BRAIN IMAGING AND COMPUTERS

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CHUV - Lausanne

BIOVISION
Alexandria - 2012

MULTIOMIC DATA

sub-cellular resolution

- miroarrays
- Electron Microscopy
- Confocal Microscopy
- Single Cell PCR
- Protein quantification
- magnetic bead labeling
- Gene sequencing
- Gene silencing
- Gene over-expression
- Genetic vectors
- Two-hybrid system
- protein separation

cellular resolution

- Wholecell & Inside-Out Patch
- Laser micro-dissection
- Cell culture
- Fluorescence microscopy
- Cellular tracing
- Cell sorting
- In situ hybridization
- Rhodopsin vectors
- immuno-detection amplified by T7
- Mass-spectroscopy
- Organelle transfection
- Spatial Proteomics

tissue resolution

- Immunostaining
- Multi Electrode Array Extracellular Recording
- Dye Imaging
- 2DE proteomics
- tissue transfection
- HPLC
- Voltammetry
- 2-photon live imaging
- In vivo-binding studies
- enzymatic-activity measurement

whole brain scale

- Behavioral Studies
- ultramicroscopy
- Magnet Resonance Diffusion Imaging
- fMRI
- EEG
- Transgenic lines

Legend:

- Exploration
- Research
- Prototype

ALZHEIMER'S DISEASE - DO WE NEED TO THINK AGAIN?

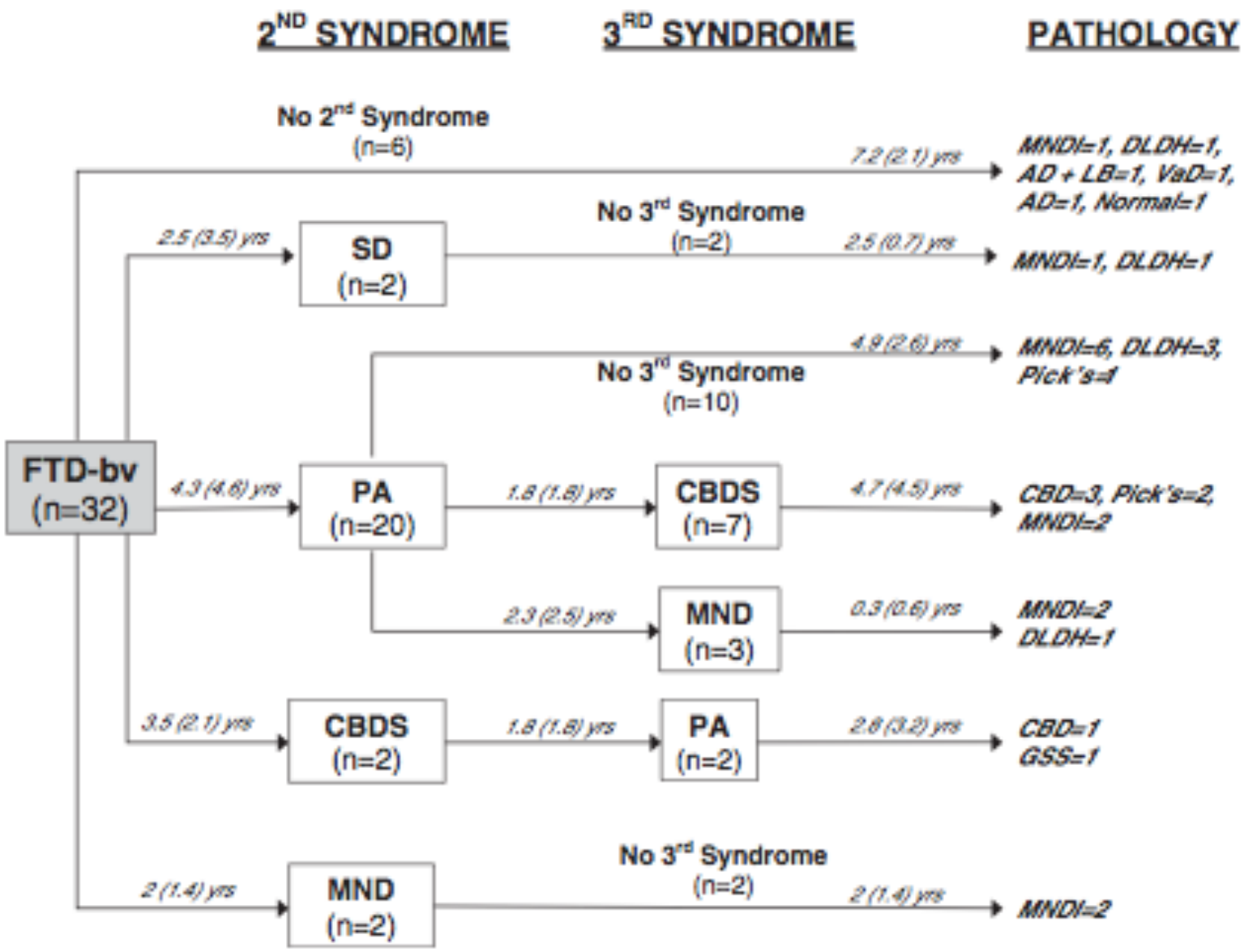
PATHOGENESIS

Role of genes and gene-environment interactions
Aetiology and pathogenic mechanism; role of protein misfolding
Amyloid present in abundance with MCI prior to hypometabolism
Amyloid as an AMP (anti-microbial protein)
Amyloid immunization – clearance without improvement
Amyloid – symptom mismatch

TREATMENT

Experimenter bias – anatomical and clinical
Differential compensation
Extent of redundancy
In vivo pathology or behavioural symptoms
« Ineffectual » treatments targeting the ACh system
Pre-clinical treatment

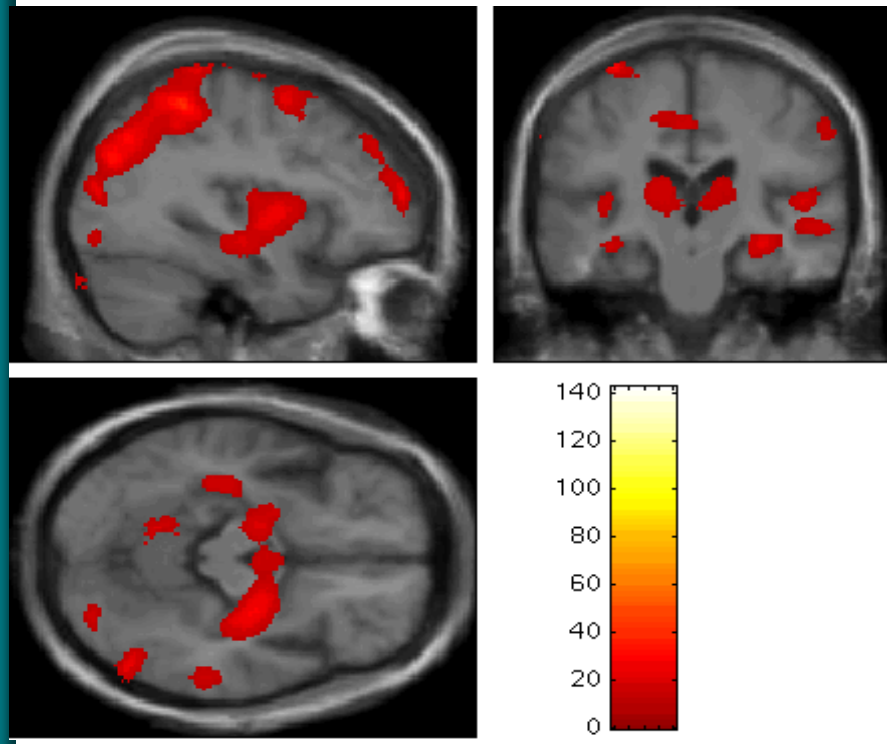
CLINICAL SYNDROMES AND FINAL PATHOLOGY IN CASES BEGINNING WITH FTD

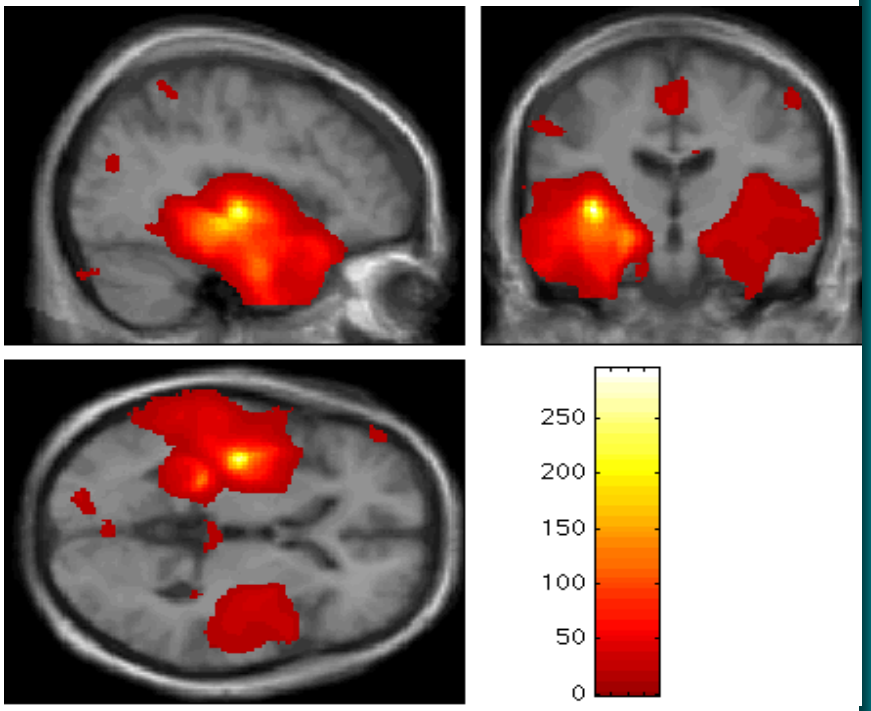


Kertesz et al, *Brain* 2005

VOXEL BASED MORPHOMETRY

MULTIVARIATE ANALYSIS – GREY AND WHITE MATTER

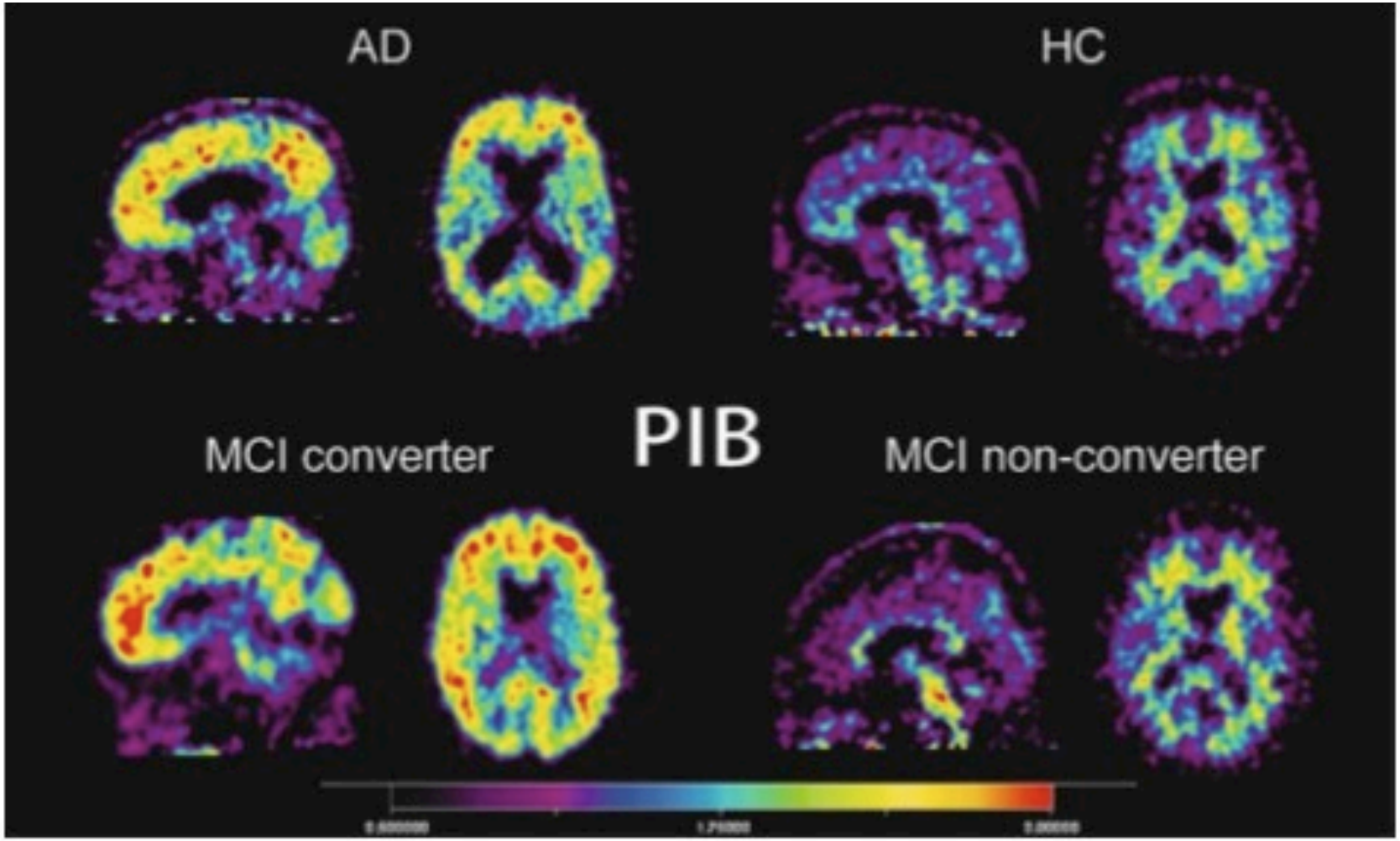




ALZHEIMER'S DISEASE

SEMANTIC DEMENTIA

AMYLOID LOAD IN MCI

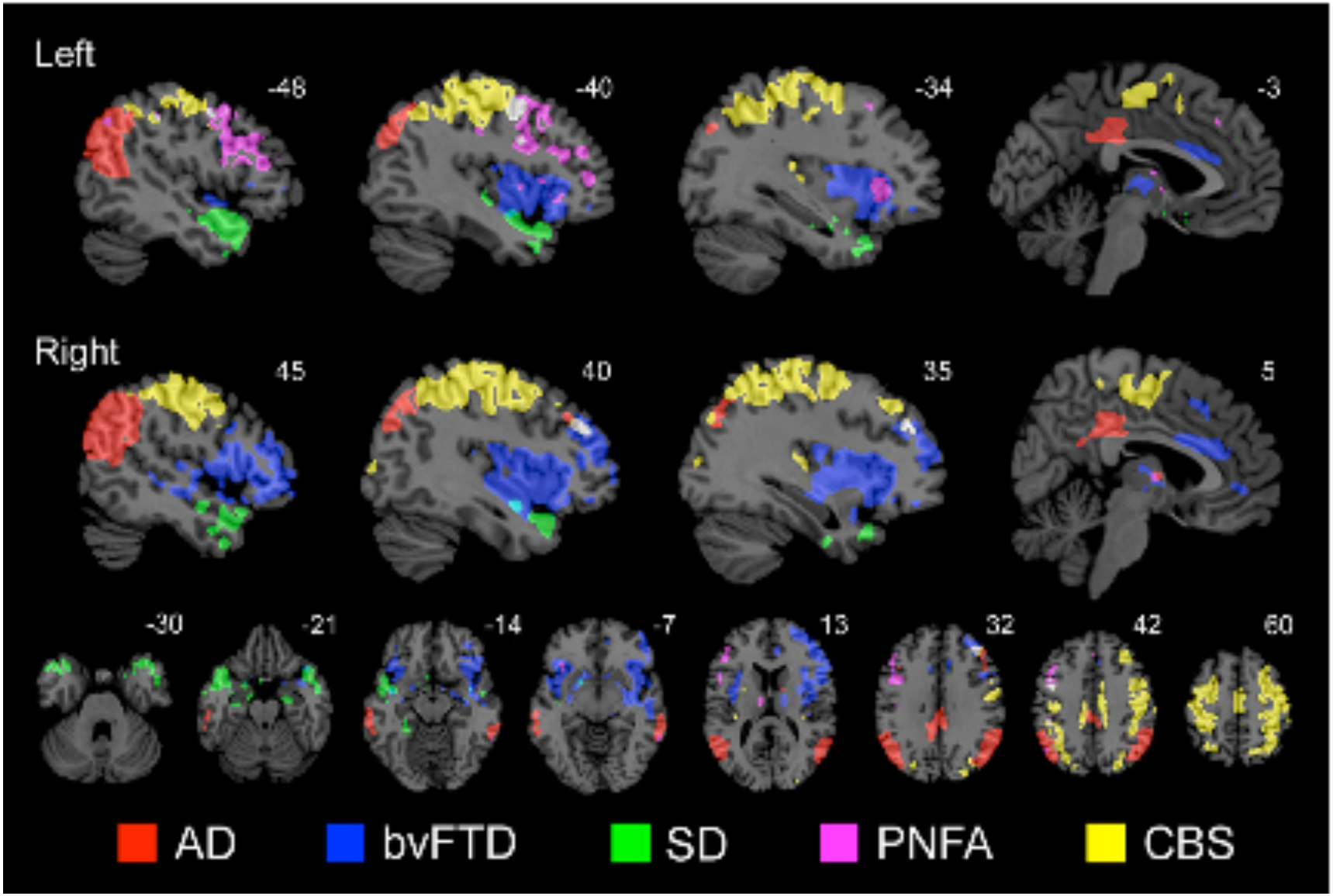


INCREASED RETENTION OF 11C-PIB IN MCI PATIENTS, ESPECIALLY MCI TO AD CONVERTERS

Sojkova et al. 2008

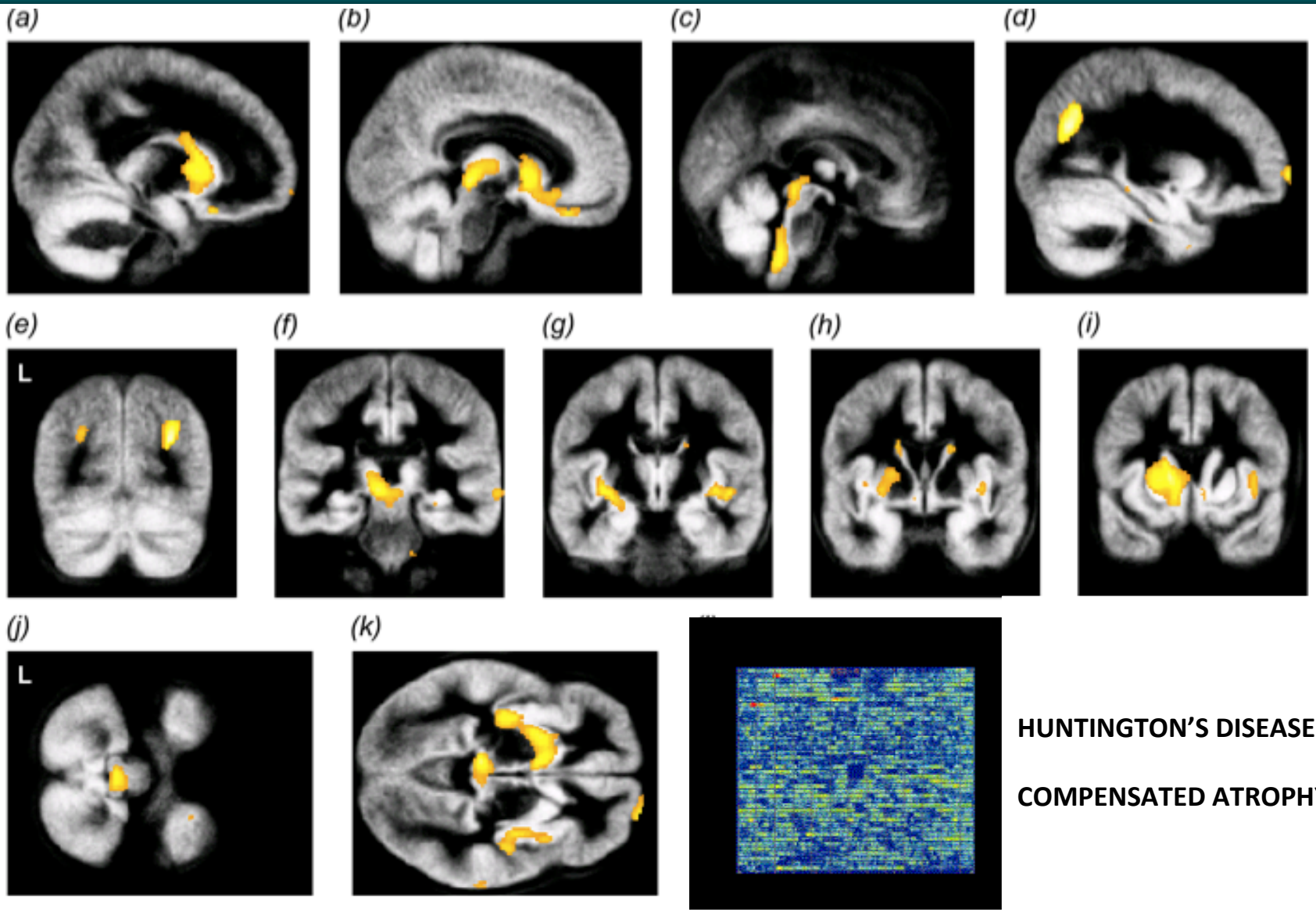
Forsberg et al. 2008

SYSTEM DEPENDENT DEGENERATIONS



From WW Seeley *et al*., Neuron 62, 42–52, 2009

PRE-SYMPTOMATIC DIAGNOSIS - BRAIN RESERVE



HUNTINGTON'S DISEASE

COMPENSATED ATROPHY

IMAGE CLASSIFICATION AND DIAGNOSIS - RADIOLOGY

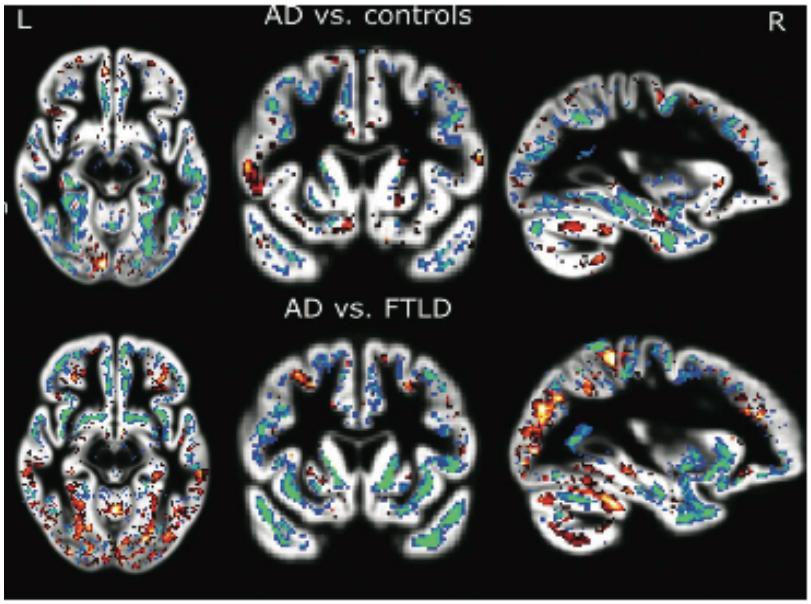
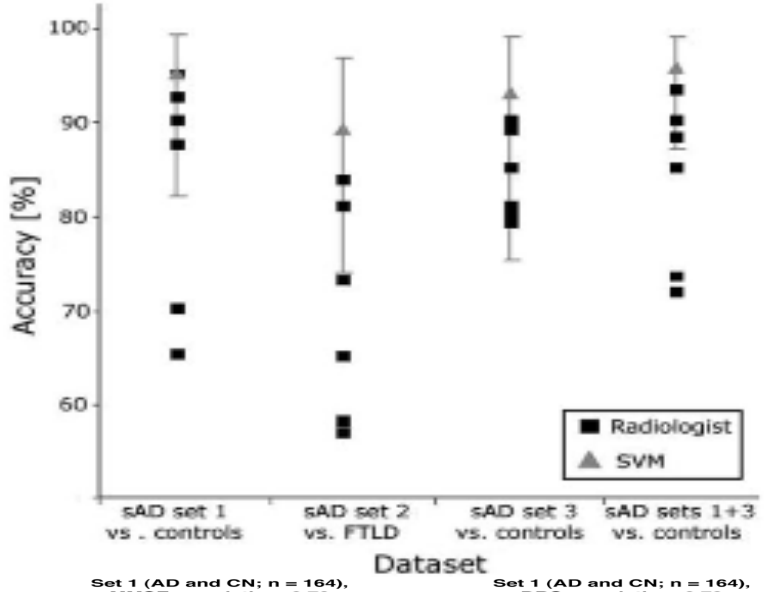
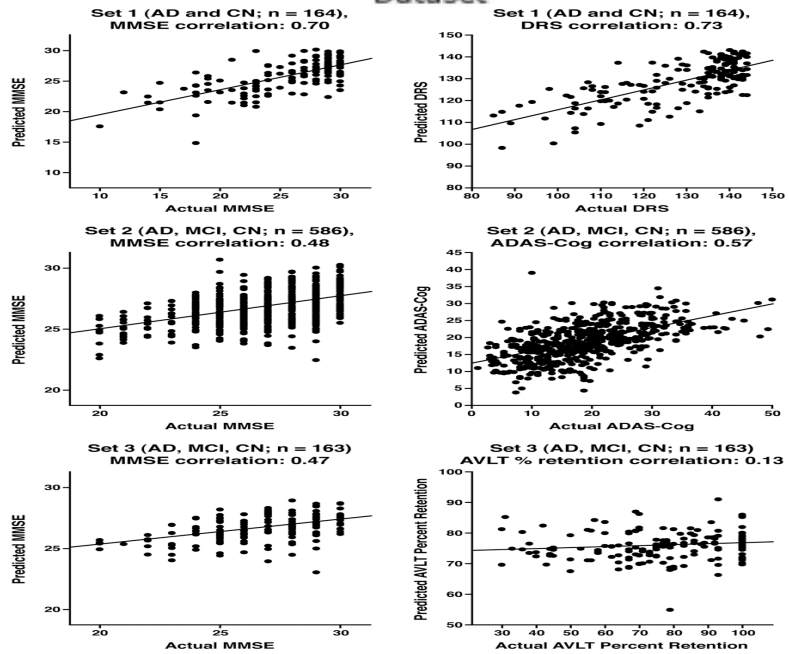


Table 2 Results of SVM classification using grey matter from the whole brain for image analysis

Group	Correctly classified (%)	Sensitivity (%)*	Specificity (%)*
AD and controls Group I	95.0	95.0	95.0
AD and controls Group II	92.9	100	85.7
AD and controls Group III	81.1	60.6	93.0
Dataset I for training, set II for testing	96.4	100	92.9
Dataset II for training, set I for testing	87.5	95.0	80.0
Group I + II	95.6	97.1	94.1
AD from Dataset II and FTLD Group IV	89.2	83.3	94.7

*Considering a correctly identified AD case as a true positive.





LEVELS OF ANALYSES

MOLECULAR & CELLULAR LEVEL

Genes & molecules

Molecular machines:

- Postsynaptic density
- Spines
- Signaling pathways

Synaptic function and modulation

Microcircuits

- Columns
- CPGs
- Striosomes
- Cerebellar microzones

Systems

INTEGRATED FUNCTIONS

Action & Perception

- Perceptual evaluation
- Motor representations
- Control machinery
- Motor programs

Learning & memory

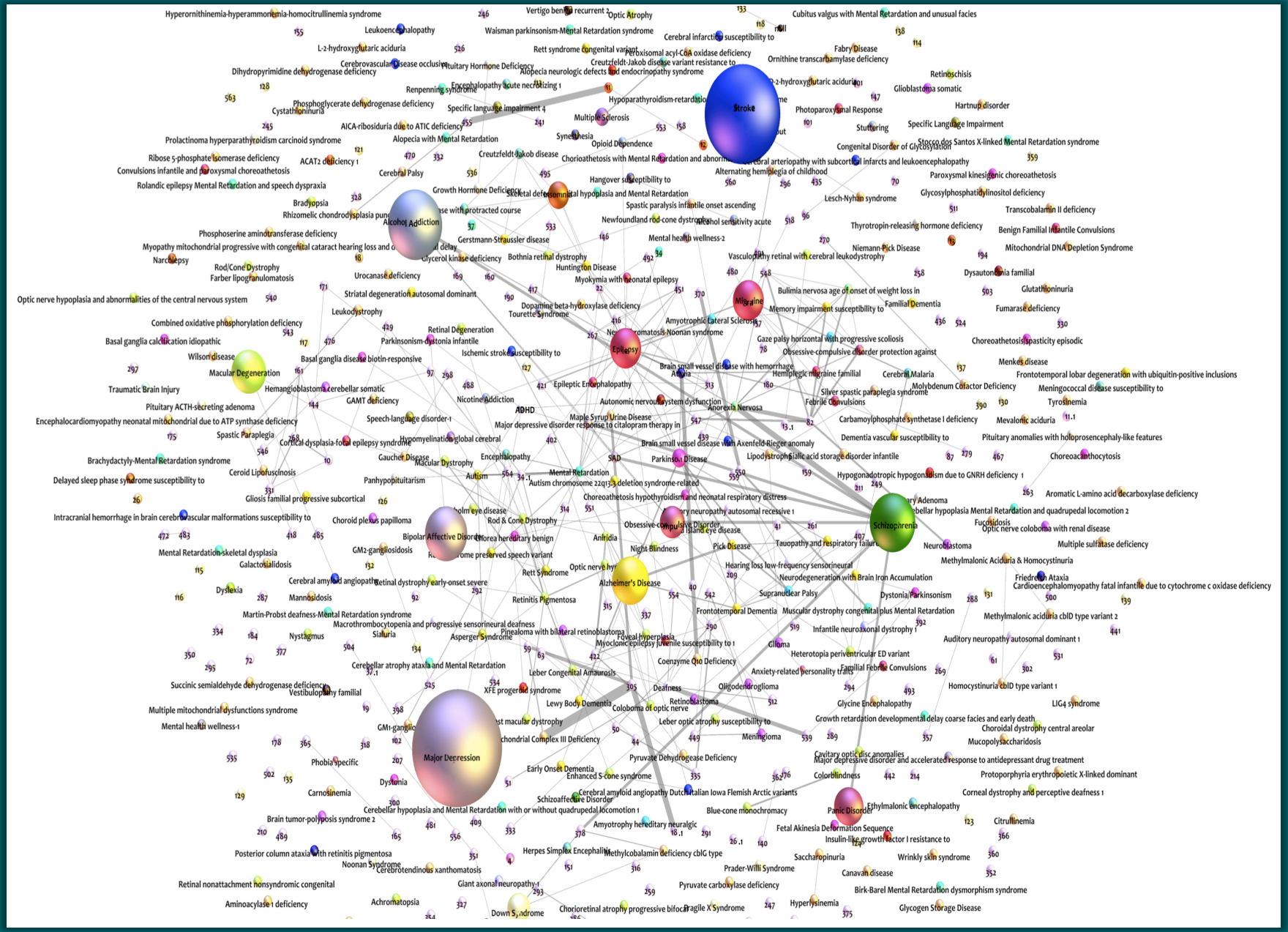
- Storage
- Retrieval

Emotions

- Interpreting internal stimuli
- Interpreting external stimuli

Selective attention

THE DISEASEOME


Stroke
Alcohol Addiction
Epilepsy
Migraine
Macular Degeneration
Bipolar Affective Disorder
Schizophrenia
Alzheimer's Disease
Major Depression
Panic Disorder
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Paroxysmal kinesigenic choreoathetosis
Glycosylphosphatidylinositol deficiency
Lesch-Nyhan syndrome
Transcobalamin II deficiency
Benign Familial Infantile Convulsions
Thyrotropin-releasing hormone deficiency
Niemann-Pick Disease
Mitochondrial DNA Depletion Syndrome
Vasculopathy retinal with cerebral leukodystrophy
Dysautonomia familial
Glutathioninuria
Fumarase deficiency
Choreoathetosis/spasticity episodic
Gaze palsy horizontal with progressive scoliosis
Obsessive-compulsive disorder protection against
Bulimia nervosa age of onset of weight loss in
Memory impairment susceptibility to
Familial Dementia
Amyotrophic lateral Sclerosis
Alcohol sensitivity acute
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Alzheimer's Disease
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Auditory neuropathy autosomal dominant 1
Heterotopia periventricular ED variant
Anxiety-related personality traits
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Ornithine transcarbamylase deficiency
Retinoschisis
Glioblastoma somatic
Hartnup disorder
Specific Language Impairment
Stuttering
Photoparoxysmal Response
Congenital Disorder of Glycosylation
Santos X-linked Mental Retardation syndrome
Specific language impairment 4
Multiple Sclerosis
Opioid Dependence
Chorioathetosis with Mental Retardation and abnormal
Creutzfeldt-Jakob disease
Alopecia with Mental Retardation
Alopecia neurologic defects and endocrinopathy syndrome
Creutzfeldt-Jakob disease variant resistance to
Peroxisomal acyl-CoA oxidase deficiency
Pituitary Hormone Deficiency
Encephalopathy acute necrotizing 1
Renpenning syndrome
Phosphoglycerate dehydrogenase deficiency
AICA-ribosiduria due to ATIC deficiency
Hypoparathyroidism-retardation
Rett syndrome congenital variant
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Vertigo benign recurrent 2
Optic Atrophy
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NOVEL ENABLING TECHNOLOGIES - A PARADIGM SHIFTING TIPPING POINT?

COMPUTER POWER

DATABASE TECHNOLOGY

HUMAN GENOME PROJECT

(HUMAN) IMAGING

COMPLEXITY MATHEMATICS

HIGH LEVEL GRAND CHALLENGE

A PARADIGM SHIFT:

FROM PHENOMENA TO BIOLOGY IN DEFINING DISEASE

DATABASES – MODELING – MATHEMATICAL TOOLS

Excessive accumulation of neuroscience data at all levels of analysis

- Difficult to integrate and fundamentally understand
- Ehow to extend comprehension from genes to cognition and diseases

Fragmentation from super-specialisation out of holistic context

Many dynamic, non-linear, complex, interactive processes

IT developments promise efficient neuroinformatics contribution

Neuroinformatics needs complementary rigorous experimentation

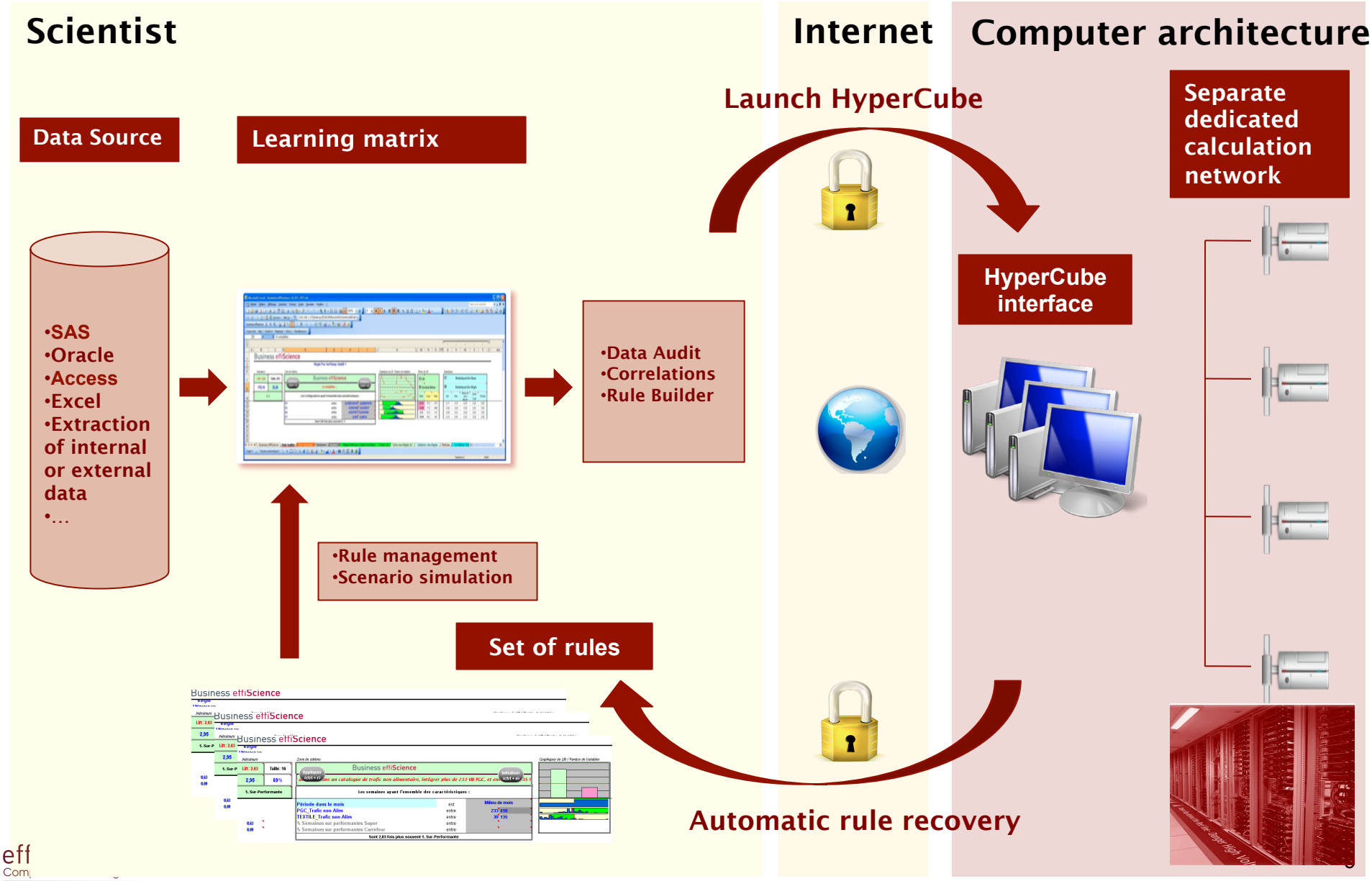
MEDICAL INFORMATICS - THE ROAD MAP

DATA INTEGRATION
AND
CAUSAL ANALYSIS

DISEASE SIGNATURES

THEN
MEDICAL PHENOMENOLOGY
GENETIC & –OMIC CHARACTERISATION
DYSFUNCTIONAL SYSTEM IDENTIFICATION
(POLY)PHARMACOLOGY

HYPERCUBE

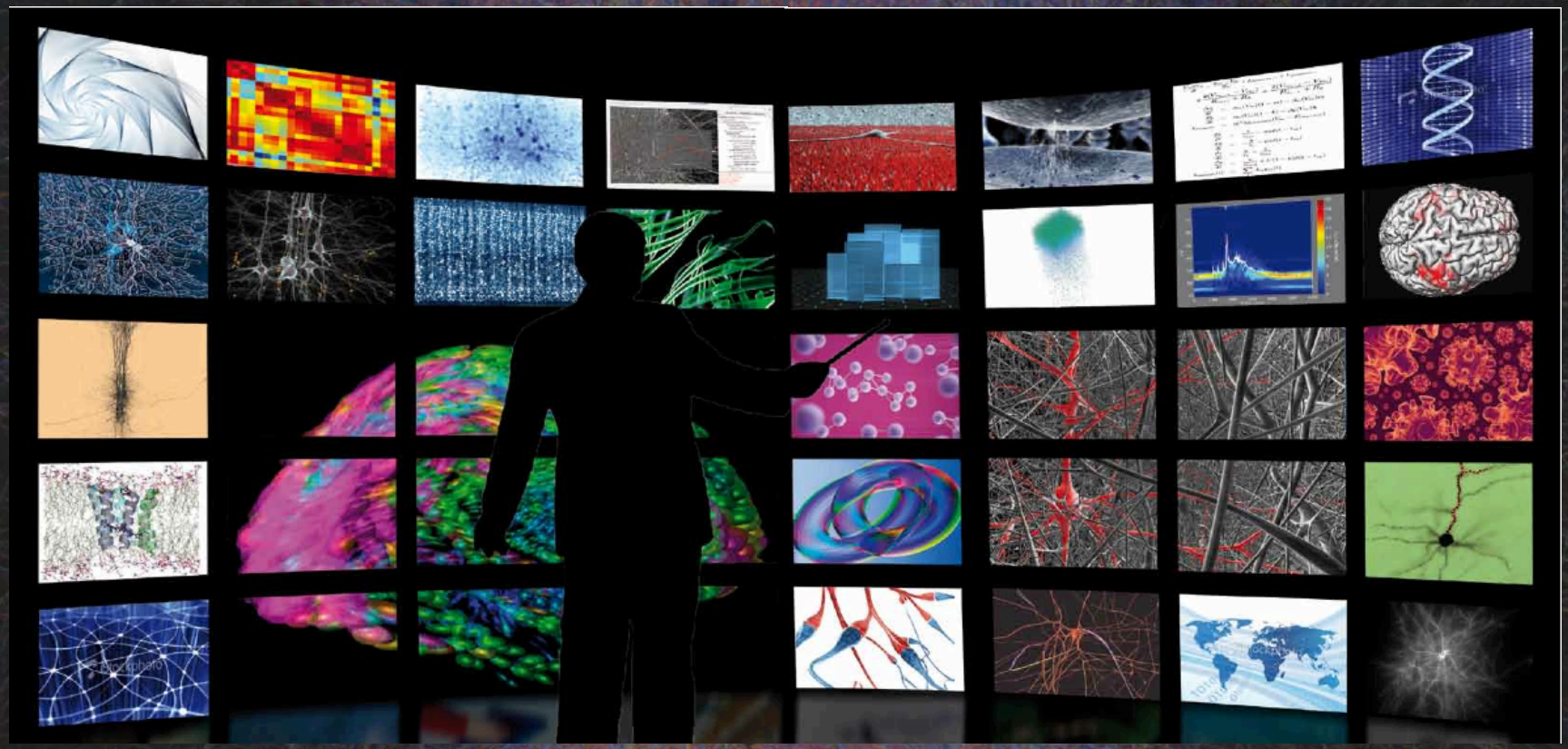

Scientist
Internet
Computer architecture
Data Source
Learning matrix
Launch HyperCube
Separate dedicated calculation network
•SAS
•Oracle
•Access
•Excel
•Extraction of internal or external data
•…
•Data Audit
•Correlations
•Rule Builder
HyperCube interface
•Rule management
•Scenario simulation
Set of rules
Automatic rule recovery

HUMAN BRAIN PROJECT

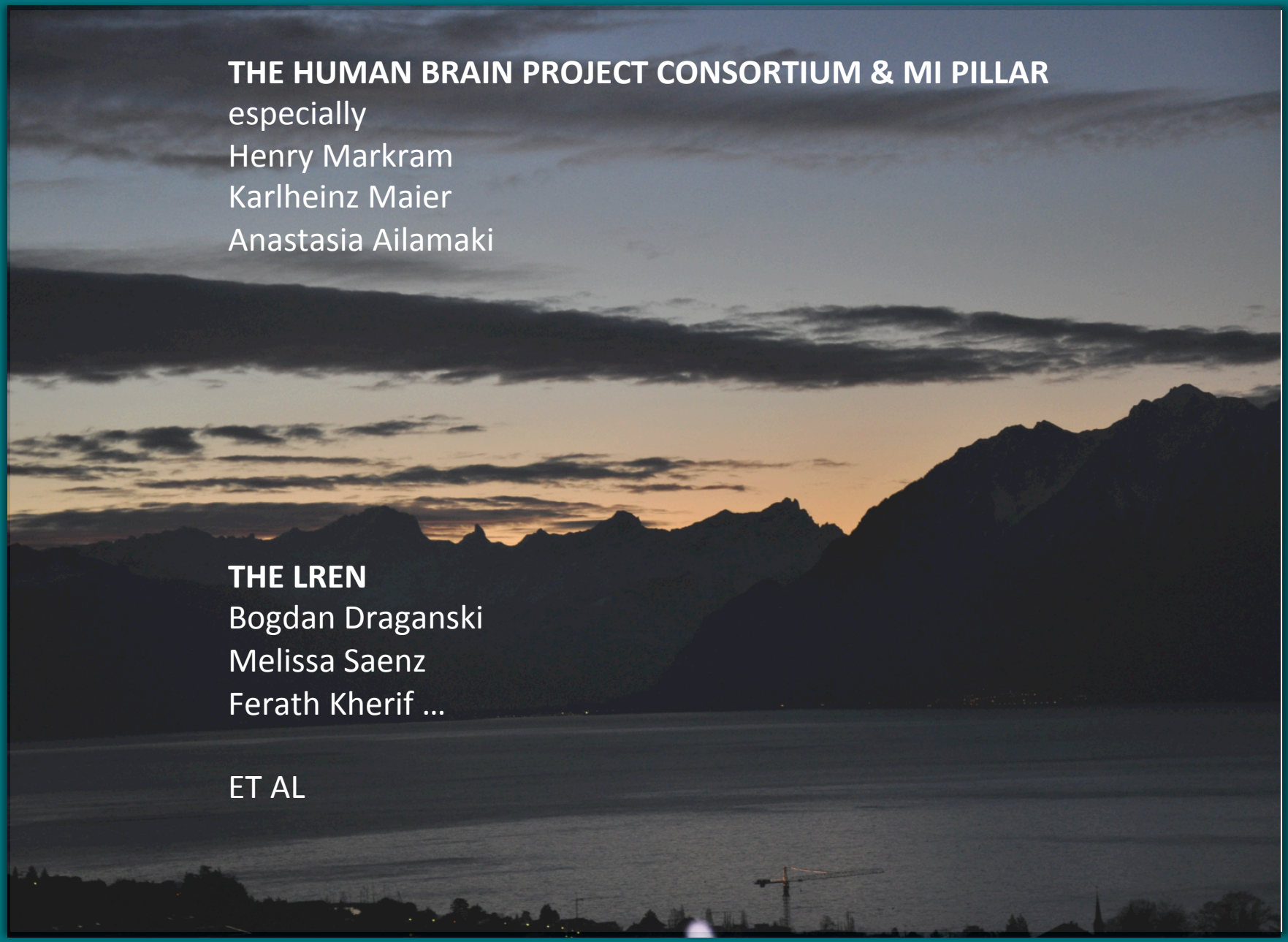
THE MEDICAL INFORMATICS FACILITY

- to define brain mechanisms causing brain diseases and to treat them

FEDERATE INTEGRATE AND SIMULATE CLINICAL DATA



WITH THANKS TO:



THE HUMAN BRAIN PROJECT CONSORTIUM & MI PILLAR
especially
Henry Markram
Karlheinz Maier
Anastasia Ailamaki

THE LREN
Bogdan Draganski
Melissa Saenz
Ferath Kherif …

ET AL