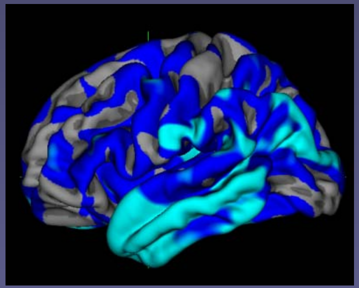
AddNeuroMed Update
WWADNI : July 2011



Andy Simmons

for the AddNeuroMed Group

European Federation of Pharmaceutical Industries and Associations, Pharmidex Pharmaceutical Services, Capsant Neurotechnologies LTD, Università degli Studi di Perugia, Aristotle University of Thessaloniki, Roskilde University, AstraZeneca, Kungl Tekniska Högskolan, Karolinska Institutet, King's College, London, Centre Hospitalier Universitaire de Toulouse, GlaxoSmithKline Research & Development Ltd, Proteome Sciences PLC, University College London, University of Southampton, Hunter Fleming Limited, BioWisdom, Cerebricon Ltd.

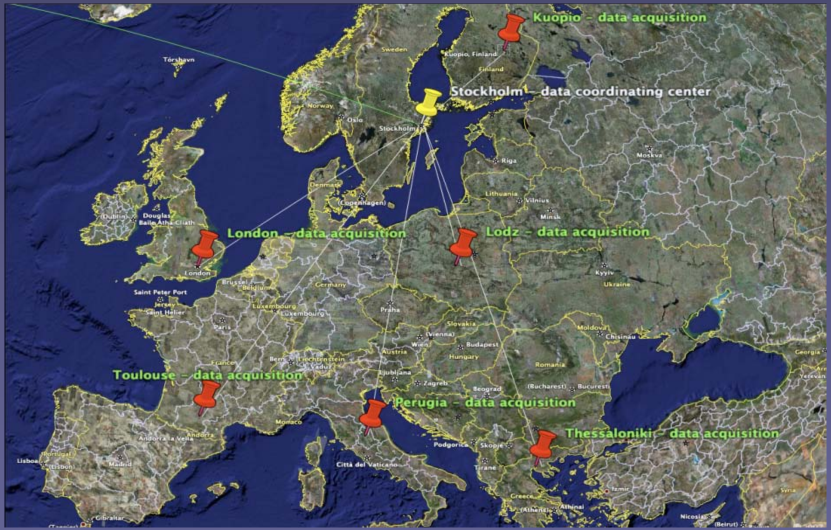
Institute of Psychiatry and South London and Maudsley Neuroimaging

Overview

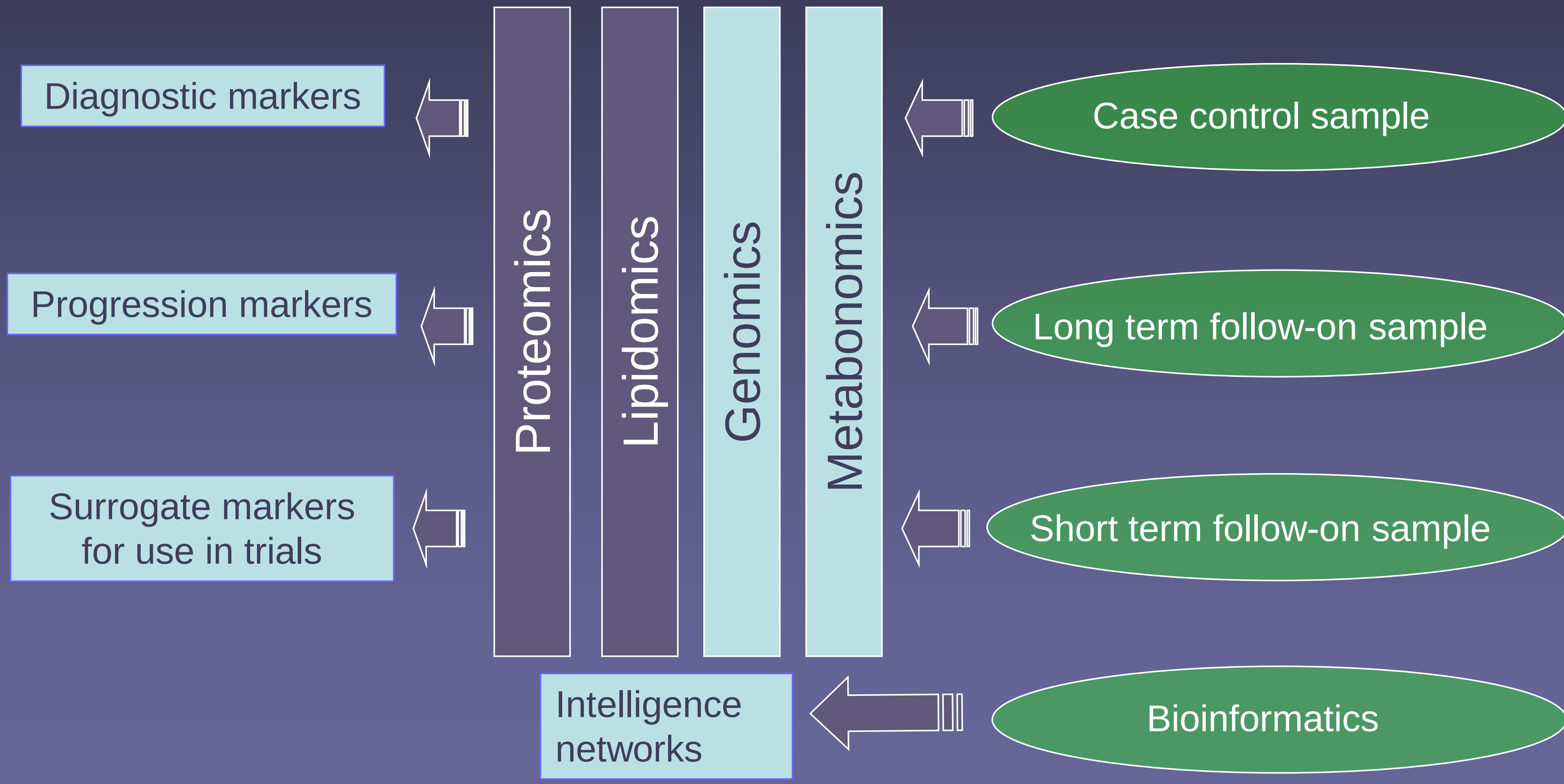
- Study design and recruitment
- Imaging update
- Blood plasma proteomics update
- Combining imaging and omics

AddNeuroMed Study

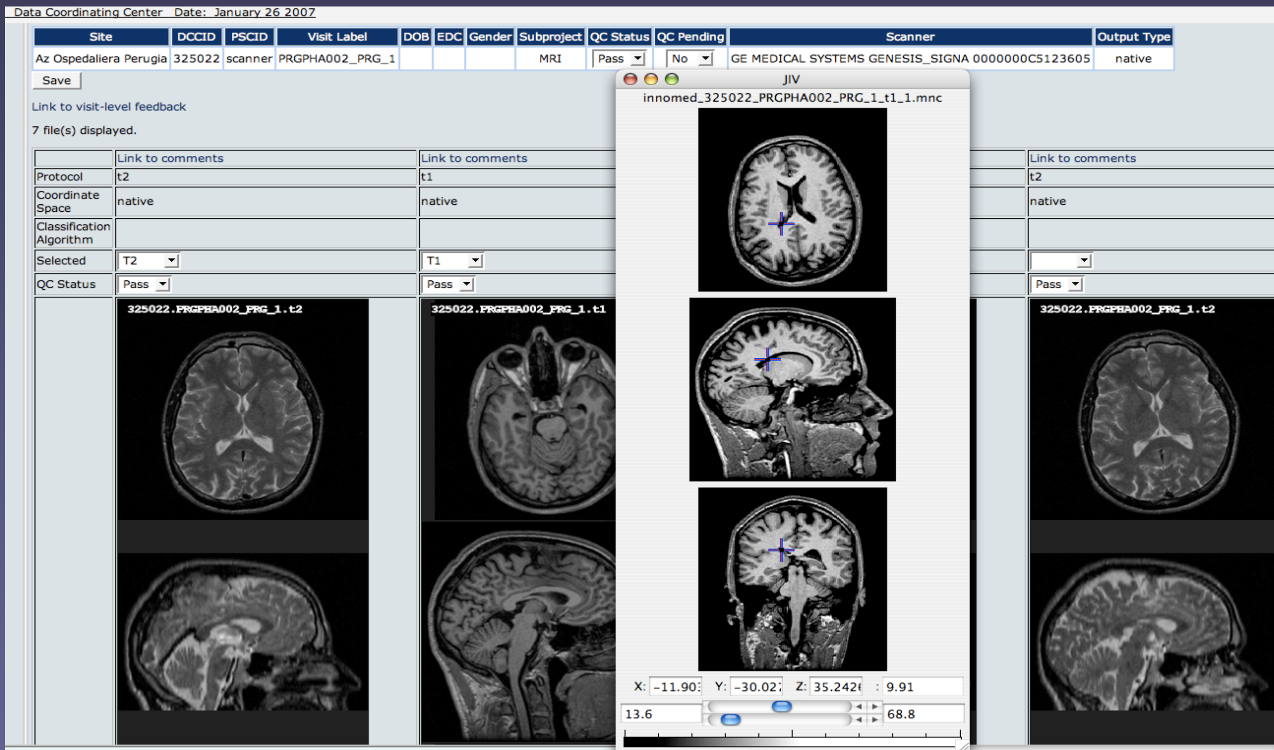
- Six European sites
- 385 subjects with MRI (of total > 700 subjects)
  - 133 AD, 134 MCI, 118 Controls
- All subjects
  - Clinical / cognitive assessments
  - Blood / plasma / RNA
  - 1.5 T structural MRI
- Imaging time points
  - Baseline, 3 months, 1 year, 2 year, 3 year

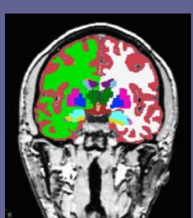


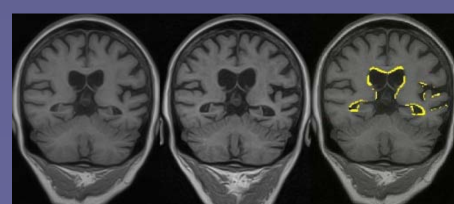
Human studies



Imaging-omics-clinical database







Institute of Psychiatry and South London and Maudsley Neuroimaging

385 AddNeuroMed
- 0, 3, 12m

821 ADNI
- 0, 6, 12, 18, 24, 36m

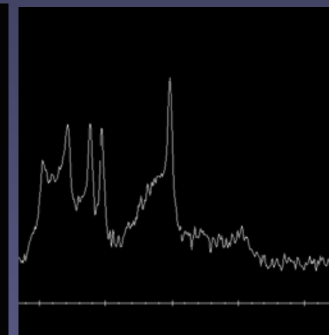
200 London cohort
- 0, 12, 24, 36m

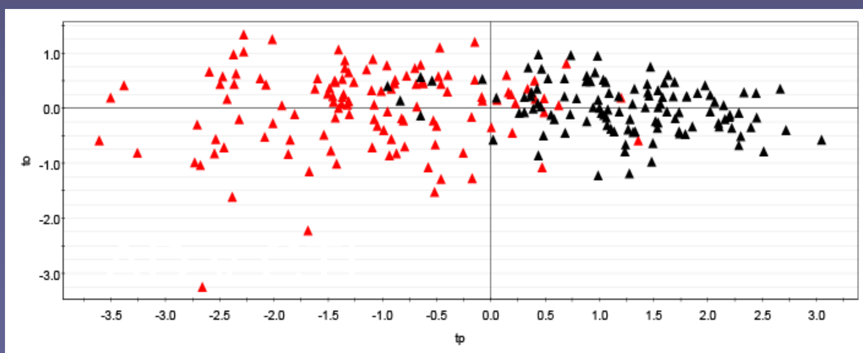
130 Memory clinic
- 0m

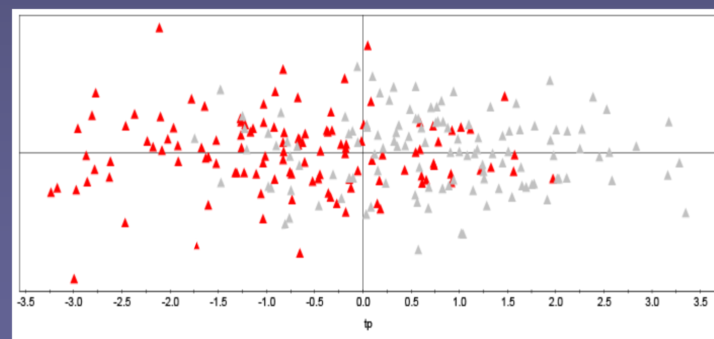
2000 Young controls

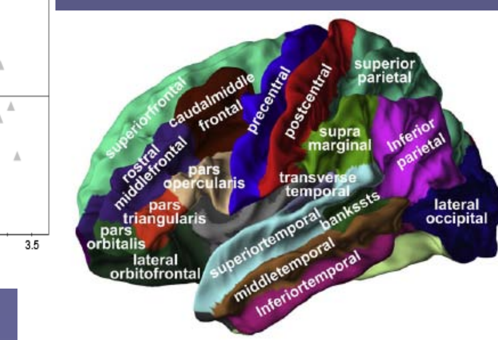
Multivariate Analysis

- Orthogonal partial least squares (OPLS)
- Regional cortical thickness measures
- Regional MRI volumes
- Total of 75 MRI measures









Institute of Psychiatry and South London and Maudsley Neuroimaging

Multivariate Analysis

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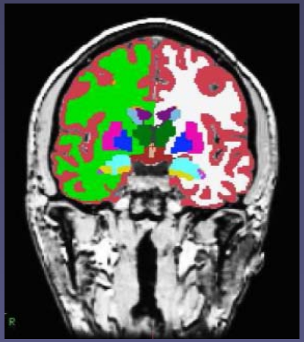

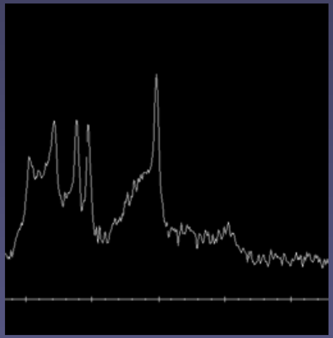

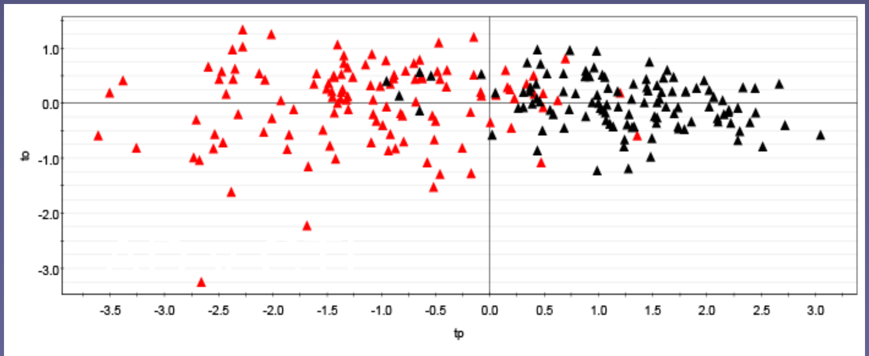

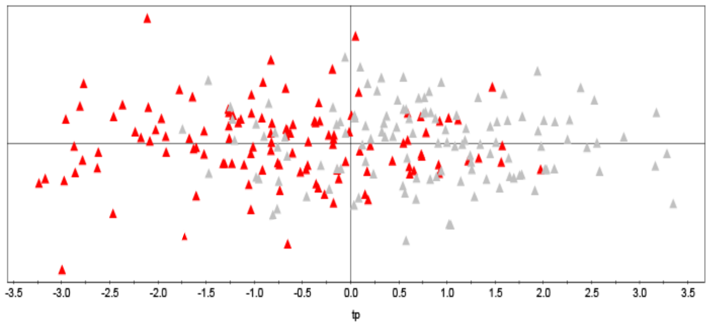

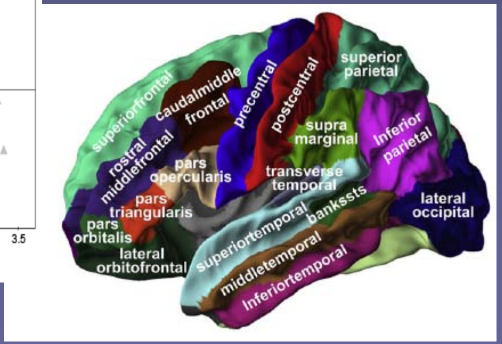

Contents lists available at ScienceDirect

NeuroImage

journal homepage: www.elsevier.com/locate/ynimg

ELSEVIER

Multivariate analysis of MRI data for Alzheimer's disease, mild cognitive impairment and healthy controls

Eric Westman [a,*], Andrew Simmons [b,c], Yi Zhang [a], J-Sebastian Muehlboeck [d], Catherine Tunnard [b], Yawu Liu [f], Louis Collins [e], Alan Evans [e], Patrizia Mecocci [g], Bruno Vellas [h], Magda Tsolaki [i], Iwona Kłoszewska [j], Hilkka Soininen [f], Simon Lovestone [b,c], Christian Spenger [d], Lars-Olof Wahlund [a] for the AddNeuroMed consortium

Combining MRI and MRS to Distinguish Between Alzheimer's Disease and Healthy Controls

Eric Westman[a,*], Lars-Olof Wahlund[a], Catherine Foy[b], Michaella Poppe[b], Allison Cooper[b], Declan Murphy[b], Christian Spenger[d], Simon Lovestone[b] and Andrew Simmons[b,c]

Visual Assessment Scales and Multivariate Analysis

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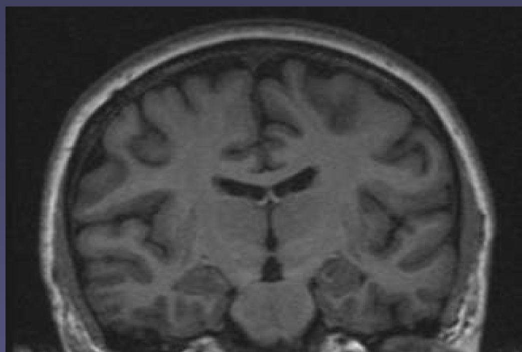

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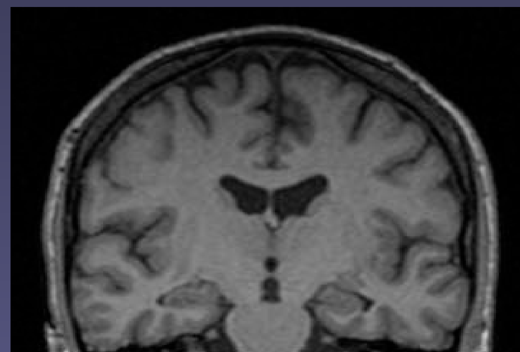

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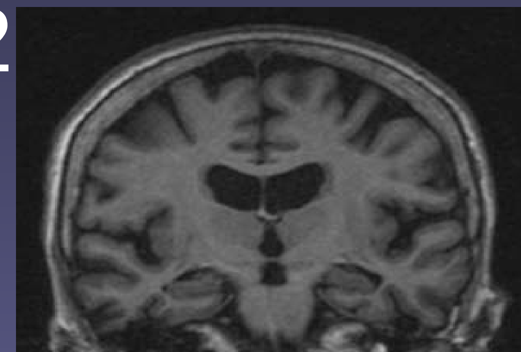

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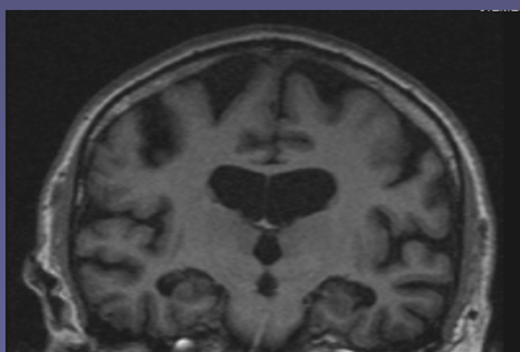

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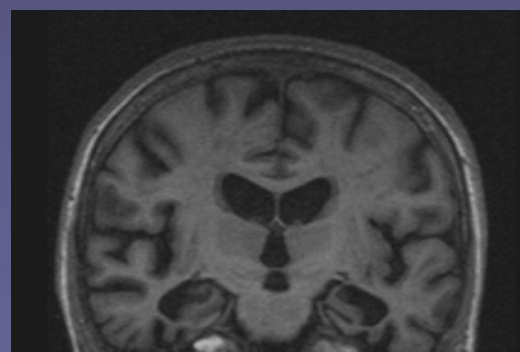


Visual assessment of hippocampus proper, dentate gyrus, subiculum, parahippocampal gyrus, entorhinal cortex and surrounding CSF spaces such as temporal horns and choroid fissure.

MTA 0-4 Increasing atrophy

Westman et al
PlosOne 2011

Multivariate Analysis Comparison - ADNI and AddNeuroMed

Table 2
Sensitivity/specificity and likelihood ratio for the different cohort models

	Sensitivity	Specificity
AddNeuroMed (cross-validation)	79.0	90.0
ADNI (cross-validation)	86.9	86.7
Combined (cross-validation)	83.4	87.8

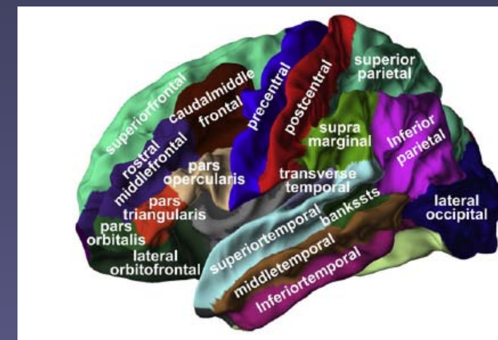


Table 3
MCI predictions subjects characteristics

	Number	AD-like	CTL-like
AddNeuroMed MCI converters	22	14 (64%)	8 (36%)
ADNI MCI converters	62	46 (74%)	16 (26%)

Westman et al, Neuroimage 2011, on line

MCI Conversion & Hippocampal Shape

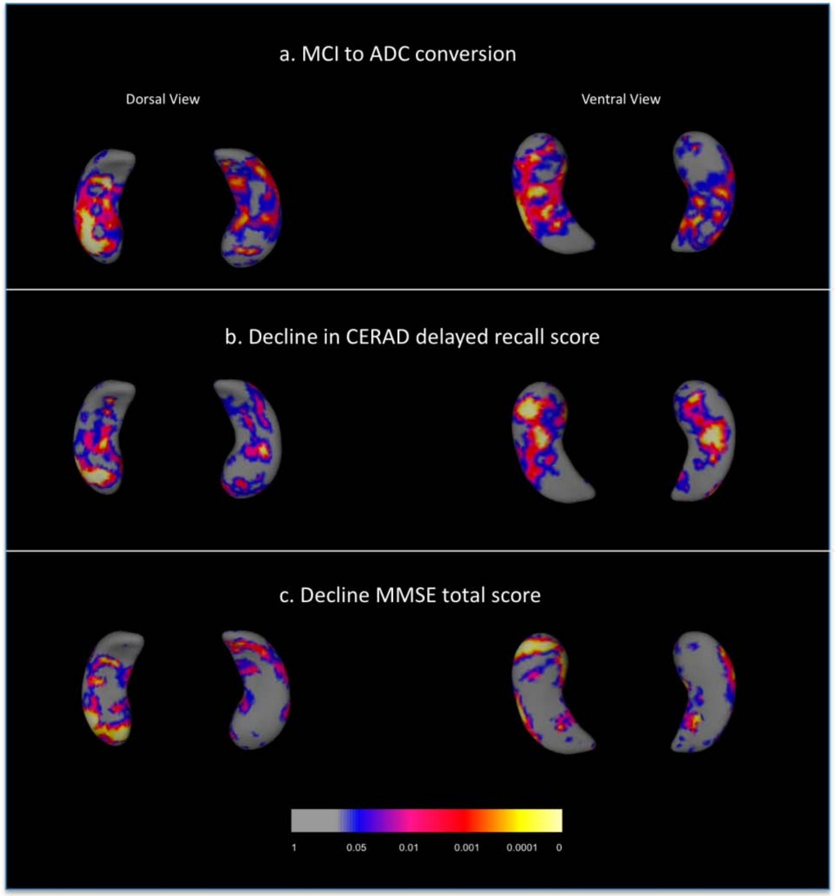


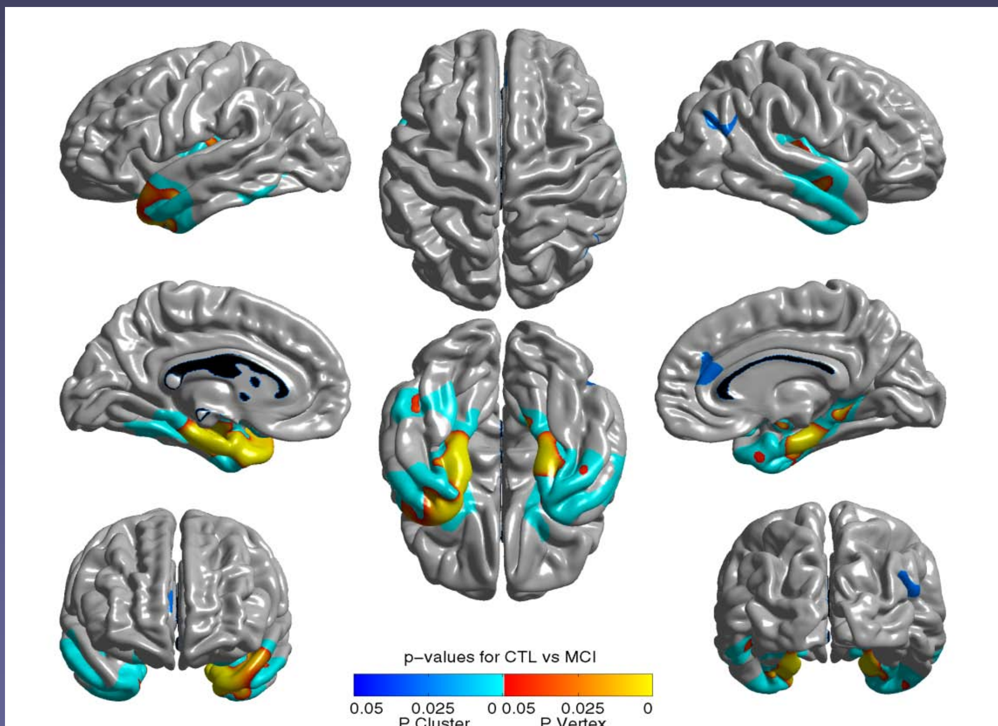
Figure 1.

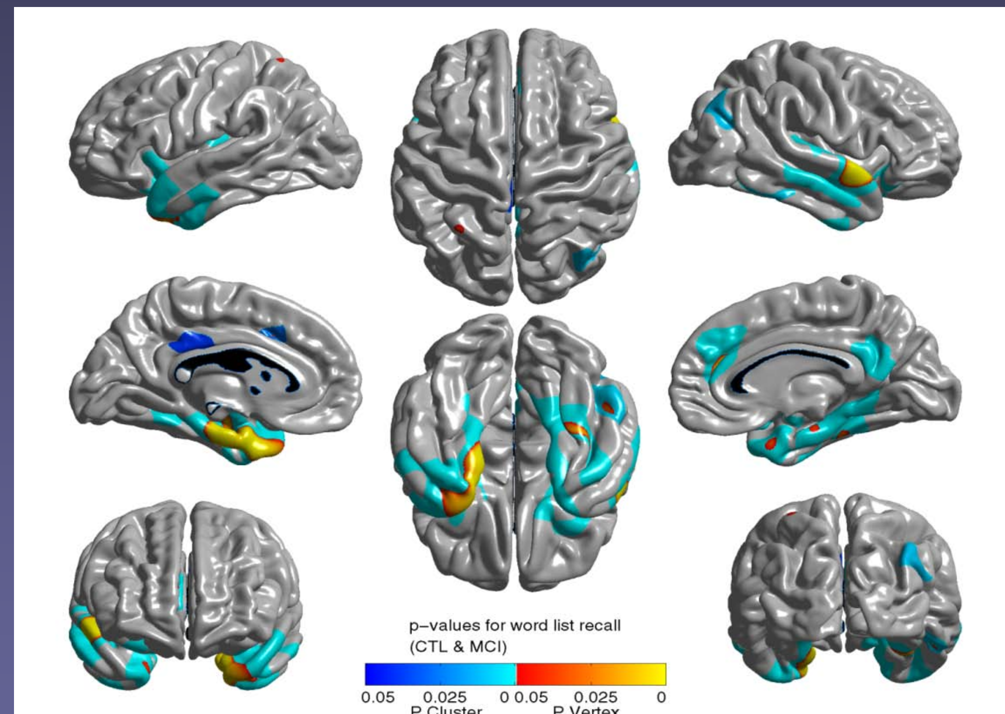
	Shape	Volume
True Positive	17	16
True Negative	65	60
False Positive	16	21
False Negative	5	6
Sensitivity %	77	73
Specificity, %	80	74
PPV, %	52	43
NPV, %	93	91
Accuracy, %	80	74
Model significance	<0.0001	0.0008

Costafreda et al, Neuroimage 2011

Cortical Thickness and Neuropsych

Paajanen et al, submitted



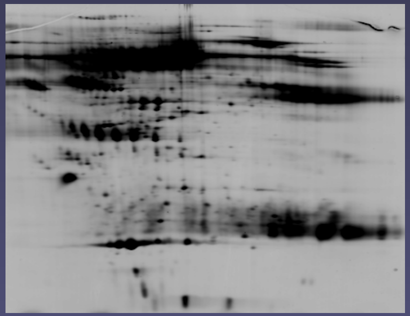


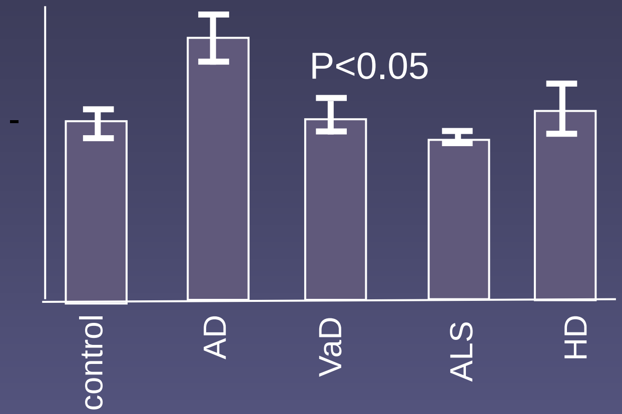
- CTl v MCI cortical thickness differences
- Correlation of word list recall with cortical thickness in CTL+MCI group

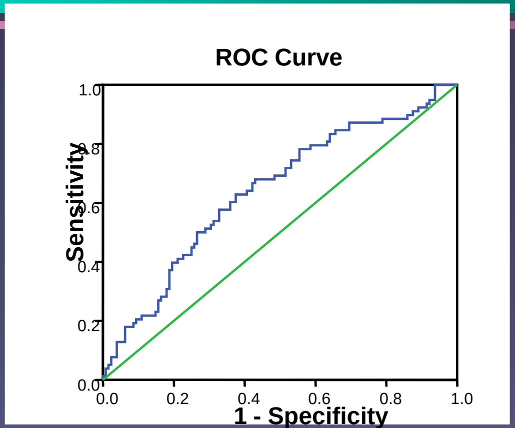
AddNeuroMed Proteomics Studies

- Approach I *'diagnostics discovery'*
  - » Case - control study
  - » 2DGE & LC-MS/MS; immuno-validation
- Approach II *'severity markers discovery'*
  - » imaging correlation study
  - » Gel and MS based methods; immuno-validation
- Approach III *'progression markers discovery'*
  - » Longitudinal study; serial time points
  - » Proteomics and genomics

Approach I : Diagnostics Discovery







- Exploratory multivariate analyses and class prediction
  - Parametric statistics, test and replication sets
  - Sensitivity 56% ;Specificity 80%
- 15 spots prioritised by FDR and identified by mass spectrometry
  - Fold change 1.5 – 13.8; P<0.04 to <0.0005
  - Two most significant ; CFH and α2M

Hye et al (2006) Proteome-based plasma biomarkers for Alzheimer's disease. Brain 129: 3042-3050.

Approach 1 - CFH and α2M correlate with MRS Markers of Disease

CFH

r= 0.34
p 0.03

AD+MCI+Control

α2M

r= 0.36
p 0.02

Thambisetty et al (2008) Proteome-based identification of plasma proteins associated with hippocampal metabolism in early Alzheimer's disease. J Neurol 255: 1712-1720.

Approach 2: Plasma Biomarker Panel Correlation with Imaging Markers

- 2DGE correlation with hippocampal volume
- Multivariate analyses (partial least squares)
- Cross validation analysis of model prediction of ‘large’ / ‘small’ hippocampi
- N~250

R=0.2

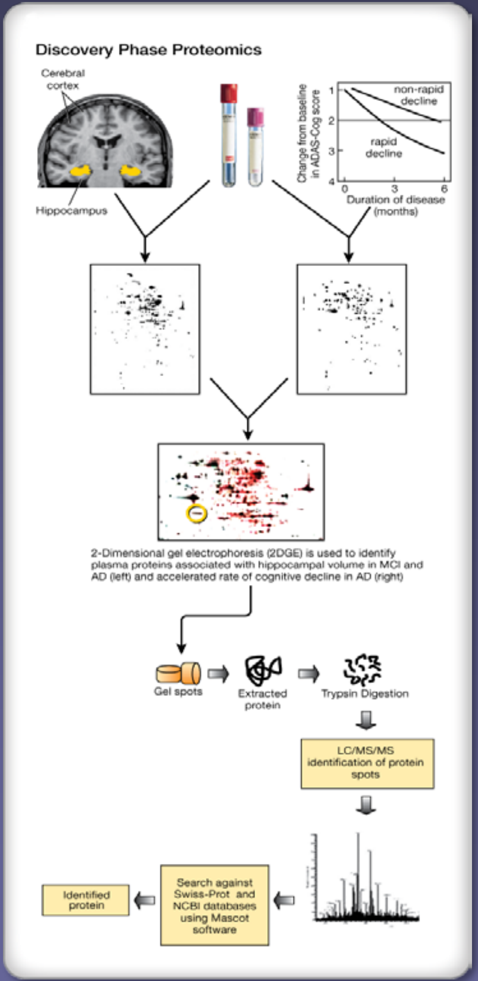
P=0.02

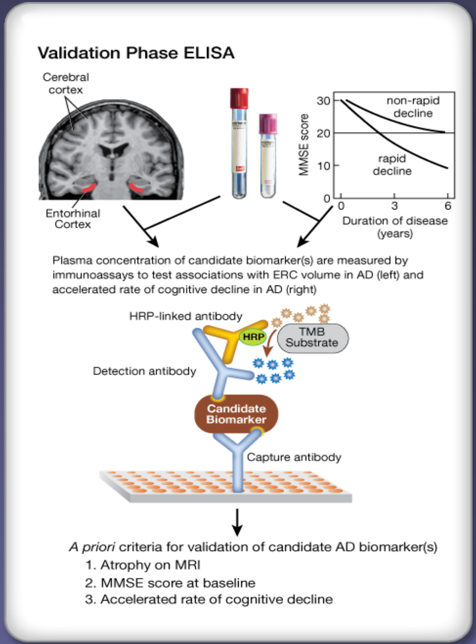
R=0.26

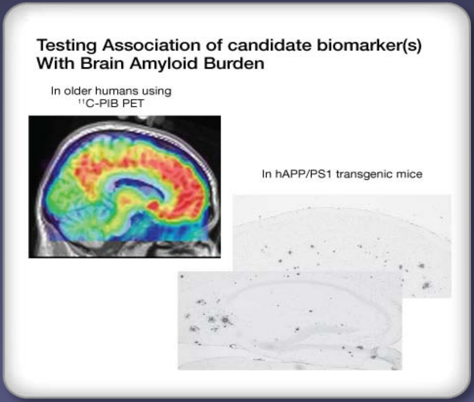
P=0.003

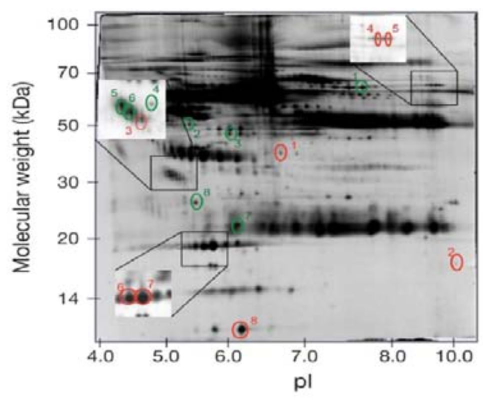
- PLS model accounts for 30% of atrophy variance
- Protein x gene interaction

Clusterin Association with Severity, Pathology and Progression in AD









Protein ID (green)	Accession Number
1 Complement C3	P01024
2 γ Fibrinogen	P02679
3 Serum albumin	P02768
4 Complement factor-I	P05156
5 Clusterin	**P10909**
6 Clusterin	**P10909**
7 Serum amyloid-P	P02743
8 α-1-microglbulin	P02760

Protein ID (red)	Accession Number
1 Complement C4a	P0C0L4
2 Complement component C8	P07360
3 Clusterin	**P10909**
4 Complement C4a	P0C0L4
5 Complement C4a	P0C0L4
6 Apolipoprotein-AI	P02647
7 Apolipoprotein-AI	P02647
8 Transthyretin	P02766

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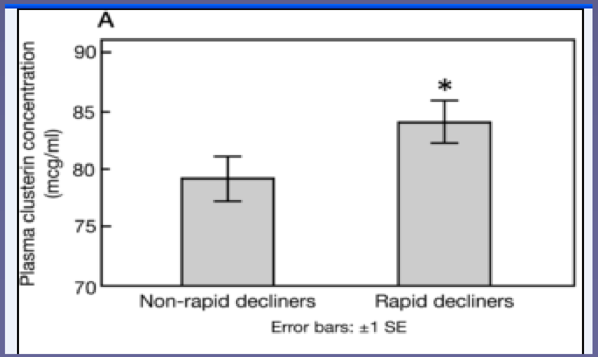
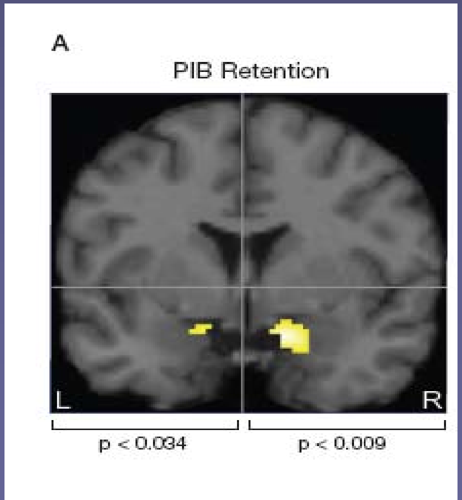
Plasma Clusterin is Associated with

- Volume of ERC in AD (N=113, R=-0.31, p=0.001)
- MMSE at Baseline in AD+MCI (N=576, R=-0.22, p<0.001)
- Rapid Clinical Progression ie decline >2 MMSE points per year (N=344, p=0.0007)



- Higher antecedent Clusterin concentration is associated with greater PIB retention in the Entorhinal Cortex



Approach 3 :In silico Identification of a Potential Marker for AD

- Sofia^{TM} (BioWisdom), used to generate an Intelligence Network, from public domain sources, for the discovery of AD biomarkers

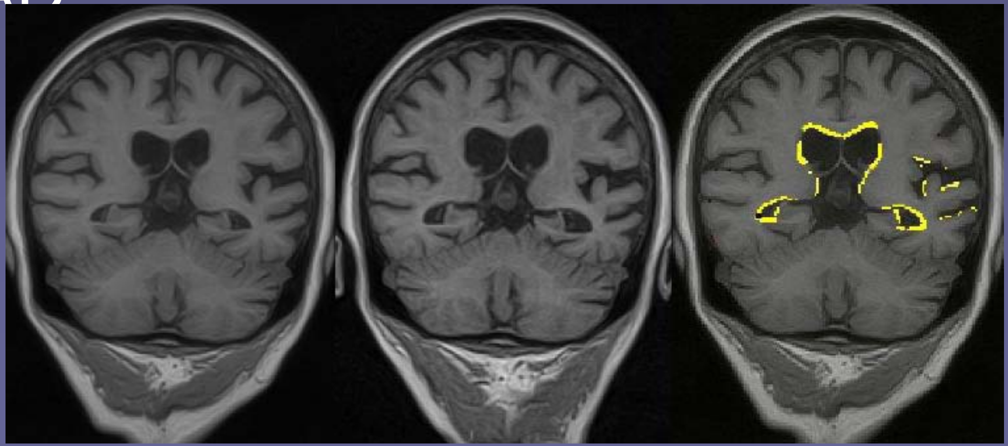
- The intelligence consisted of assertions describing proteins expressed ***and*** upregulated in AD tissue, and proteins involved in AD pathology, for e.g.

  - » AD hippocampus ***has increased*** Nerve Growth Factor
  - » AD ***is associated with*** Cerebral Atrophy

biowisdom

Candidate AD Progression Biomarker

- No significant association between baseline measure and MMSE (controlling for age)
- Highly significant correlation between baseline measure and rate of brain atrophy in AD
  - » Spearman r = -0.79, p=0.001



AddNeuroMed–ADNI GWAS Imaging

- Data acquisition used the ADNI acquisition protocol on > sixty 1.5 T MR systems
- WBV, ventricular volume, hippocampal volume, entorhinal cortical volume and thickness selected compared to SNP data (1121 subjects)
- 1118 subjects run on Illumina 610 Quadcore array.
- Exclusion of related individuals, individuals with SNP missingness >2%, MAF < 5%, SNP gender different to clinical gender.
- Generalised linear model run in PLINK.

$$Y = \beta 0 + \beta 1ADD + \beta 2\ DS + \beta 3ADD*DS + \varepsilon$$

Y is the quantitative trait (QT), DS is the disease status, ADD is a term for the additive effects of minor allele dosage on the QT in the model, ADD*DS is a term assessing the interactive effects of diagnosis and the model, β1... β3 the regression coefficients of the model terms and ε, the random error.

AddNeuroMed-ADNI GWAS Imaging

- One SNP with a disease-specific effect associated with entorhinal cortical volume in an intron of the *ZNF292* gene
    - rs1925690; p-value = 2.6×10^{-8}; corrected p-value for equivalent number of independent quantitative traits = 7.7×10^{-8}
- One intergenic SNP, flanking the *ARPP-21* gene, with an overall effect on entorhinal cortical thickness
    - rs11129640; p-value = 5.6×10^{-8}; corrected p-value=1.7×10^{-7}
- Gene-wide scoring highlighted *PICALM* as the most significant gene associated with entorhinal cortical thickness
    - p-value = 6.7×10^{-6}

Combining Imaging and Omics

- Gene expression and imaging
- Vitamin E forms and imaging
- Proteomics and imaging
- Genetics and imaging

Combinatorial Markers of Mild Cognitive Impairment Conversion to Alzheimer's Disease - Cytokines and MRI Measures Together Predict Disease Progression

Simon J. Furney[a], Deborah Kronenberg[b], Andrew Simmons[a], Andreas Güntert[a], Richard J. Dobson[a], Petroula Proitsi[a], Lars Olof Wahlund[c], Iwona Kloszewska[d], Patrizia Mecocci[e], Hilkka Soininen[f], Magda Tsolaki[g], Bruno Vellas[h], Christian Spenger[i] and Simon Lovestone[a,*]

Magnetic Resonance Imaging and Magnetic Resonance Spectroscopy for Detection of Early Alzheimer's Disease

Eric Westman[a,*], Lars-Olof Wahlund[a], Catherine Foy[b], Michaela Poppe[b], Allison Cooper[b], Declan Murphy[b], Christian Spenger[d], Simon Lovestone[b] and Andrew Simmons[b,c]

Next Steps

- RNA analysis studies
  - » Differential expression analysis of disease status
  - » Genetic / network analysis of peripheral blood expression
- Proteomic studies
- Vitamin E forms
- Combined imaging-omics MCI conversion studies
- AddNeuroMed 2

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Celine Caillaud
Pierre Payoux

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