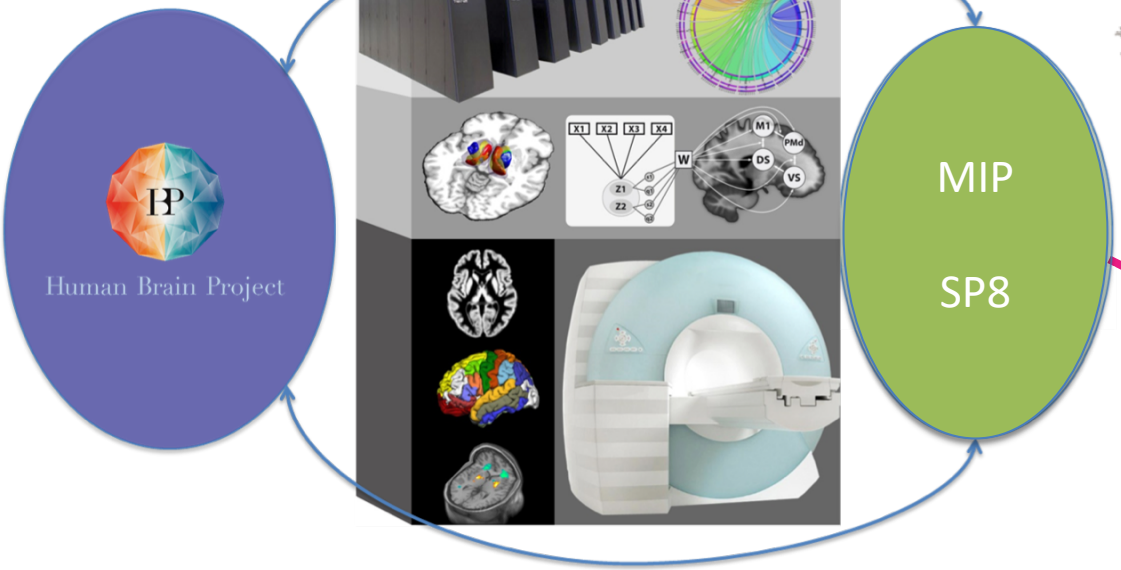
MIRACUM SYMPOSIUM – ERLANGEN 2018

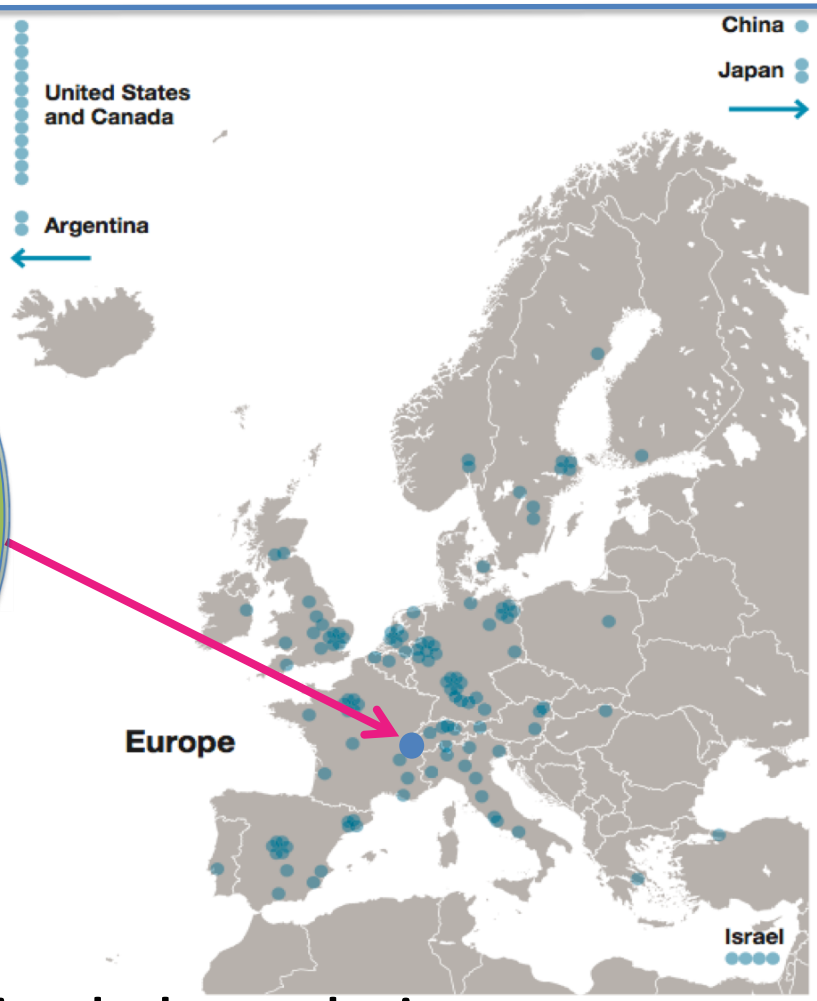
THE ROLE OF NEUROIMAGING IN THE MEDICAL COMPONENT OF THE HBP

Richard Frackowiak
EPFL/CHUV/UCL/ENS

HUMAN BRAIN PROJECT

MEDICAL INFORMATICS PLATFORM





EU funded Collaborative project for understanding the human brain

25 Countries

400 Researchers

2013

10 Years

Richard FRACKOWIAK

THE MEDICAL COMPONENT OF THE HBP

Alzheimer's disease: **20 per cent** beyond the age of 80; dependent within 3-5 years of onset.

Depression: the second most common condition in the world (WHO): **6 per cent** of the population in the Western world.

Cerebral vascular accidents: first cause of adult motor disability. **75 per cent** suffer residual disability.

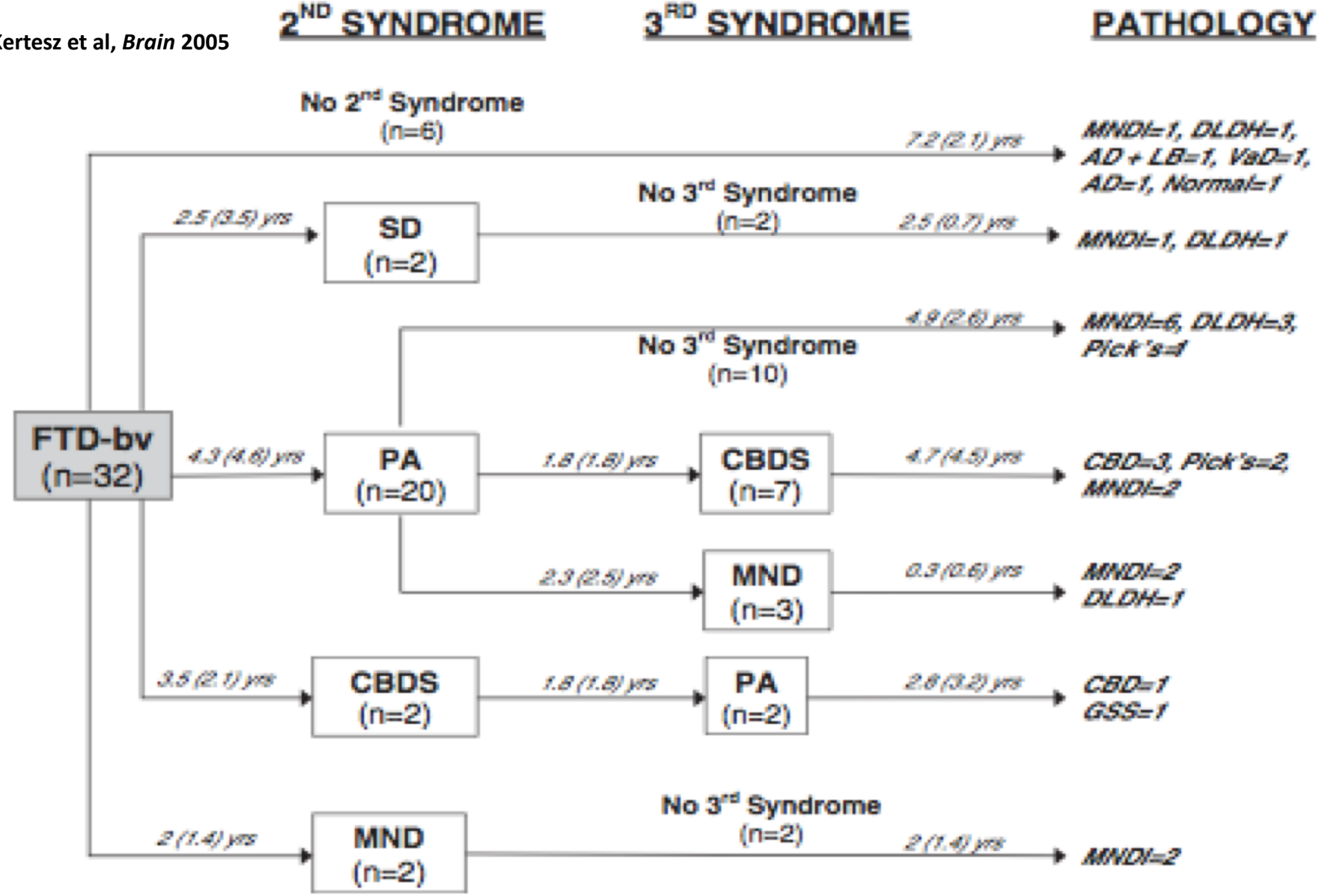
Parkinson's disease: second cause of motor disability. Affects **0.2 per cent** of the population.

Multiple sclerosis: mainly young people with dependency in **30 per cent**.

Epilepsy: 50 million people globally of which almost **50 per cent** are aged < 10 years**.** Social and familial repercussions are **lifelong.**

HAVE WE REACHED A DEAD END CLINICALLY?

Kertesz et al, *Brain* 2005



HYPOTHESIS 1

Phenomenology alone

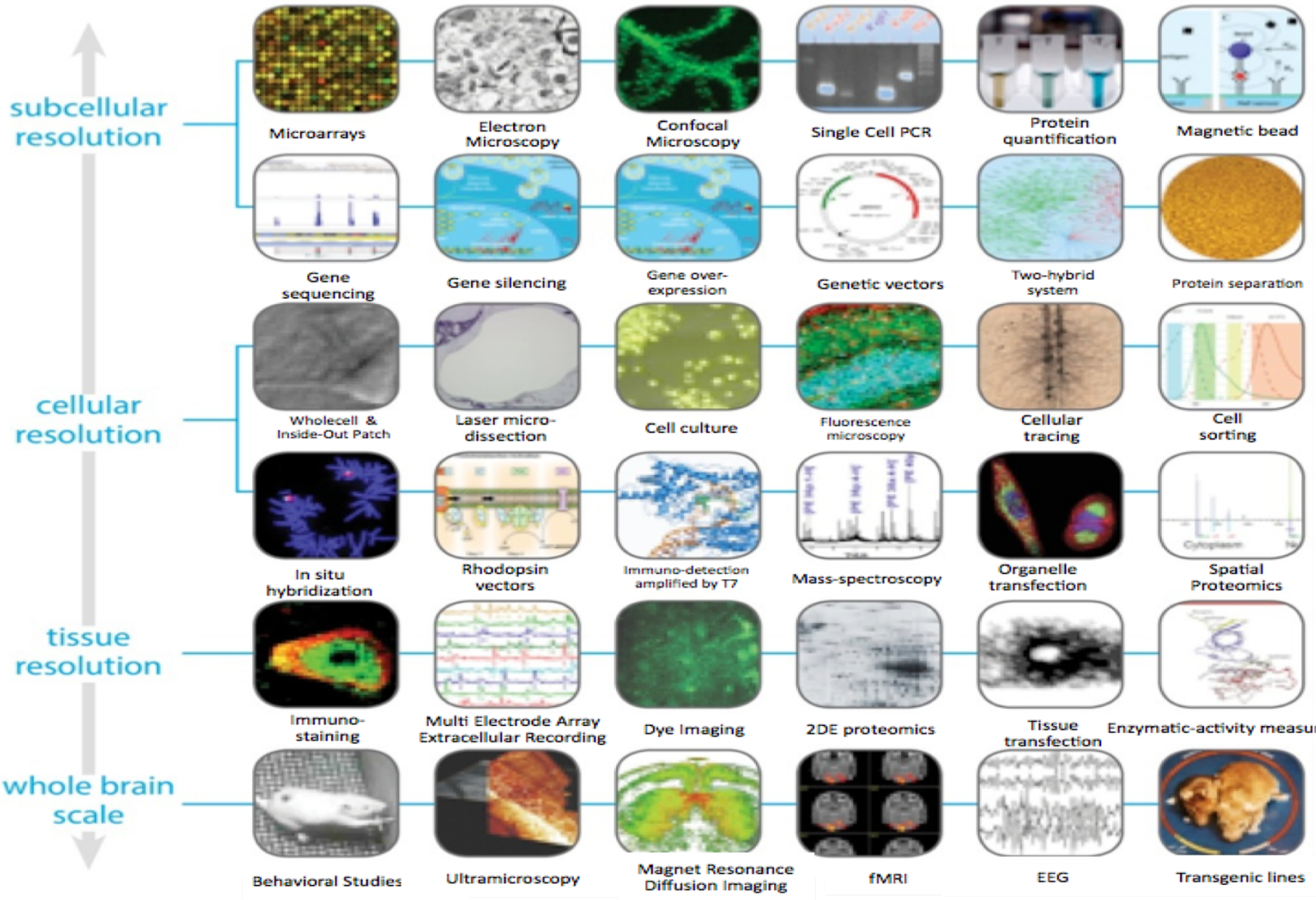
is insufficiently discriminative

for diagnosis and prognosis

Genotyping does not

replace descriptive medicine

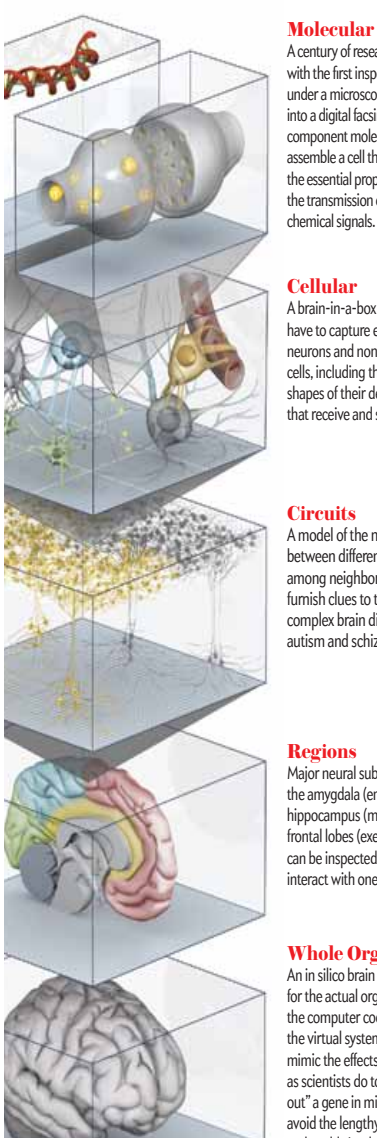
NEUROSCIENCE DATA ACROSS SCALES

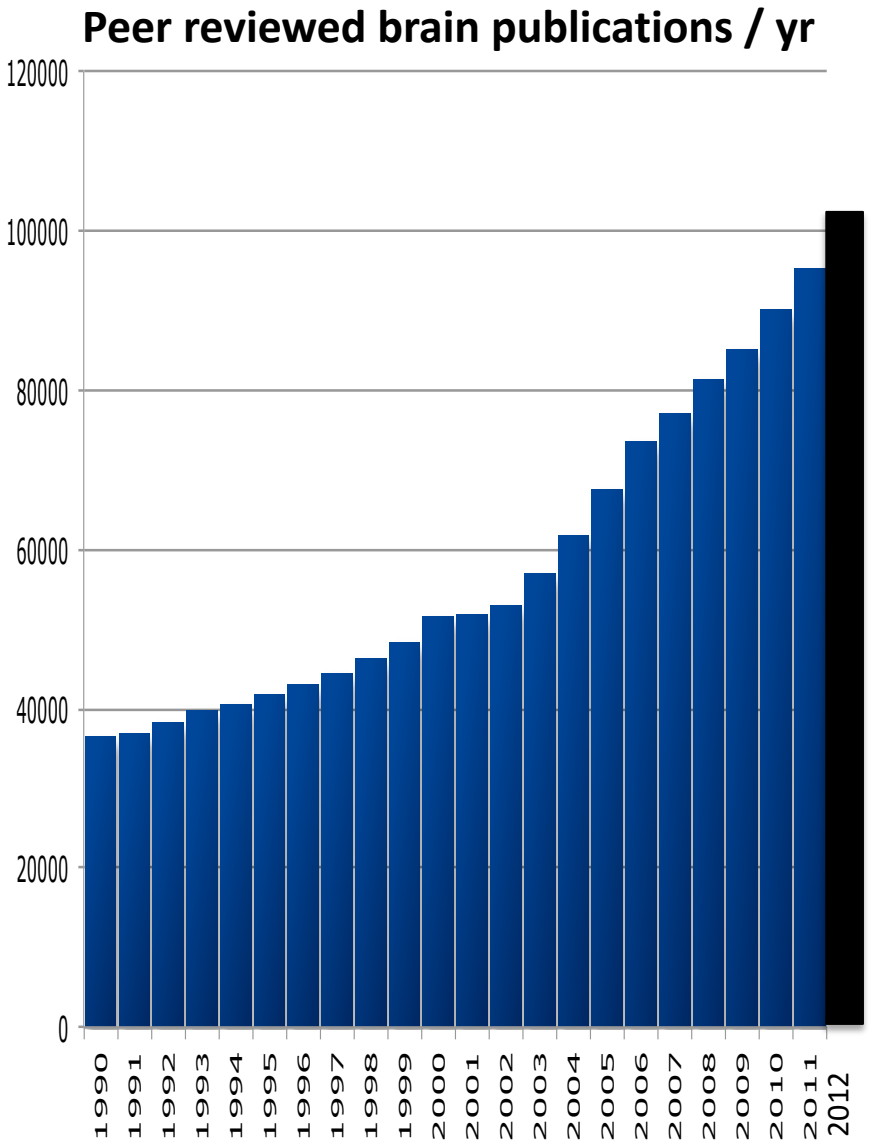


INTEGRATING DATA

- Exponential growth
- Fragmented knowledge
- Societal benefits
- Economic health burden

- Data integration plan
- Data curation plan
- Linking across levels
- Knowledge transfer between species
- Beyond classical disease definitions

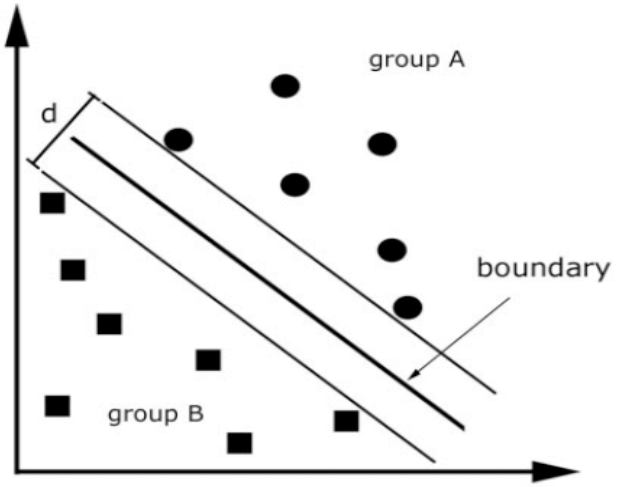




INFORMATICS CLASSIFY PATTERNS

	CORRECT	SENSITIVITY	SPECIFICITY
AD & CONTROLS **CLINICAL**	81%	61%	93%
AD 1 & CONTROLS **PATHOLOGY**	95%	95%	95%
AD 2 & CONTROLS **PATHOLOGY**	93%	100%	86%
AD 1 & CONTROLS vs AD 2 **PATHOLOGY**	96%	100%	93%

BINARY CLASSIFICATION BY SUPPORT VECTOR MACHINE



INFORMATICS REFINE DIAGNOSIS

	CLINICAL AD	CLINICAL NC	
PATHOL AD+	15	3	**18**
PATHOL AD-	5	17	**22**
	20	**20**	

ADNI DATABASE

Accuracy 100%

Sensitivity 73%

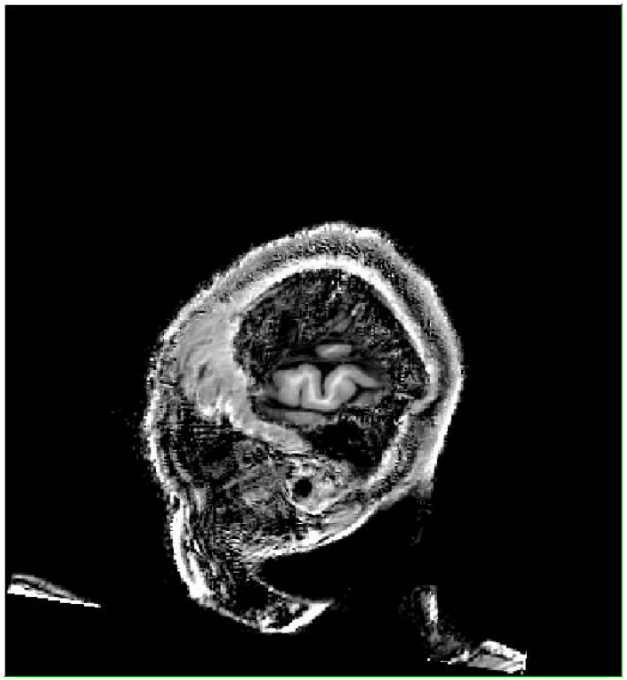
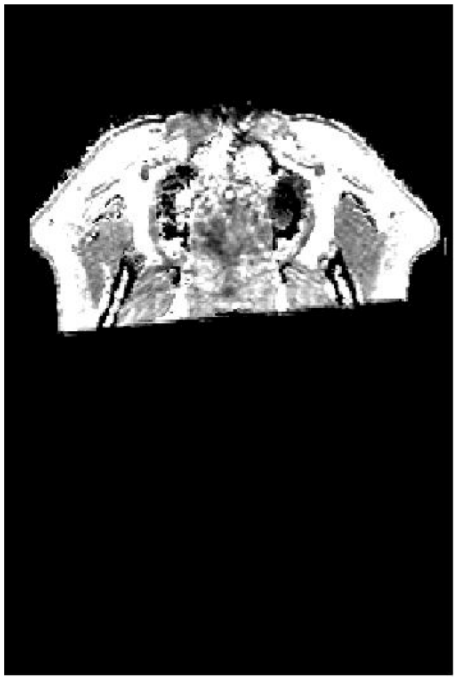
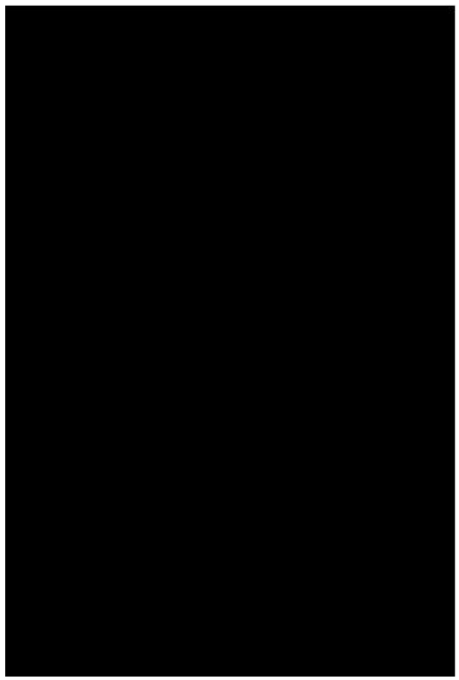
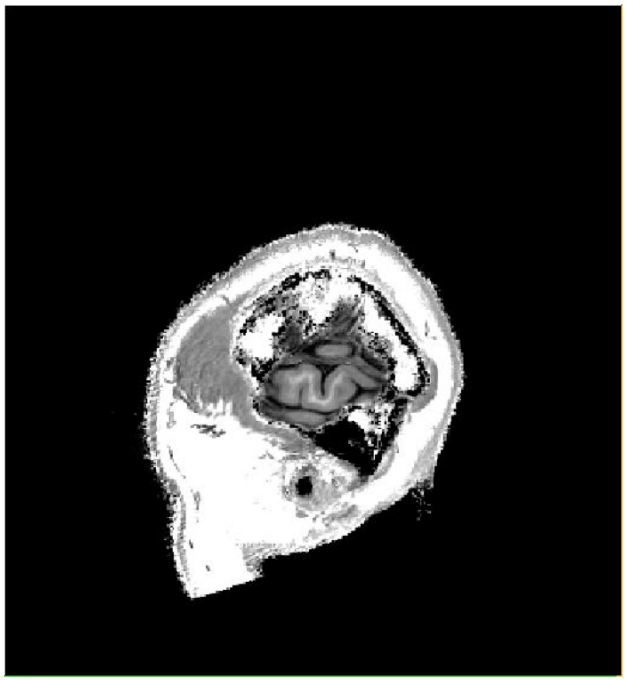
Specificity 85%

SVM ANALYSIS

False +ve 27%

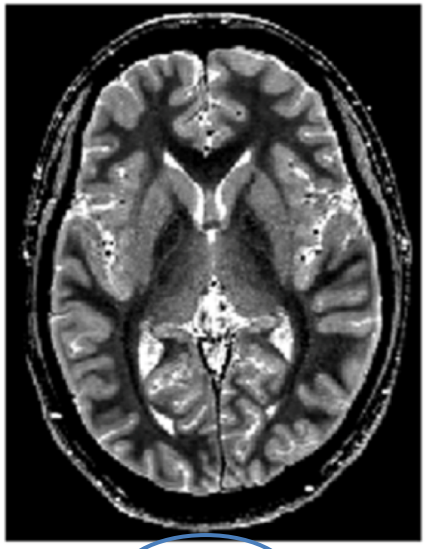
False –ve 17%



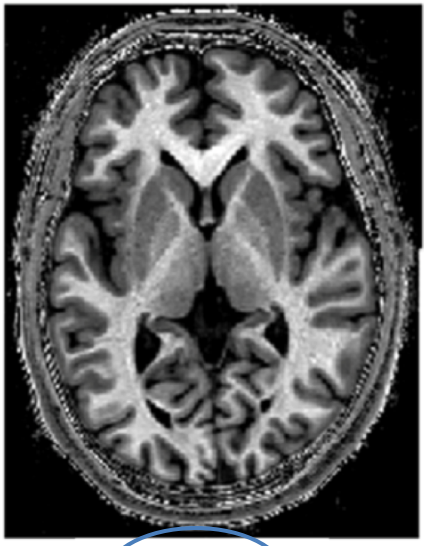
QUANTITATIVE MULTI-PARAMETER MAPPING BASED ON BIOPHYSICAL MODELS

Lorio et al., 2016 *HBMapp*
Lutti et al., 2012 *PLOS One*
Draganski et al., 2011 *NeuroImage*



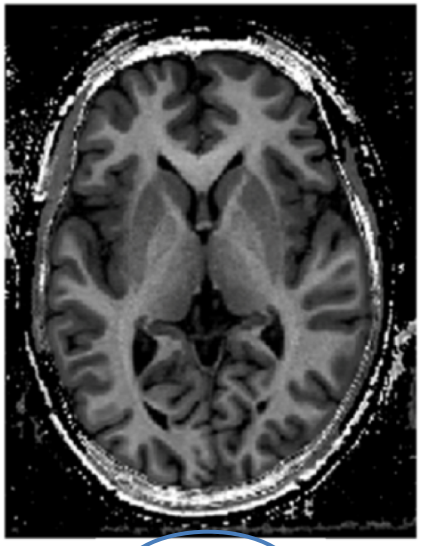
PD map

Proton density
Water content



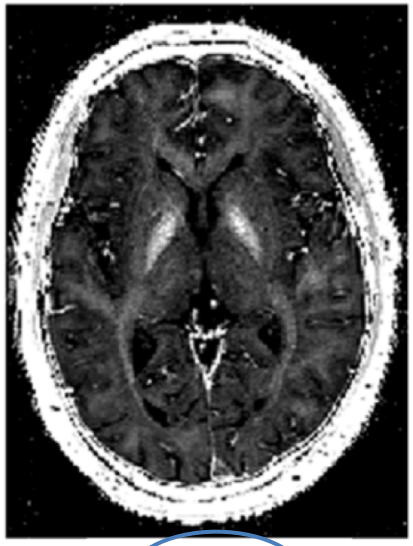
MT map

Magnetization transfer saturation
Myelin content



R1 map

Longitutinal relaxation rate
Myelin content & water compart-mentalisation



R2* map

Effective transverse relaxation rate
Iron content

HYPOTHESIS 2

PATTERNS OF PIXEL ABNORMALITIES

ARE OF DIAGNOSTIC

and/or

PROGNOSTIC SIGNIFICANCE

BIG DATA & INFORMATICS

RUBBISH IN ⫽ **RUBBISH OUT**

Signal additive
Noise suppressed
Avoids myth of perfect controls – whither RCTs?

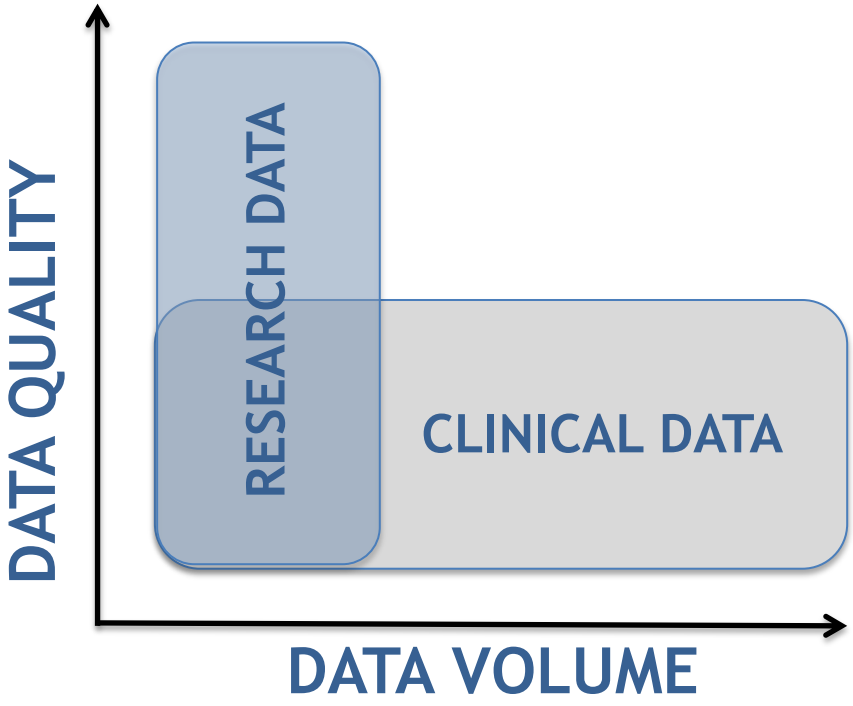
→ **GENERATES HYPOTHESES**

How big data can help: Bradford Hill (1965)

Biologically plausible
Explores multiple (all) models
Multi-scale & dimensional patterns
Additive over time
Built in reproducibility

→ **PREDICTIVE & CAUSAL**

DATA SOURCES AND CHALLENGES



HOSPITAL DATABASES

- NOT COMPLETE
- NOT STRUCTURED
- NOT STANDARDISED
- NOT CLEAN
- PROTECTED FOR PRIVACY
- PROTECTED AGAINST CORRUPTION

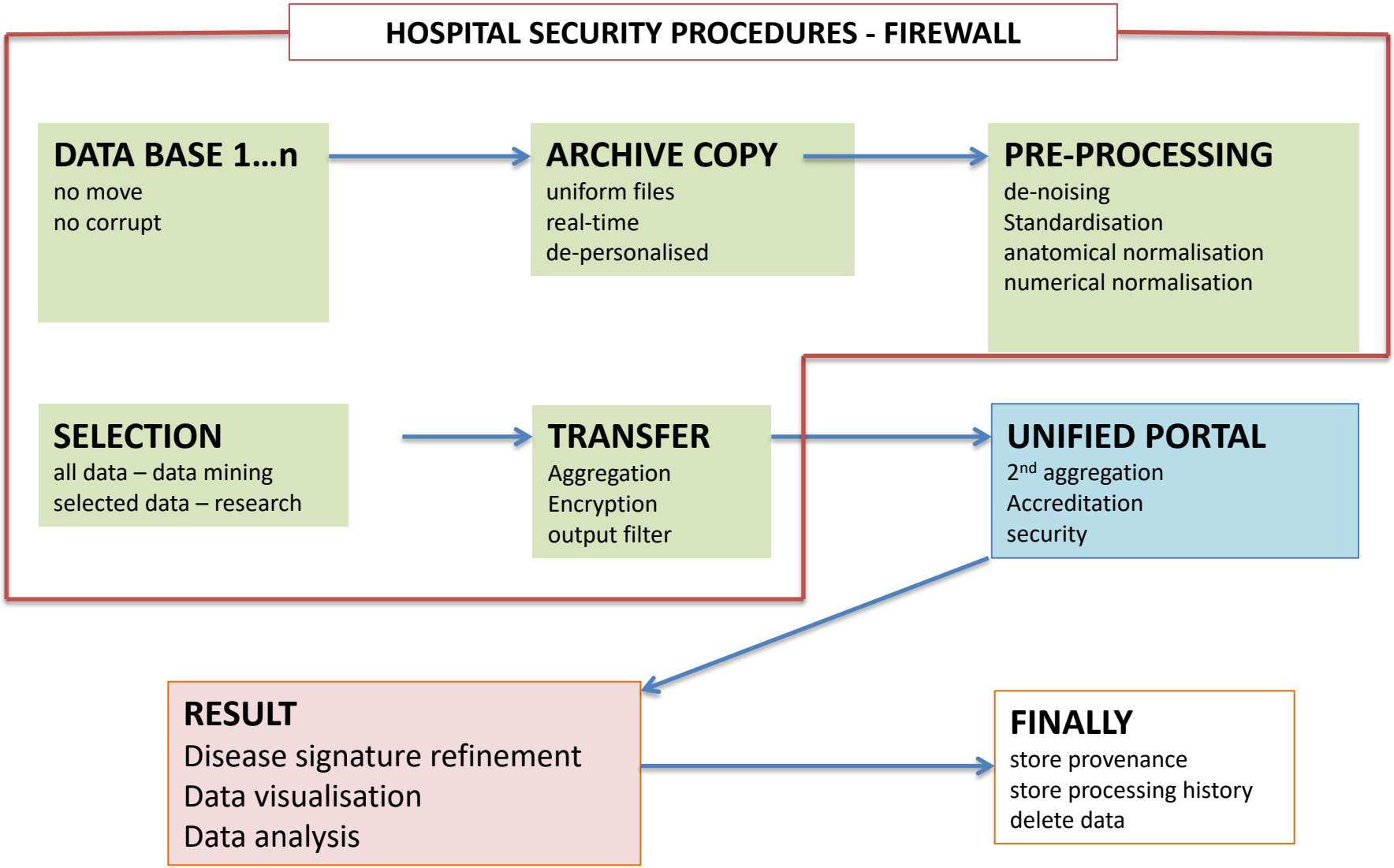
RESEARCH DATABASES

- PROTECTED CULTURALLY

PHARMACEUTICAL DATABASES

- PROTECTED COMMERCIALLY

MEDICAL INFORMATICS PLATFORM
FEDERATING DATA



ETHICAL CHALLENGES

PRIVACY

- DE-PERSONALISATION
- ANONYMISATION

CONSENT

- BROAD CONSENT
- RETROSPECTIVE – PROSPECTIVE

MANAGEMENT OF ETHICS

- LOCAL ETHICS COMMITTEES
- VALUE AND CREDIBILITY OF SCIENCE

REAL ETHICAL QUESTIONS

IN MEDICINE IS IT ETHICAL TO…

- ✓ TO UNDERUSE INFORMATION (hospital databases)
- ✓ TO MISUSE COMMUNITY RESOURCES (taxpayers money)
- ✓ TO RETARD ACQUISITION OF KNOWLEDGE BY RESEARCH

- ✓ FAIL TO BALANCE RISKS (car driving vs taking treatment)
- ✓ FAIL TO BALANCE RIGHTS (health and privacy)
- ✓ FAIL TO BALANCE SAFETY AGAINST EFFICACY (individual risk from treatment)

- ✓ USE INADEQUATE METHODS IN RESEARCH (linear vs complex analytics)
- ✓ DO UNDERPOWERED RESEARCH (statistics)
- ✓ FAIL TO COMMUNICATE RESULTS ACCURATELY (sensationalism vs education)

??????????

SUBJECTS & METHODS

We used 912 AD subjects – ADNI DATABASE

For a subsample of 508 we knew gender and age
For a subsample of 184 we knew the MMSE score

We used 5566 normal individuals – THREE CITIES EPIDEMIOLOGICAL STUDY, FRANCE

For a subsample of 2096 we knew gender and age
For a subsample of 2091 we knew the MMSE score

For learning we used half the dataset to create the classifier

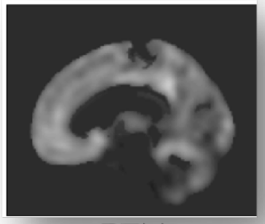
The learning set = 3239 individuals (465 AD, 2774 controls)

The other half was used to validate the classifier

The testing set = 3239 individuals (447 AD, 2792 controls)

DATA INTEGRATION

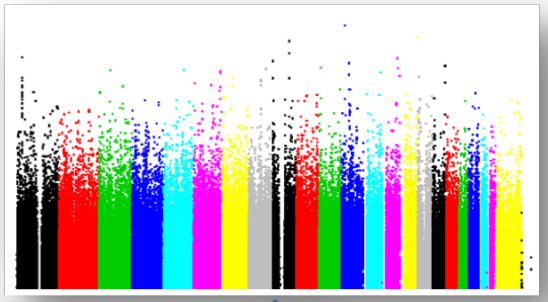
BRAIN IMAGING



PET

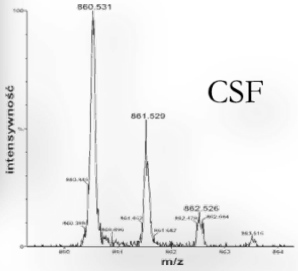
MRI

CLINICAL SCALES & MEASUREMENTS

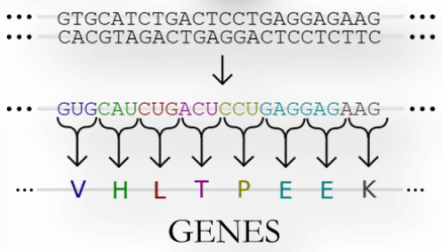


Organising
Tabulating

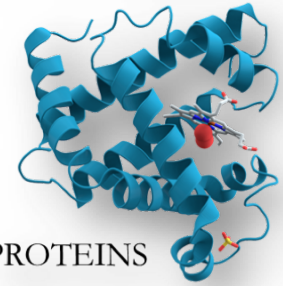
Processing…



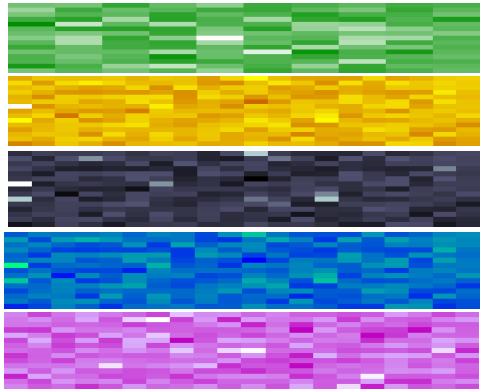
CSF



GENES



PROTEINS



MRI data

PET data

Gene data

CSF data

Protein data

912 Alzheimer's patients
5566 Healthy controls

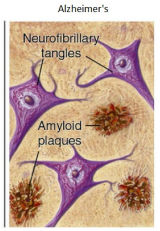
- Phenotype-led Semi-supervised clustering
- Biologically led classification
- High dimensional feature learning

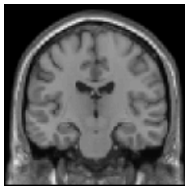
USING ANATOMY TO CONSTRAIN DIAGNOSIS

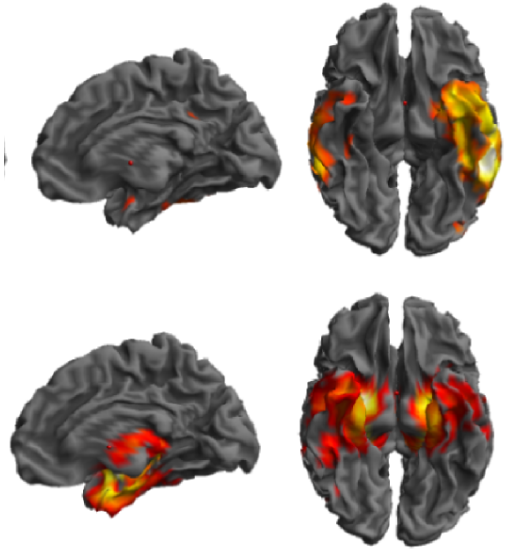
CLINICAL (SYNDROMIC) CLASSIFICATION

AD

HC







INTEGRATING PATHOLOGY INTO DIAGNOSIS

AD + : Symptoms +, Pathology +

AD - : Symptoms +, Pathology -

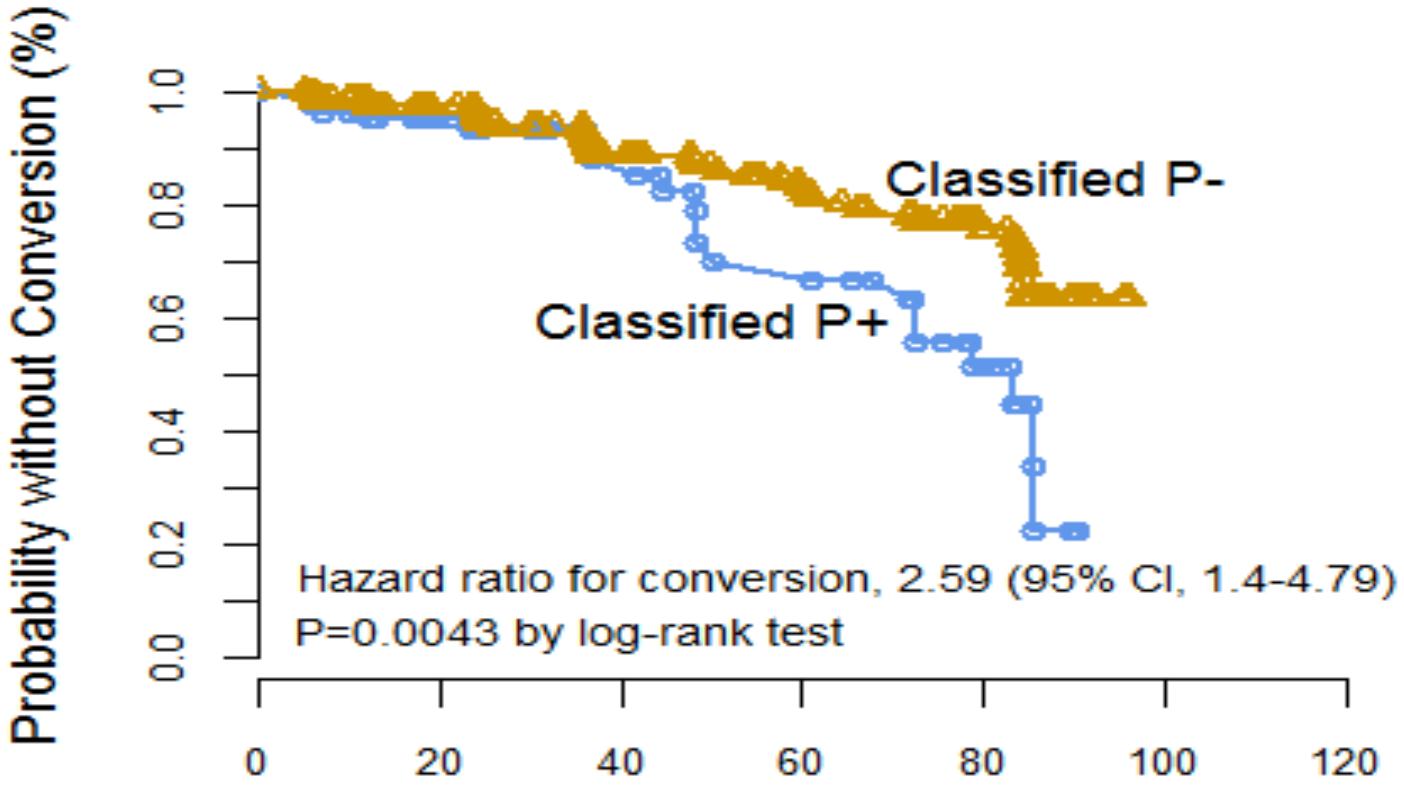
HC + : Symptoms -, Pathology +

HC - : Symptoms -, Pathology -

Brain atrophy pattern characteristic of pathological disease provides constraints on diagnosis

PREDICTING OUTCOME MORE ACCURATELY

NC subjects with two patterns of brain atrophy



ALL COGNITIVELY NORMAL ON RECRUITMENT AT BASELINE = 0

Result in terms of K-M survival

Jing Cui 2016 - in preparation

CONFRONTING PARADIGMS

CARTESIAN MODEL (TOP DOWN)

Mentally generated hypothesis
Mathematically expressed in a model
Confrontation with “relevant” data
Parameterisation and optimisation of model
Correlations (non-causal)

SIMULATION MODEL (BOTTOM UP)

Multimodal and multivariate data
Exhaustive mining to demonstrate coherent models
Exploration of these mathematical models as generated hypotheses
Investigation of hypotheses – clinical, mechanistic, prognostic, therapeutic
Knowledge (& causes)

THE ROLE OF DISRUPTIVE SCIENCE IN HBP-MIP

1. Move to a "**no database**" federated data analysis infrastructure

   - ✓ Security, privacy, research, ethics considerations
   - ✓ Advances in "virtualisation" "streaming" and "peer-to-peer" technologies
   - ✓ Use of products of EC funded research (eg Exareme)
   - ✓ Open source and cross-disciplinary specification
   - ✓ Unlocking hospital databases for research

2. Breaking **conservative** medical IT culture

   - ✓ Recruitments of university hospitals
   - ✓ Recruitment of structured research databases
   - ✓ Playing to "data sharing" revolution (NIH, EC, Wellcome initiatives)

3. Introduction of "**disease signatures**" concept

   - ✓ Cultural change from pure symptomatic & syndromic disease definitions
   - ✓ Preliminary classifications

HBP MEDICAL INFORMATICS PLATFORM

- Clinical neuroscientist
- Computer scientist
- Statistician neuroscientist
- Ethics

Bogdan Draganski
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Anastasia Ailamaki
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