseline CSF p-tau levels independently predict progression of hippocampal atrophy in Alzheimer disease

ABSTRACT

Objective: To investigate whether baseline CSF biomarkers are associated with hippocampal atrophy rate as a measure of disease progression in patients with Alzheimer disease (AD), patients with mild cognitive impairment (MCI), and controls, controlling for baseline neuropsychological and MRI findings.

Methods: We assessed data from 31 patients with AD, 25 patients with MCI, and 19 controls (mean age 68 ± 8 years; 39 [52%] female) who visited our memory clinic and had received serial MRI scanning (scan interval 1.7 ± 0.7 years). At baseline, CSF biomarkers (amyloid β 1-42, tau, and tau phosphorylated at threonine 181 [p-tau]) were obtained, as well as neuropsychological data. Baseline MRI scans were assessed using visual rating scales for medial temporal lobe atrophy (MTA), global cortical atrophy, and white matter hyperintensities. Hippocampal atrophy rates were estimated using regional nonlinear "fluid" registration of follow-up scan to baseline scan.

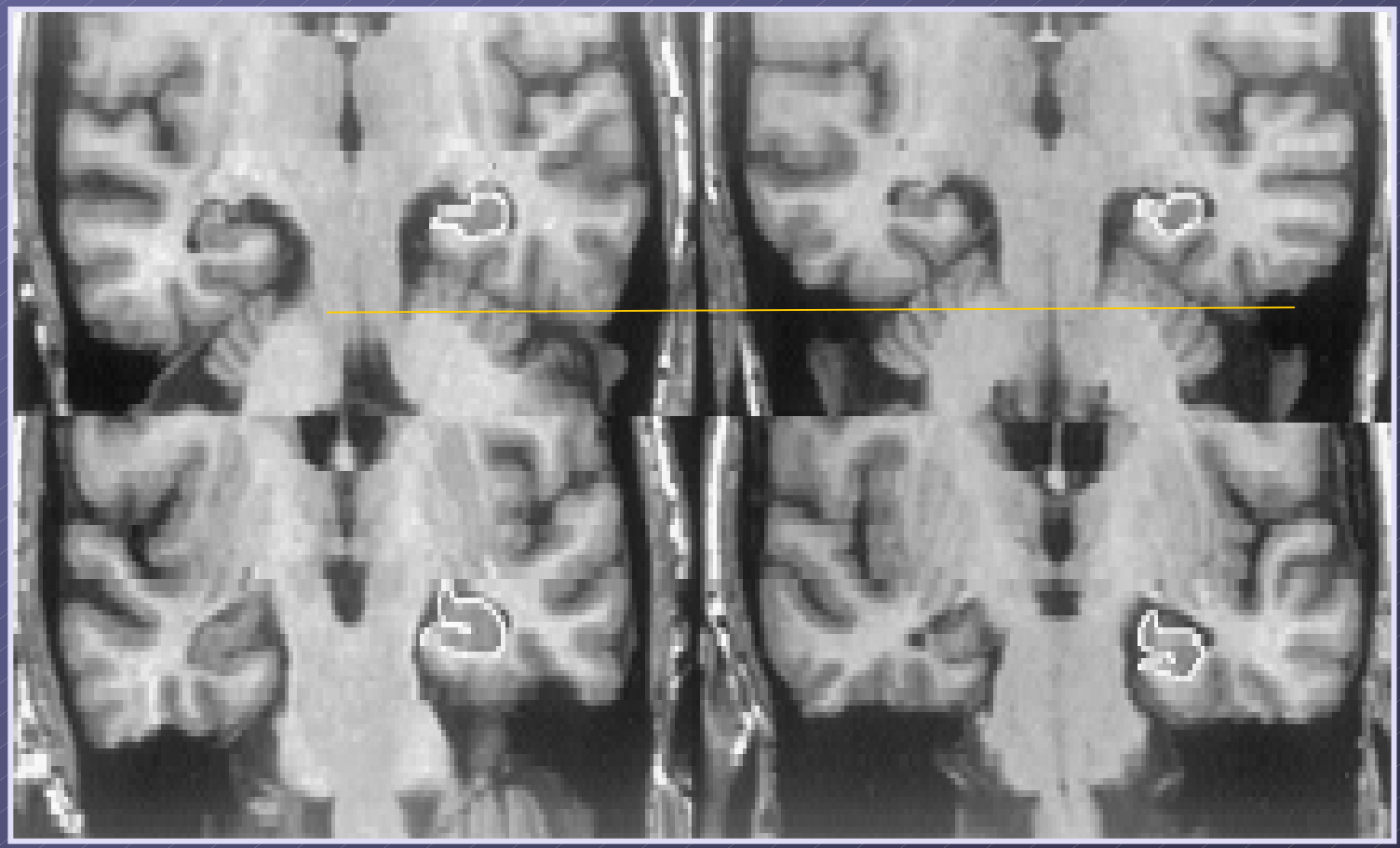
Results: Stepwise multiple linear regression, adjusted for age and sex, showed that increased CSF p-tau levels (β [standard error]: −0.79 [0.35]) at baseline was independently associated with higher subsequent hippocampal atrophy rates ($p < 0.05$), together with poorer memory performance (0.09 [0.04]) and more severe MTA (−0.60 [0.21]). The association of memory function with hippocampal atrophy rate was explained by the link with diagnosis, because it disappeared from the model after we additionally corrected for diagnosis.

Conclusions: Baseline CSF levels of tau phosphorylated at threonine 181 are independently associated with subsequent disease progression, as reflected by hippocampal atrophy rate. This effect is independent of baseline neuropsychological and MRI predictors. Our results imply that predicting disease progression can best be achieved by combining information from different modalities.

Neurology® 2009;73:935-940

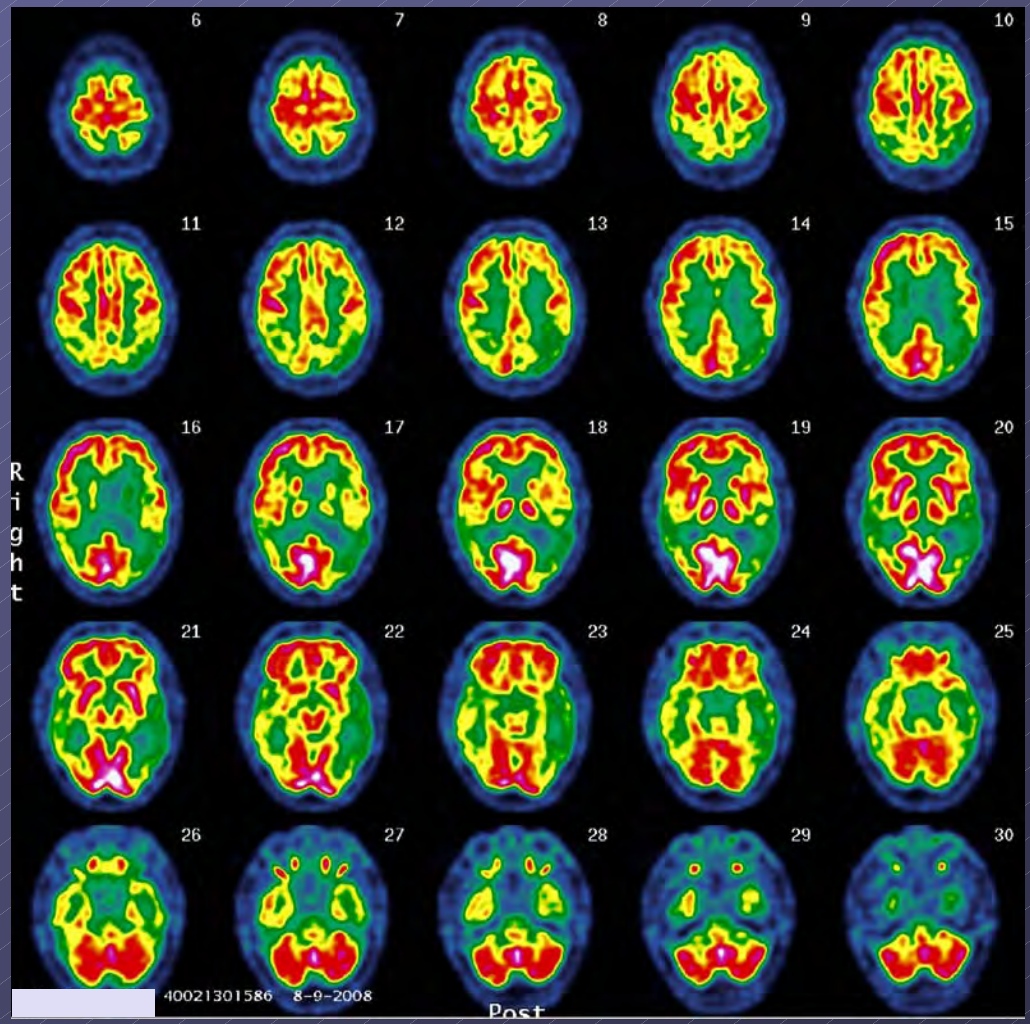
Volume hippocampique en IRM

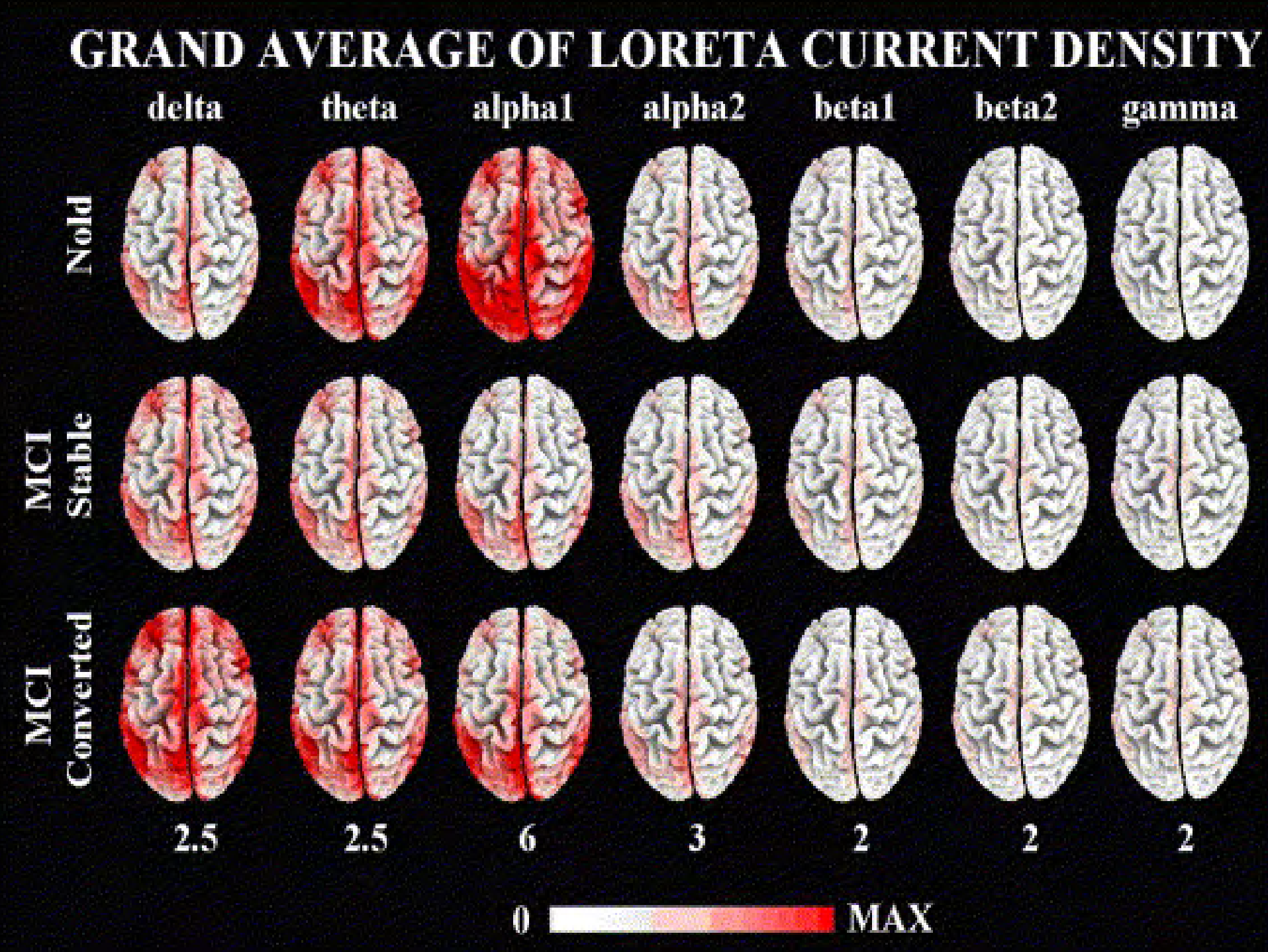
MCI: Nonconverter **MCI: Converter**



Biomarqueurs utilisé dans une étude prospective en cours

[^{18}F]-FDG-TEP
PHRC 2009 «ISALP»




GRAND AVERAGE OF LORETA CURRENT DENSITY
delta
theta
alpha1
alpha2
beta1
beta2
gamma
Nold
MCI Stable
MCI Converted
2.5
2.5
6
3
2
2
2
0
MAX

Type Biomarqueur		Dgx	Enrichis-sement population	Stratifi-cation	Evaluation de l'effet	Mécanisme d'action
Bio-LCR	Aβ (40+42)	+++	?	+	+	+++
	TotalTau	++	?	-	+	++
	Phos Tau	++	++	+	+	+++
	IATI*	+++	?	?	+	+++
	BACE 1	+		-	?	+++
Bio-Plasma	Aβ (40+42)	-	+	-	+	++
Bio-Autres	Inflam-matoires	-	-	-	-	+
	Vascu-laires	-	-	-	-	+
Génétiques	Statut ApoE	-	+++	+++	-	+
	Kits et sets de gènes	-	-	-	-	+

Type Biomarqueur		Dgx	Enrichis-sement population	Stratifi-cation	Evaluation de l'effet	Mécanisme d'action
Imagerie	PET (charge amyloïde)	+++	+++	++	++	+++
	FDG-PET	++	++	++	+++	+
	fIRM	-	-	-	+	-
	SPECT	+	-	-	+	-
	IRM structurelle	++	+	++	+++ (+ tolérance)	-
Neurophy-siologie	EEG/ Potentiels évoqués	-	+	+	?	-
Cognitif	Sd amnésique hippocam-pique	+++	+++	+	++	-

Biomarqueur cognitif :
Syndrome amnésique hippocampique

Biomarqueur diagnostique	Biomarqueur d'évaluation	Biomarqueur du mécanisme (molécule dépendant)
1- IRM+LCR	1- FDG	1- LCR+plasma
2- IRM+imagerie amyloïde	2- IRMv	2- imagerie amyloïde
3-IRM+FDG		

Phase II :

- critère de jugement
  - ✓ principal : FDG
  - ✓ secondaire : ADAS-cog
- durée : 1 an

FDG	+	-	+	-
ADAS	-	+	+	-
Go/NoGo	Go	Go	Go	NoGo

Un concept d'étude pouvant s'intégrer aux guidelines de l'EMEA eux-mêmes en évolution

CHMP Guidelines on Medicinal Products for the Treatment of Alzheimer's Disease and Other Dementias, July 2008

« A true disease modifying effect cannot be established conclusively based on clinical outcome data alone, such a clinical effect must be accompanied by strong supportive evidence from a biomarker program »

« *If* in a first step delay in the natural course of progression of the disease based on *clinical* signs and symptoms of the dementing condition can be established, this may be acceptable for a *limited claim*, eg delay of disability.

If these results are supported by a *convincing package of biological and/or neuroimaging data*, eg showing delay in the progression of brain atrophy, a *full claim for disease modification could be considered.* »

Autres propositions de la table ronde

- Promouvoir des essais académiques évaluant des stratégies combinées de traitement utilisant le même concept d'étude

- Beaucoup de travaux en cours (ADNI-2, Pharmacog, PHRC) faisant suggérer de laisser un délai avant l'organisation d'une nouvelle table ronde

- Nécessité de « laisser du temps au temps »
- car comme dit le vieil adage « trop pressé n'a plus de jus »