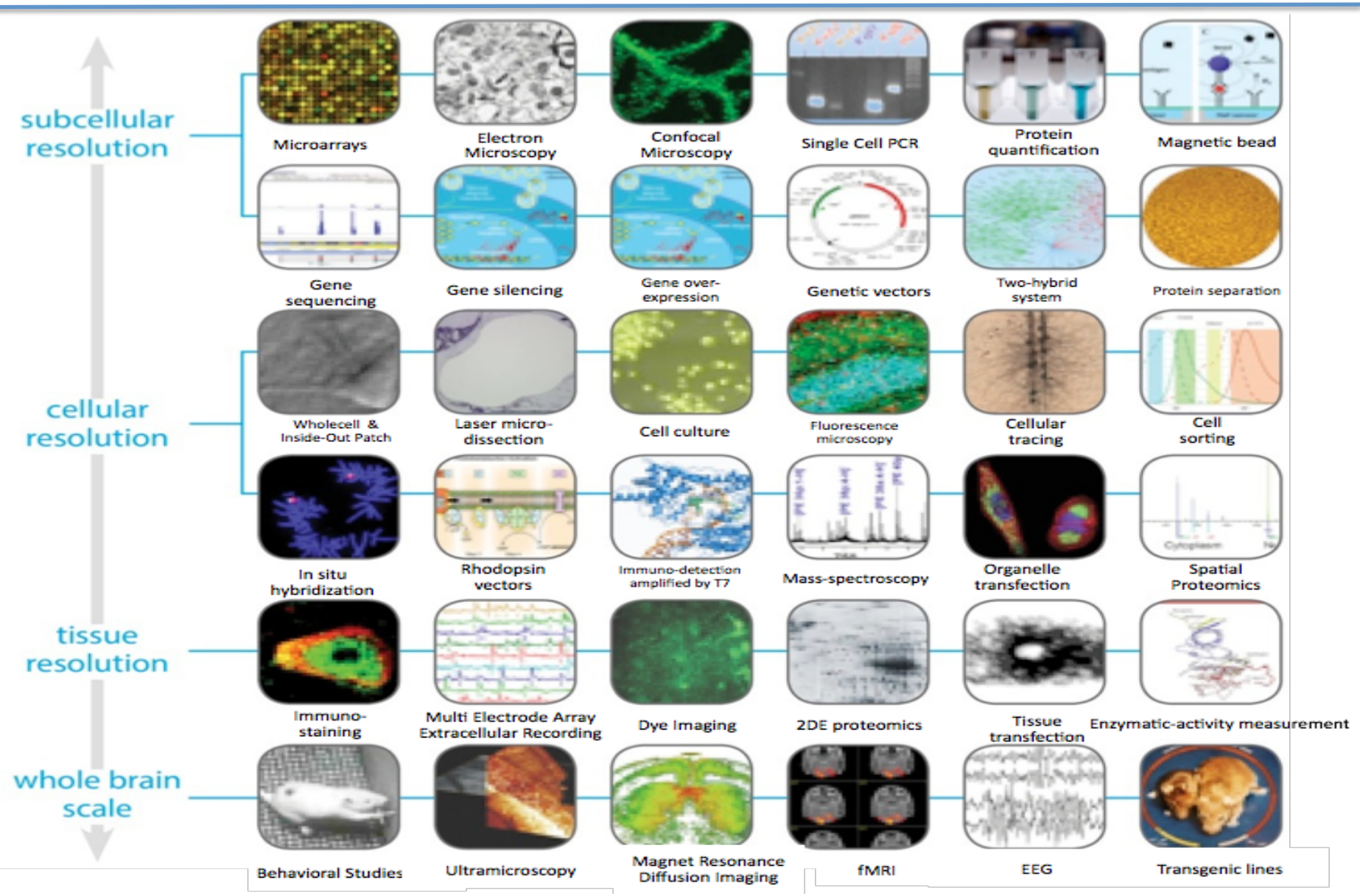

SINAPSA 2015
Medicinska fakulteta
Univerza v Ljubljani, Slovenija
In partnership with:
University of Ljubljana : Faculty of Medicine
-postgraduate program in biomedicine
HUMAN BRAIN PROJECT
IMPLICATIONS FOR NEUROSCIENCE
CHUV
Richard Frackowiak (CHUV & EPFL Lausanne)

NEUROSCIENCE ACROSS SCALES



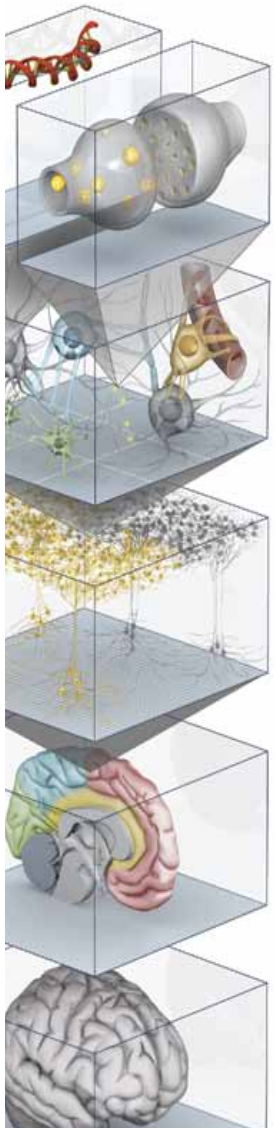
MOTIVATION 1 - DATA FEDERATION & INTEGRATION

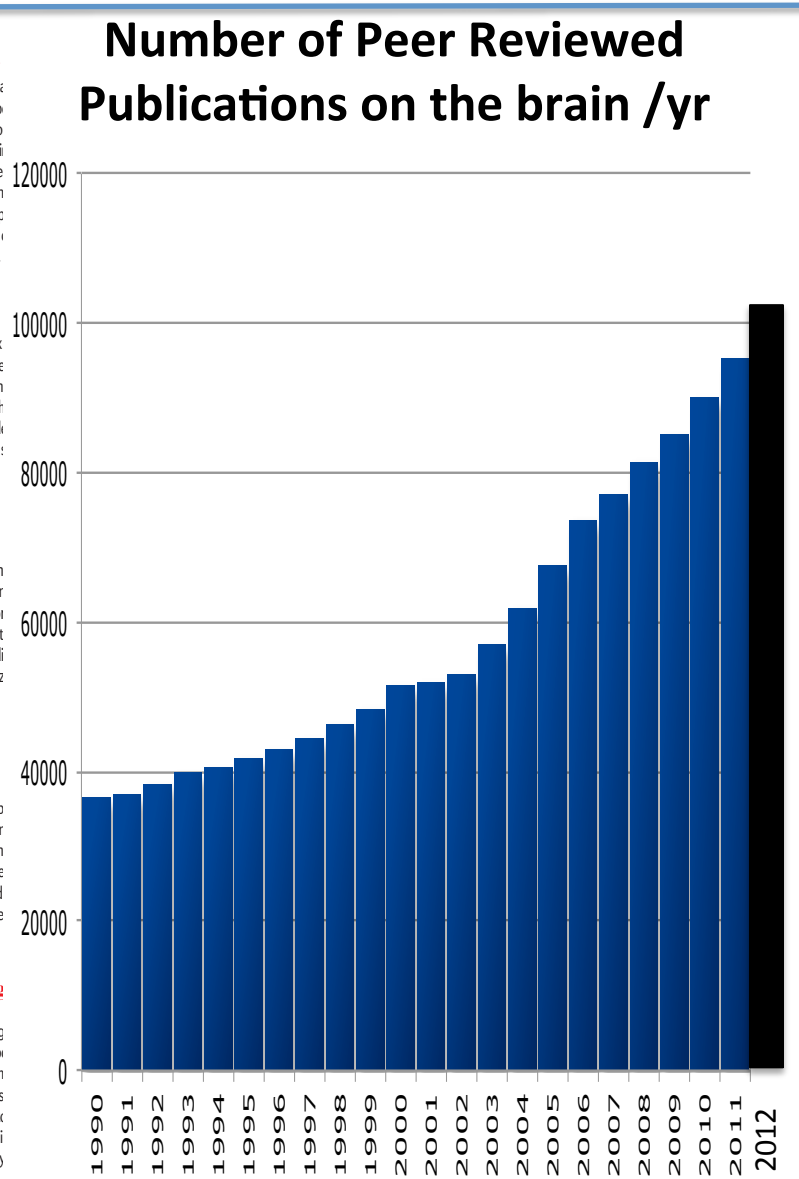
The facts:

1. Data and knowledge is **growing** exponentially
2. Data and knowledge are increasingly **fragmented**
3. Benefits for society seem to be **decreasing**
4. Economic burden increasing to **unsustainable** levels

The causes:

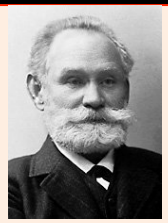
1. No integration plan
2. No data curation plan
3. No plan to link across levels
4. No plan to transfer knowledge from animal model to human
5. No plan to go beyond traditional classification of diseases

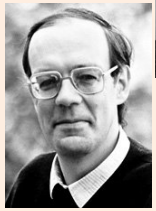


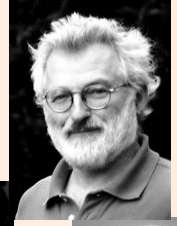


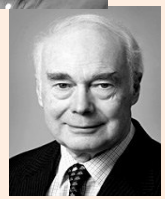
NOBEL CONTRIBUTIONS TO NEUROSCIENCE

NEUROANATOMY	**Golgi** & Ramon y Cajal
NEUROPHYSIOLOGY	Pavlov
	Barany
	Sherrington & Adrian
	Von Bekesy
	Eccles, Hodgkin & Huxley, Weisel
	Neher & Sakmann
NEUROPHARMACOLOGY	Dale & Loewi
	Katz & von Euler
	Black
	Carlsson
NEUROIMAGING	Josephson
	Hounsfield
	Mansfield
NEUROSURGERY	Moniz
SOCIAL & COGNITIVE NEUROSCIENCE	Von Frisch, Lorenz & Tinbergen
	Kahneman
GENETICS	*Crick & Wilkins*
	Sanger
	Sulston
IMMUNOLOGY	*Jerne, Milstein & Kohler*
CELL BIOLOGY	***Levi-Montalcini***
	Evans







MOTIVATION 2 – THE MEDICO-SOCIAL CHALLENGE

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.

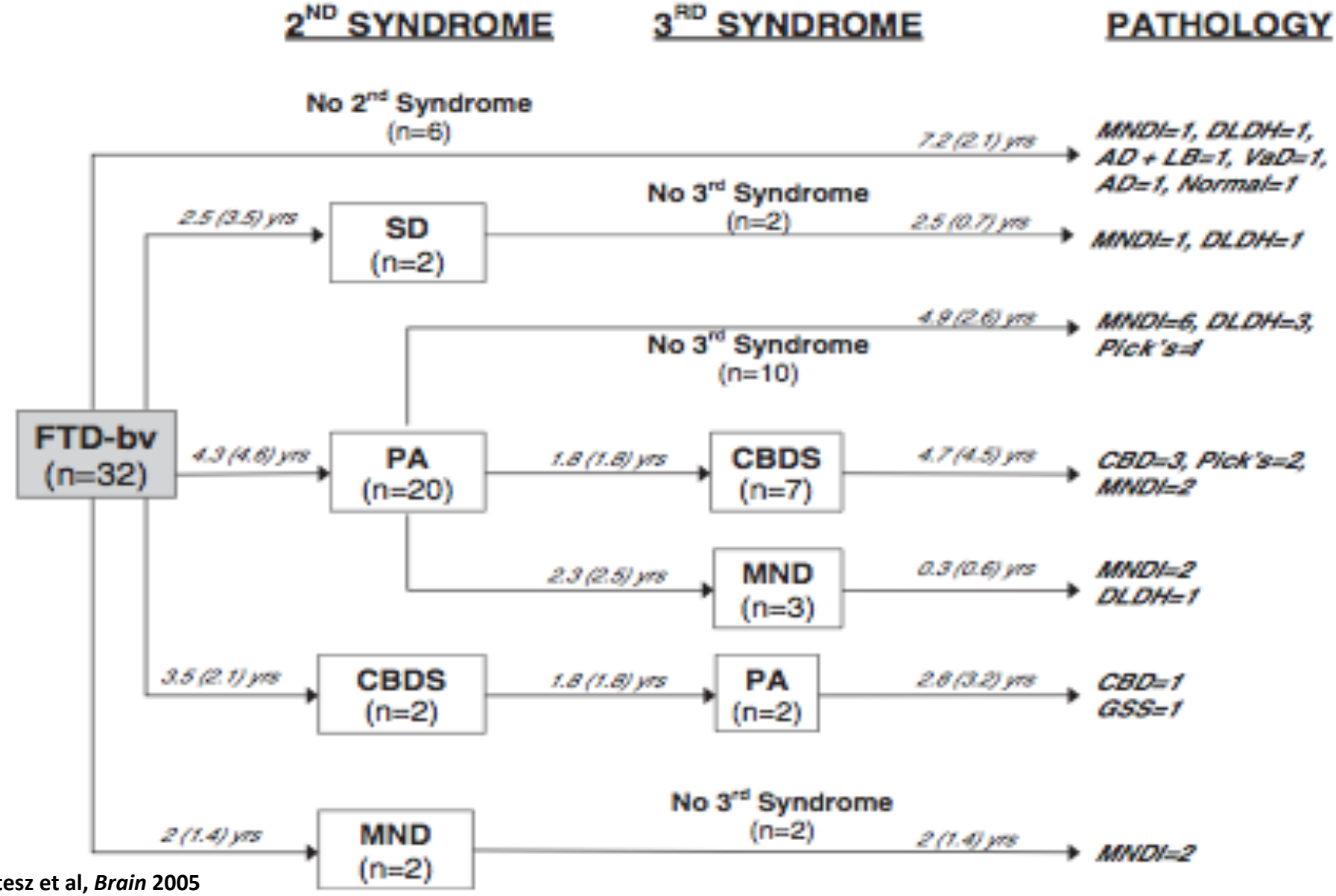
Cerebral vascular accidents: first cause of adult motor disability. **75 per cent** suffer residual disability.

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.**

HAS PHENOMENOLOGY REACHED A DEAD END?



Kertesz et al, *Brain* 2005

MOTIVATION 3 – DISCOVERING CAUSES OF DISEASE

WHAT CAUSES IT?

What mechanisms?
Role of genes?
Abnormal proteins – amyloid?
Abnormal neurotransmission – acetyl choline?

What pathophysiological abnormalities are causes and which are effects?

- **US President 1981-1989**
- **Oldest US President**
- **1994: AD admitted publicly**

HOW DO WE PREVENT IT? AND TREAT IT?

Can we diagnose it?	- **NO**
Do symptoms matter?	- **A LITTLE**
What weight to pathology?	- **END STAGE**
Do we compensate?	- **REDUNDANCY**
What about pre-symptomatic diagnosis?	- **???**
Why don't the treatments work?	- **TREAT WHAT**
And what about preventive treatment?	- **???**

WHAT IS A FLAGSHIP OF ENTERPRISE AND TECHNOLOGY

Future and Emerging Technology Flagships (FET)

Are ambitious large-scale, informatics-driven, research Initiatives that aim to achieve a visionary goal.

The scientific advance should provide a strong and broad Basis for future technological innovation and economic Exploitation in a variety of areas, as well as novel benefits for society.

The research is collaborative, internally non-competitive, inter- and trans-disciplinary, driven by a commonly agreed road-map

EUROPEAN COMMISSION

FET FLAGSHIPS

BLUE BRAIN PROJECT + NEUROIMAGING COMMUNITY

IMPACT OF ICT

VON NEUMANN MACHINES

MOORE'S LAW

ENERGY LIMITATIONS

INTERNET

DATABASE MANAGEMENT

CLOUD ENVIRONMENT

DATABASE QUERYING & ADDRESSING

REAL-TIME VISUALISATION

SUPERCOMPUTING

BEYOND EXASCALE

BANDWIDTH & ROUTING [**HTML5, Cisco**]

DISTRIBUTED [**Oracle**]

SECURITY [**Amazon, Dropbox, iCloud**]

LOCAL [**Google**] vs REMOTE [**EPFL**]

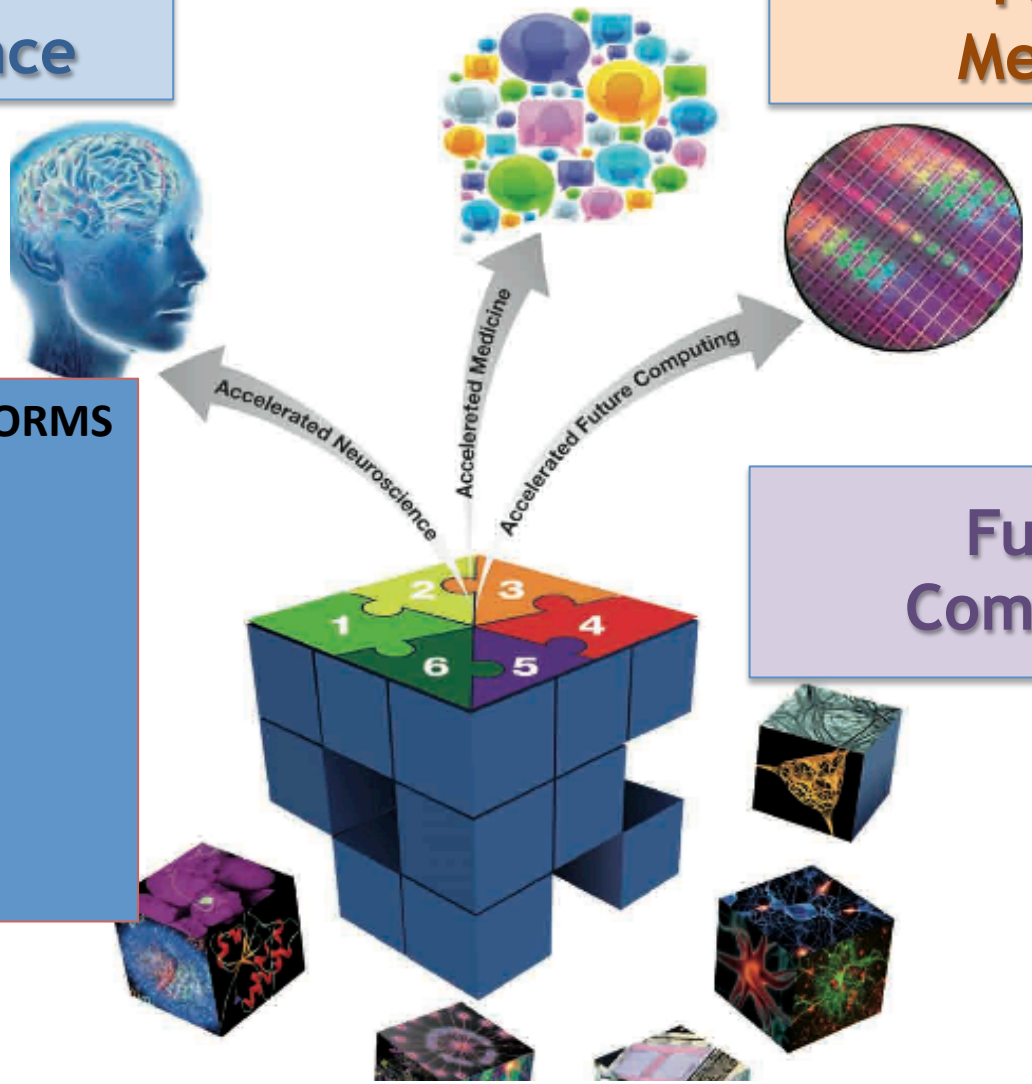
FOR SUPERCOMPUTING [**IBM, CRAY**]

NEUROMORPHIC COMPUTING

HBP – A NEUROINFORMATICS PROJECT

Future Neuroscience

Future Medicine



Future Computing

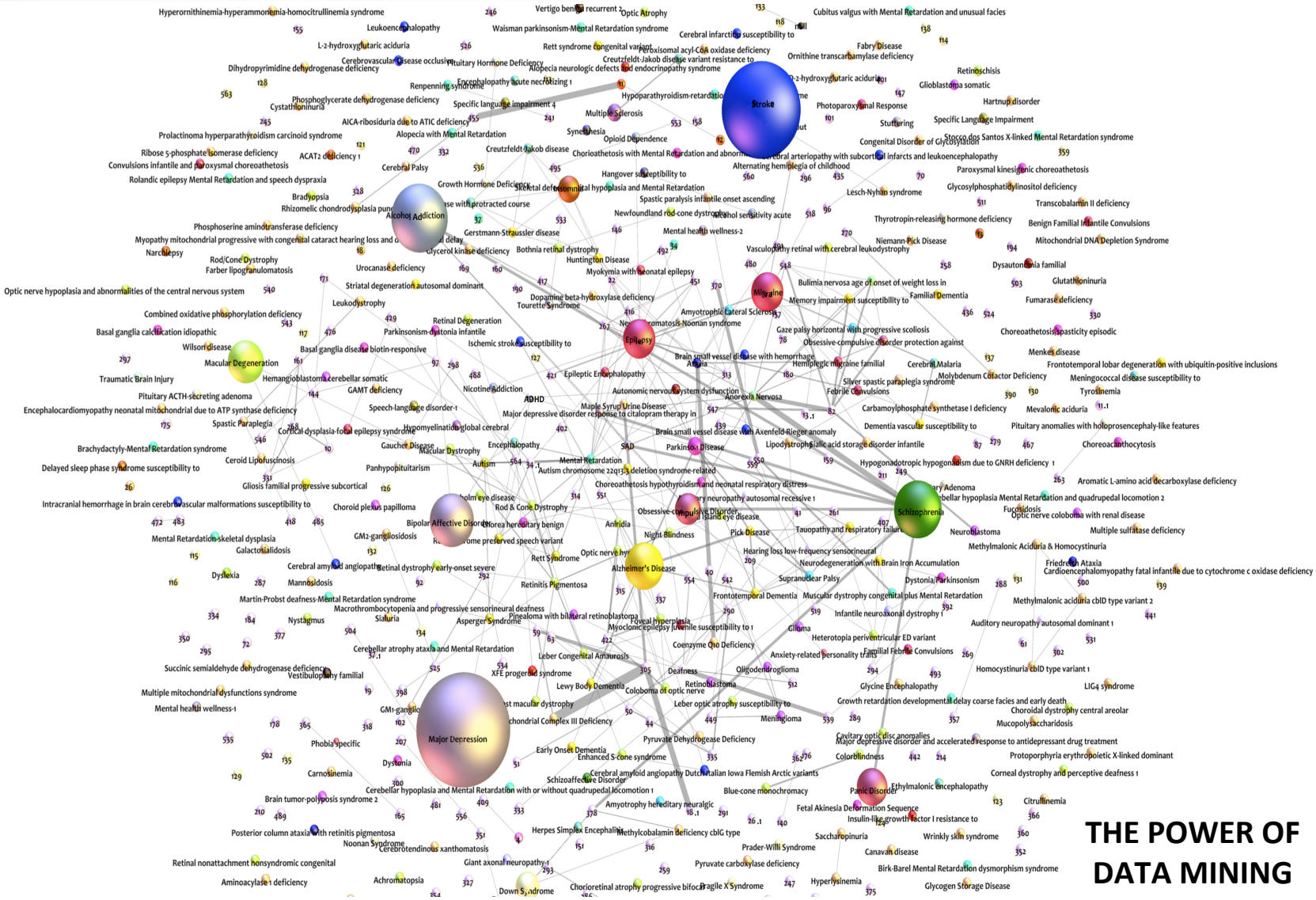
6 OPEN ACCESS PLATFORMS

HIGH PERFORMANCE COMPUTING
NEUROMORPHIC COMPUTING
NEURAL THEORY (EIT)
SIMULATION
NEUROINFORMATICS
MEDICAL INFORMATICS

CONTRACT

ACCREDITATION

DISEASE SPACE AND GENETIC ASSOCIATIONS



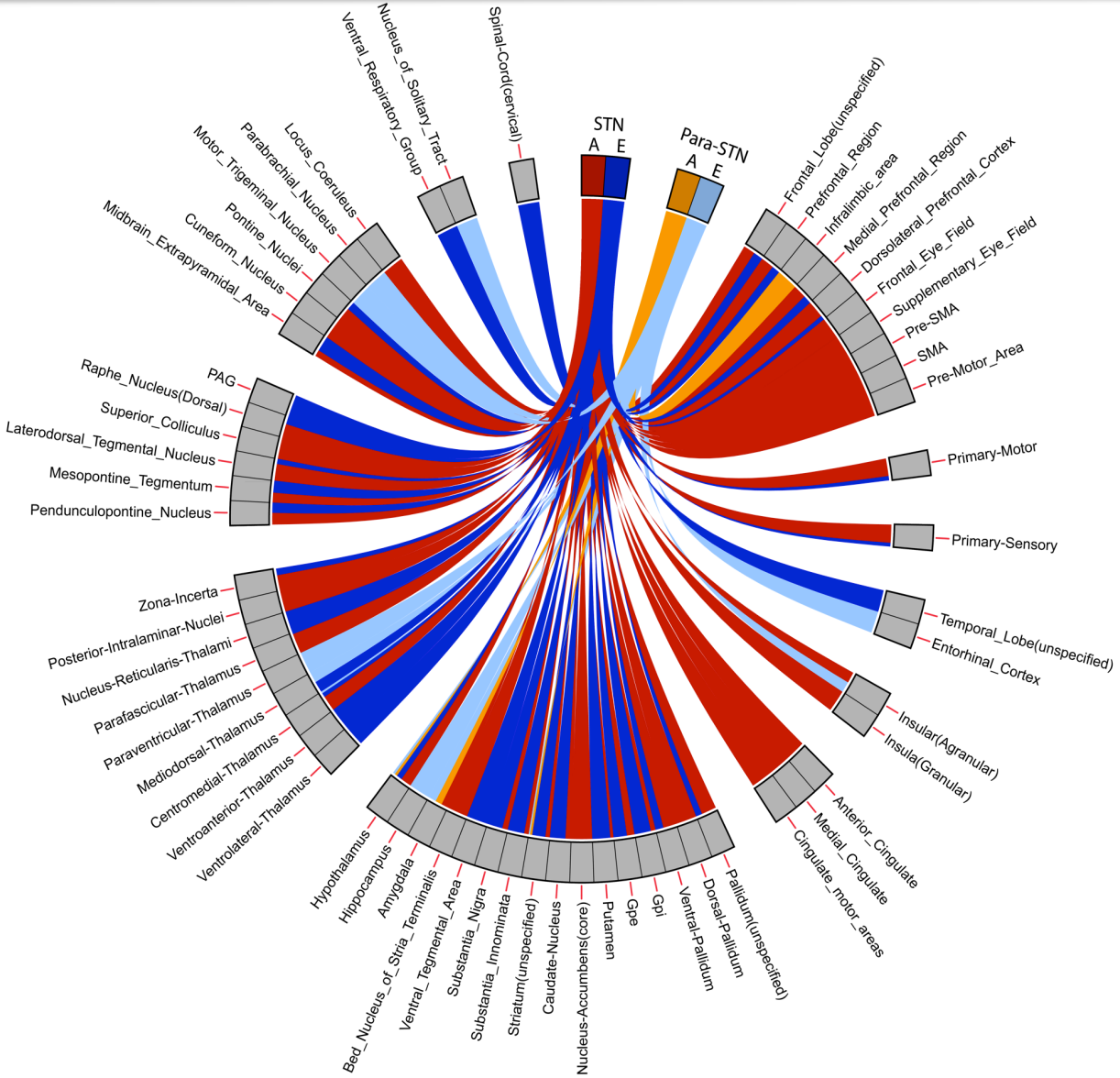
THE POWER OF DATA MINING

INFORMATICS INTEGRATE DATA

A review of the entire tract-tracing literature of the STN between 1947-2011 reveals connectivity between a broad array of cortical, sub-cortical and brainstem structures.

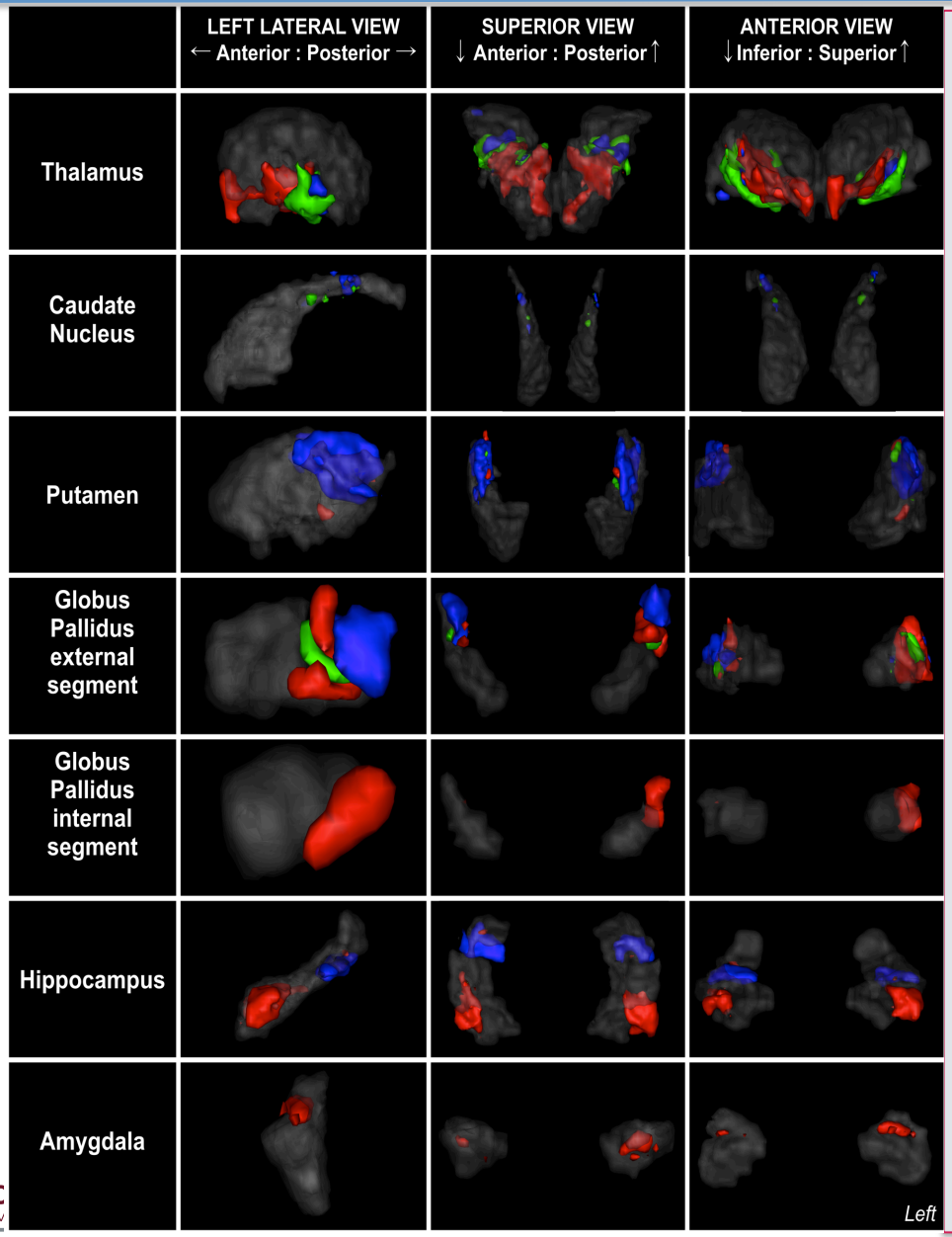
BLUE = EFFERENT

RED = AFFERENT



Lambert et al., Confirmation of functional zones within the human subthalamic nucleus: Patterns of connectivity and sub-parcellation using diffusion weighted imaging NeuroImage Volume 60, 2012 83–94

FUNCTIONAL CONNECTIONS

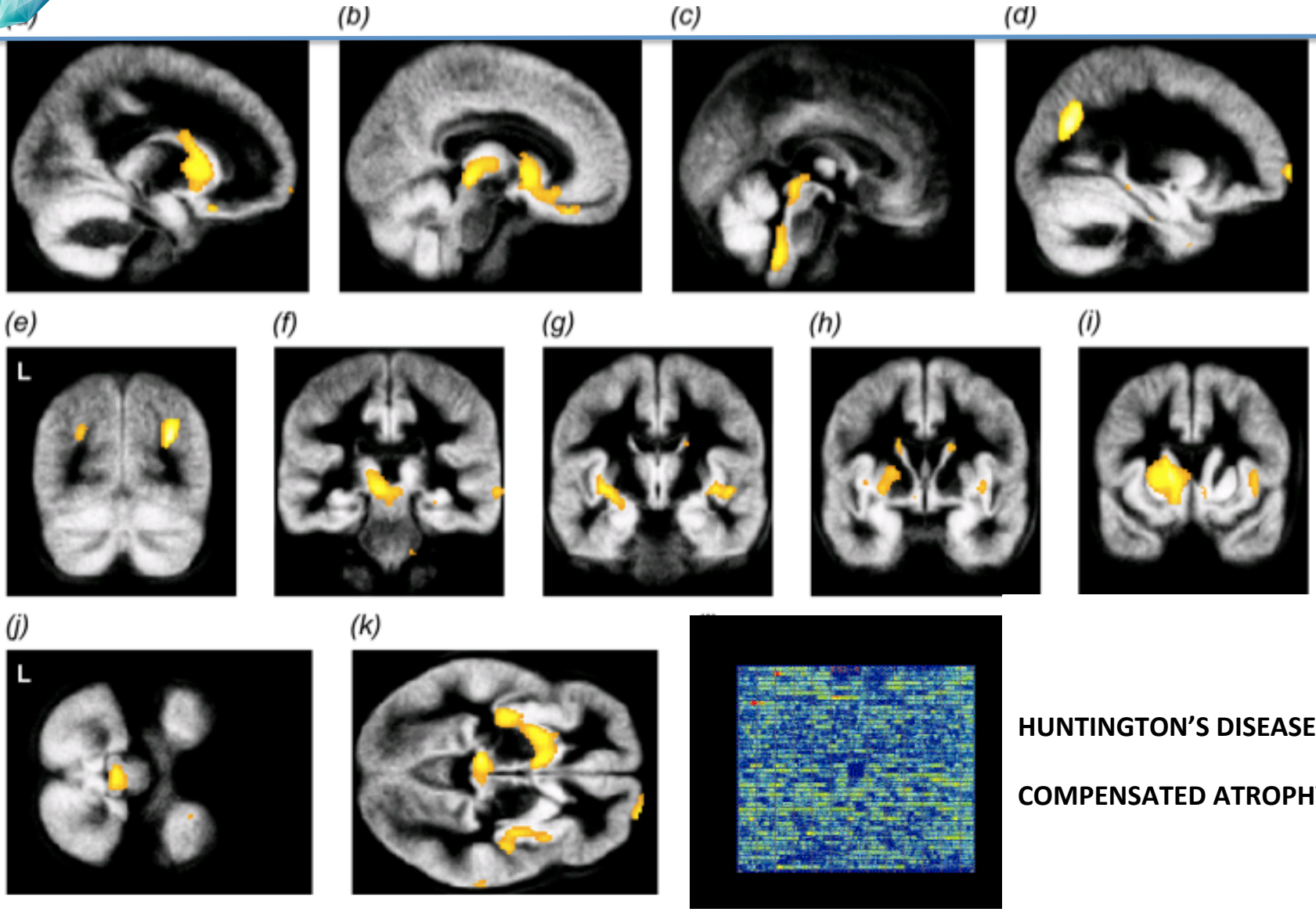


The posterior aspect of the STN projects to structures consistent with a motor structure:
Posterior putamen
Posterior GPe
Mid caudate nucleus
Ventro-lateral thalamic nuclei
Posterior Insula
Posterior hippocampus

The anterior aspect of the STN projects to structures consistent with a limbic structure:
Baso-lateral amygdala
Posterio-medial GPi
Inferio-mid putamen
Mid-GPe
Ventral-anterior and ventral-lateral thalamus
Anterior Insula
Anterior hippocampus

The middle "associative" STN projects to regions encompassing both the motor and limbic projections

STRUCTURAL SYSTEMS

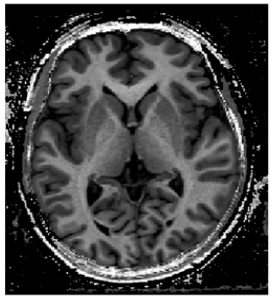


HUNTINGTON'S DISEASE

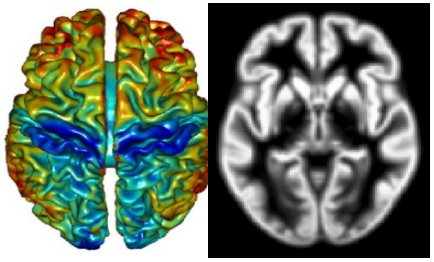
COMPENSATED ATROPHY

STRUCTURAL CHARACTERISATION

T1-weighted



Thickness/Volume



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Statistical inferences

Interpretation

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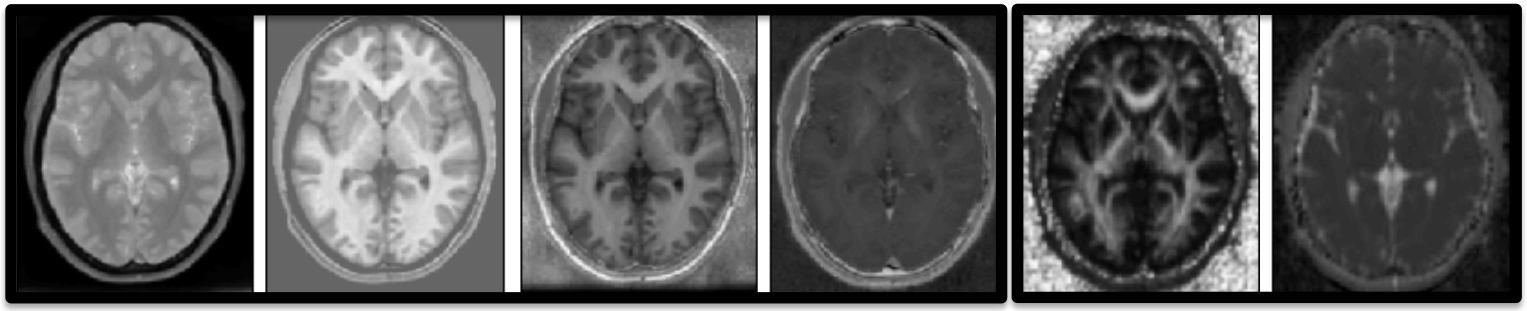
Interpretation

Quantitative and diffusion MRI

Proton density	Magnetisation transfer	R1 (1/T1)	R2* (1/T2*)	Fractional anisotropy	Mean diffusivity



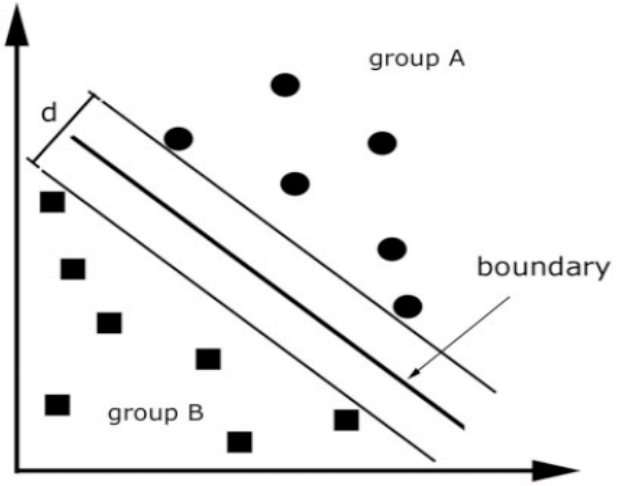
Water	Myelin	Water motility	Iron	White matter « integrity »

by A. Ruef

CLASSIFICATION & CONNECTIONS

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

SUPPORT VECTOR MACHINE CLASSIFICATION



INFORMATICS REFINE PATTERN ANALYSES

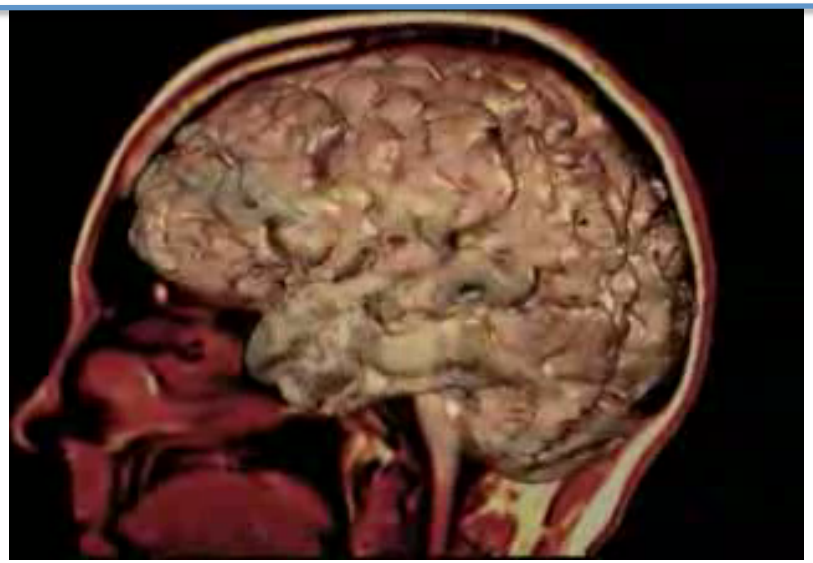
	ADNI AD	ADNI HC	Total
AD by SVM	15	3	18
HC by SVM	5	17	22
Total	20	20	40

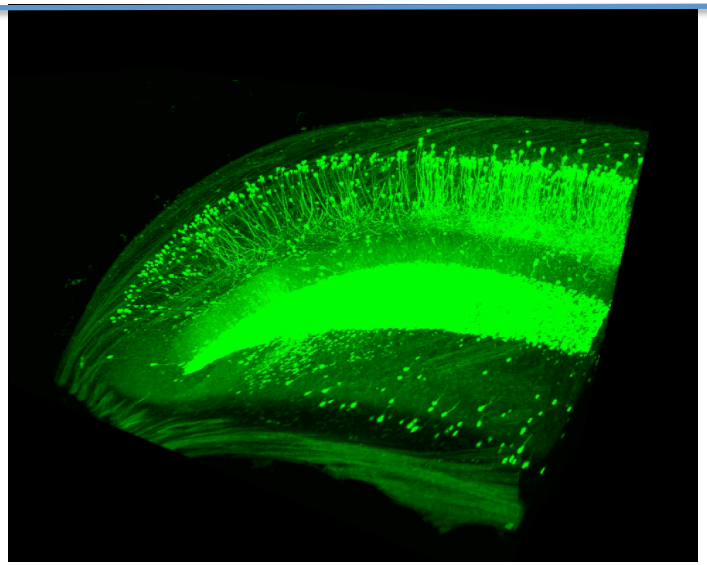
Sensitivity 75%

Specificity 85%

SVM trained on pathologically proven AD

ANATOMICAL CONNECTOMICS





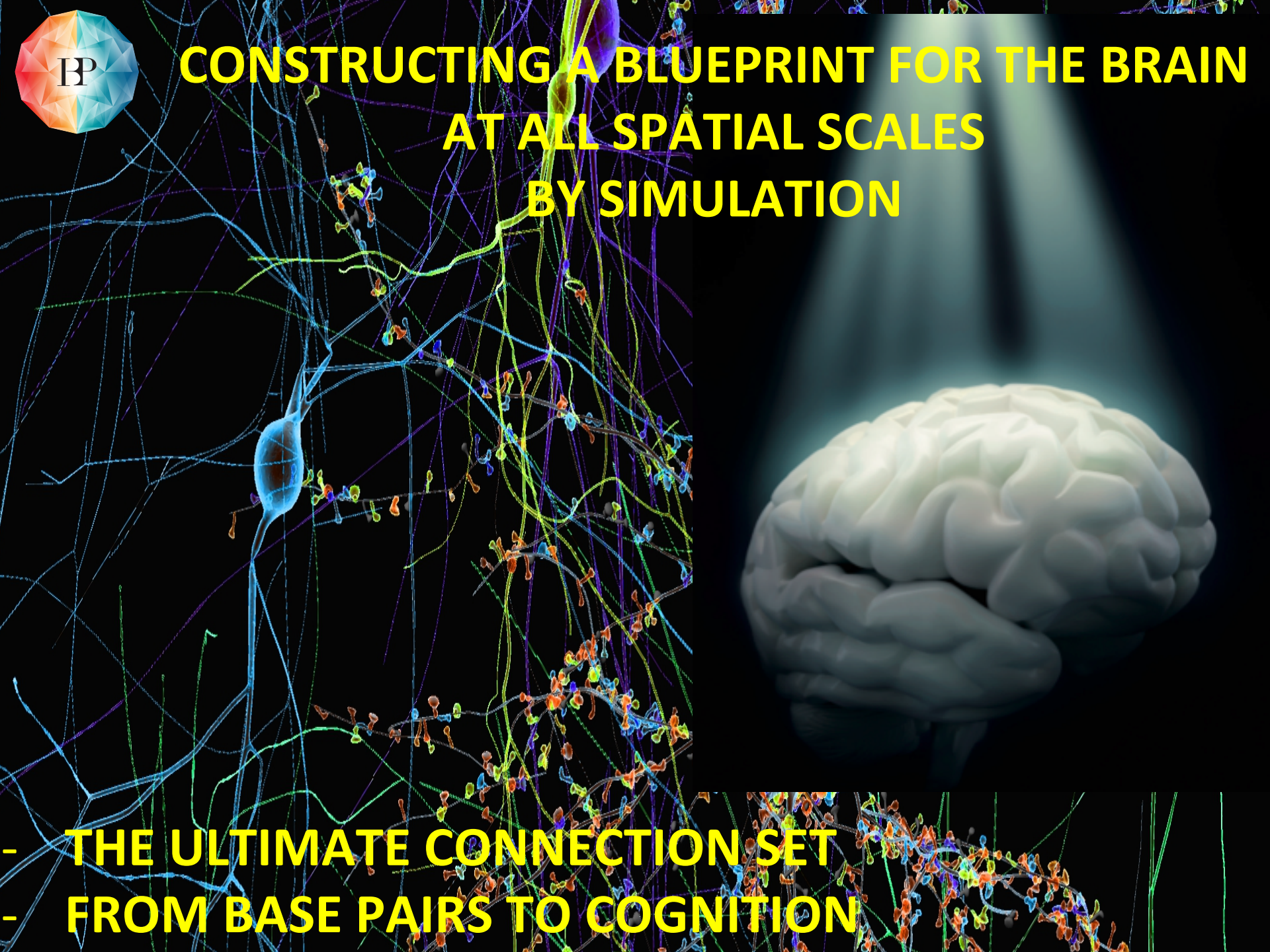
CONFRONTING PARADIGMS

CARTESIAN MODEL (TOP DOWN)

Mental theory
Mathematically expressed model
Confrontation with “relevant” data
Parameterisation and optimisation of model
Facts

SIMULATION MODEL (BOTTOM UP)

Multimodal and multivariate data
Mining to demonstrate structures by correlation &/or classification
Mathematically expressed model
Exploration of structures to generate hypotheses
Investigation of hypotheses
Knowledge

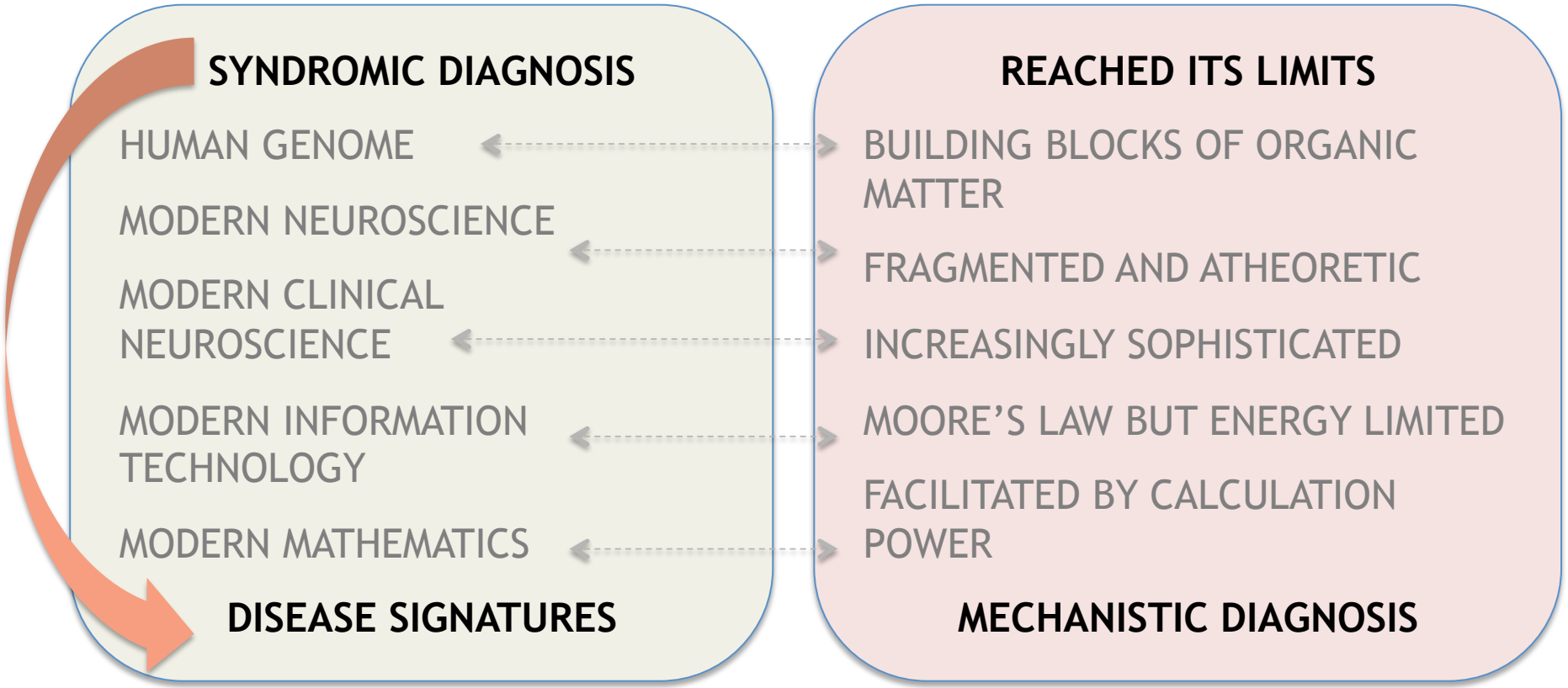


CONSTRUCTING A BLUEPRINT FOR THE BRAIN AT ALL SPATIAL SCALES BY SIMULATION

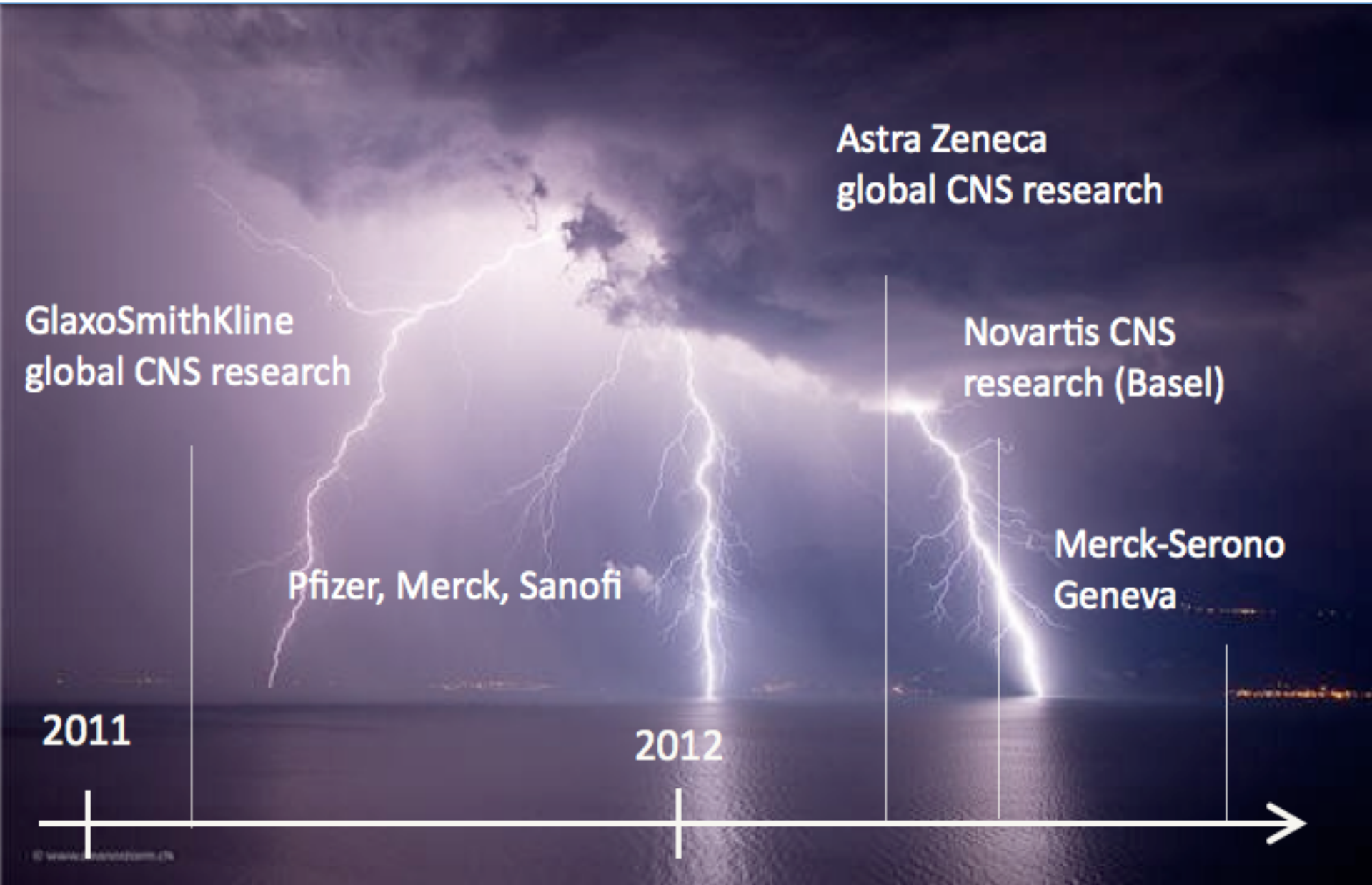
- THE ULTIMATE CONNECTION SET
- FROM BASE PAIRS TO COGNITION

FUTURE MEDICINE

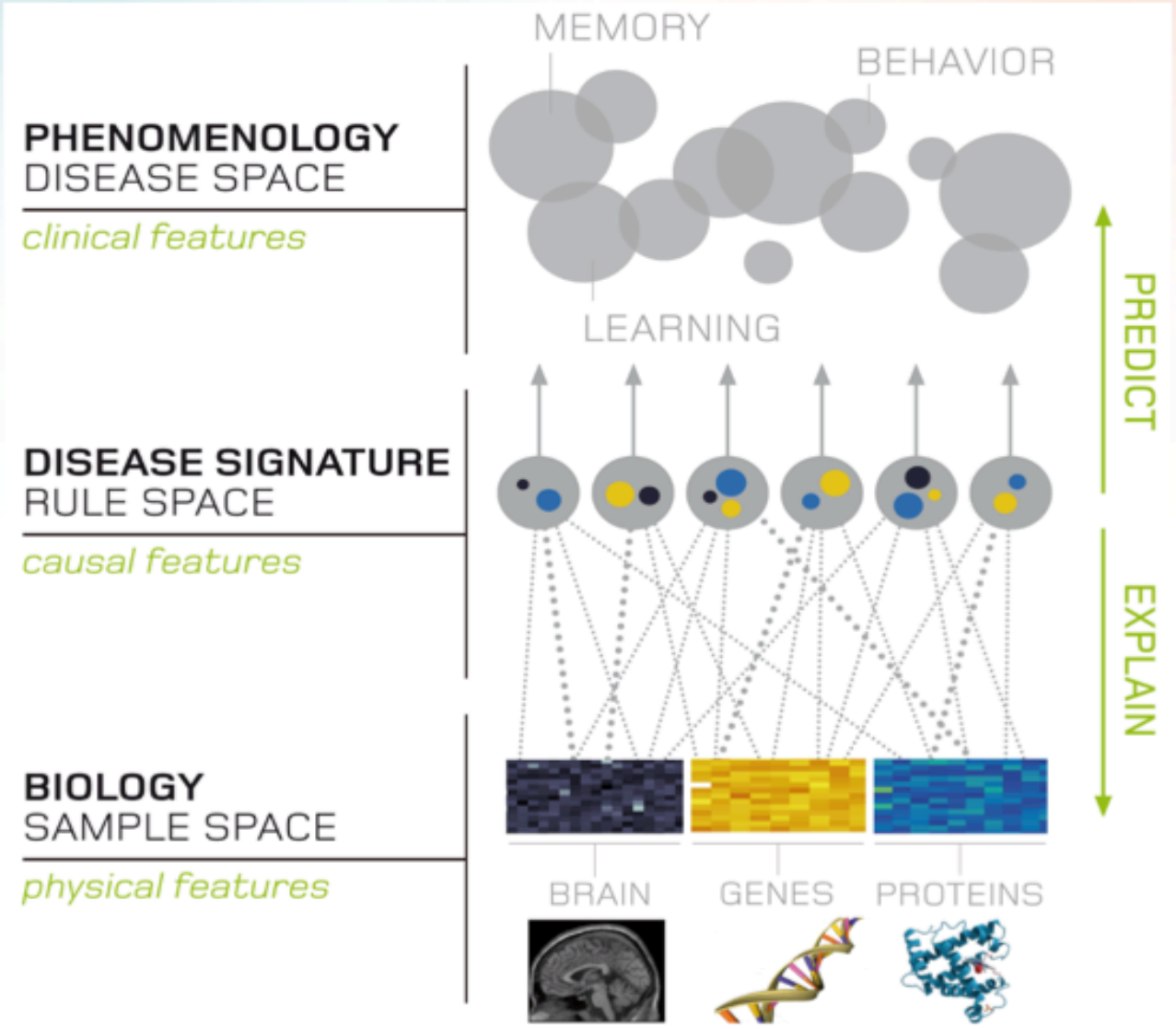
The Medical Informatics Platform



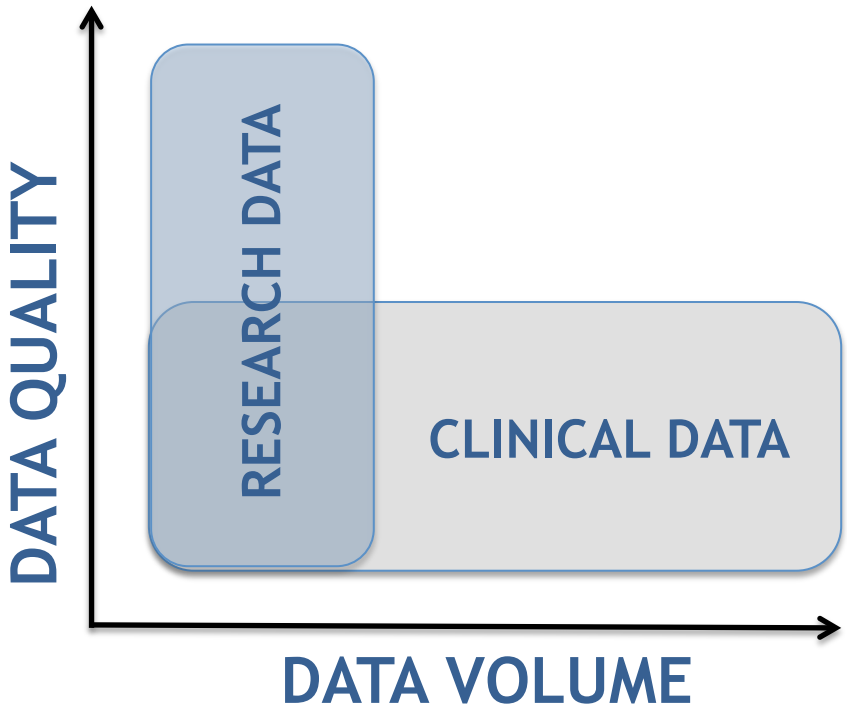
THE DECLINING INTEREST OF PHARMA



CONNECTIONS BETWEEN BIOLOGY & DIAGNOSIS



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

ETHICAL CHALLENGES

PRIVACY

- DE-PERSONALISATION
- AGGREGATION

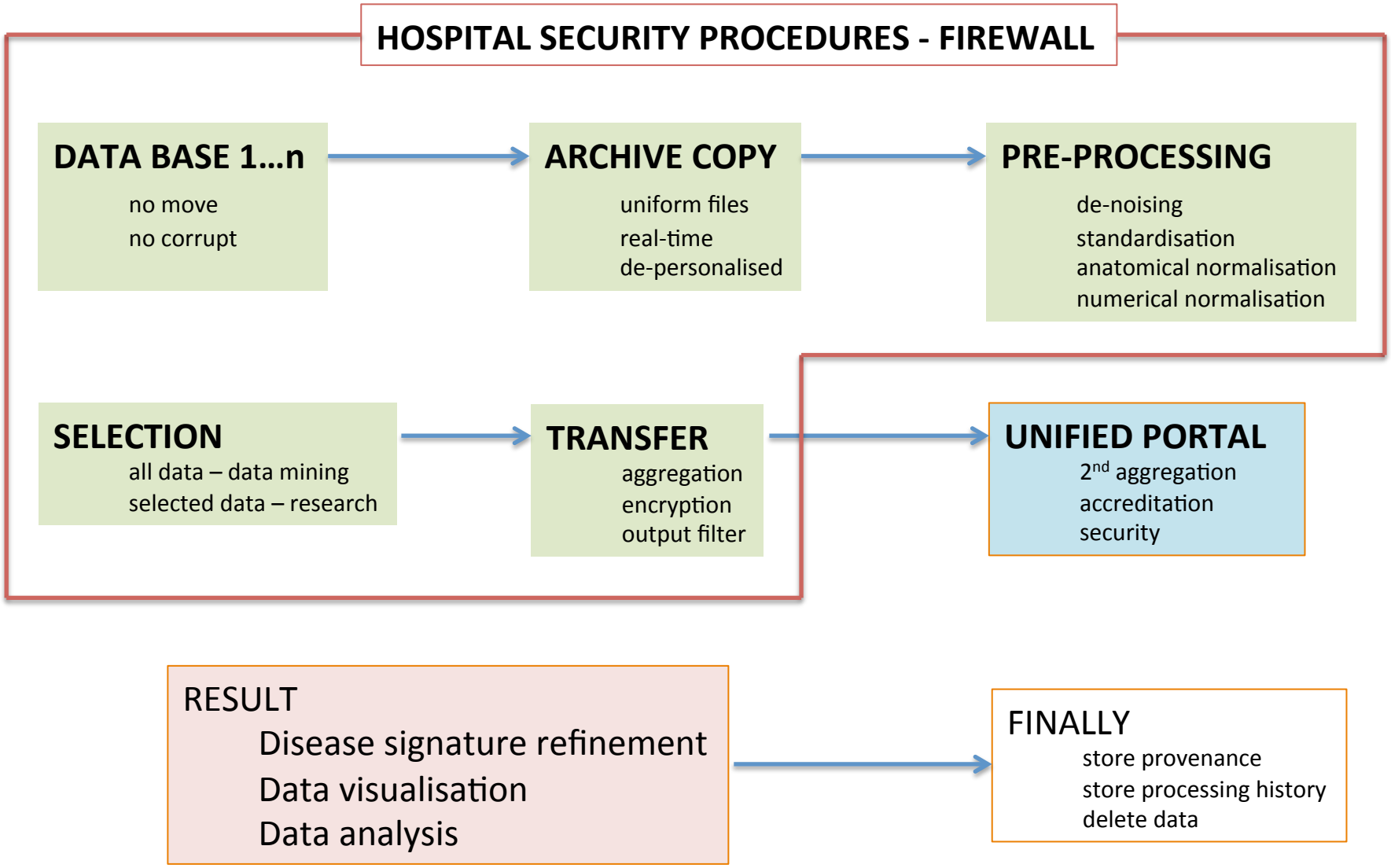
CONSENT

- BROAD CONSENT
- RETROSPECTIVE – PROSPECTIVE

MANAGEMENT OF ETHICS

- LOCAL ETHICS COMMITTEES
- VALUE AND CREDIBILITY OF SCIENCE

MEDICAL INFORMATICS PLATFORM



RECLASSIFYING DISEASE WITH DATA MINING

DISEASE SIGNATURES

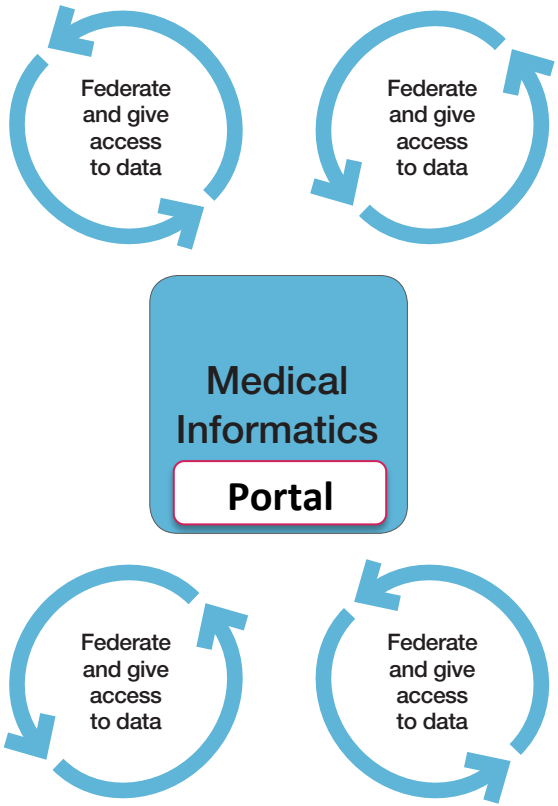
- DATA MINING
- REAL-TIME
- CONTINUOUS
- ITERATIVE

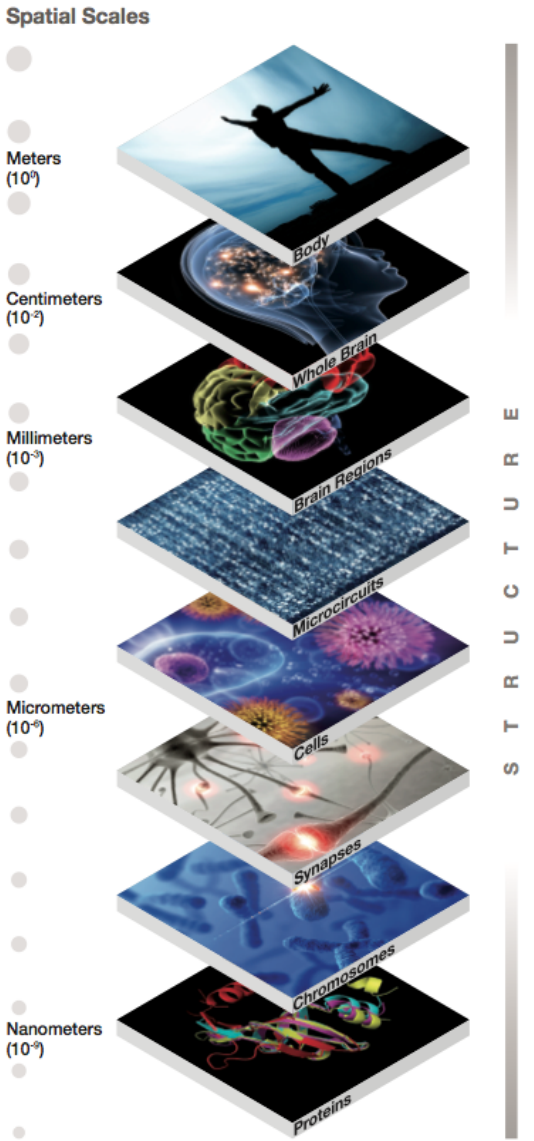
DATA VISUALISATION

- EPIDEMIOLOGY
- HEALTH SERVICES

RESEARCH

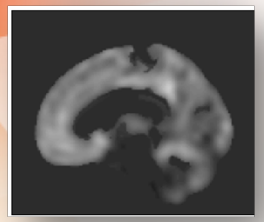
- HYPOTHESIS TESTING
- CLINICAL TRIALS





DATA INTEGRATION

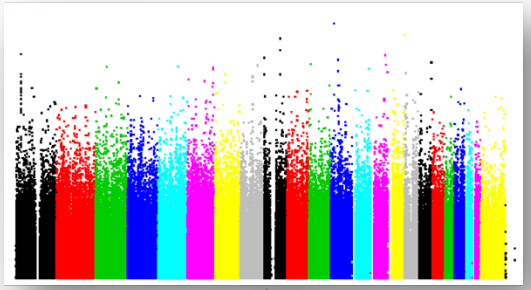
BRAIN IMAGING



PET

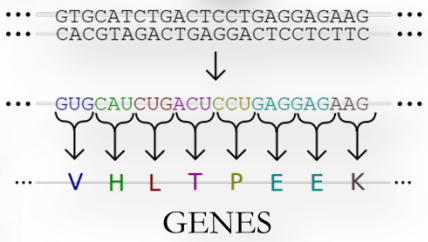
MRI

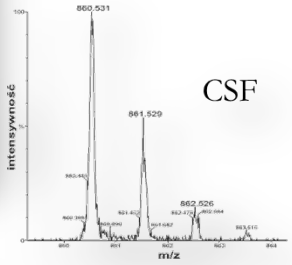
CLINICAL SCALES & MEASUREMENTS



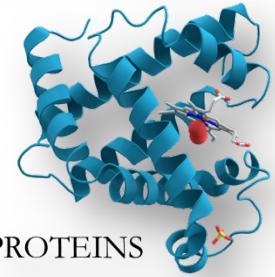
Organising Tabulating

Processing…

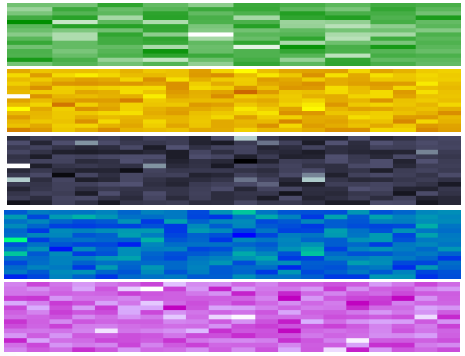




CSF



PROTEINS



MRI data

PET data

Gene data

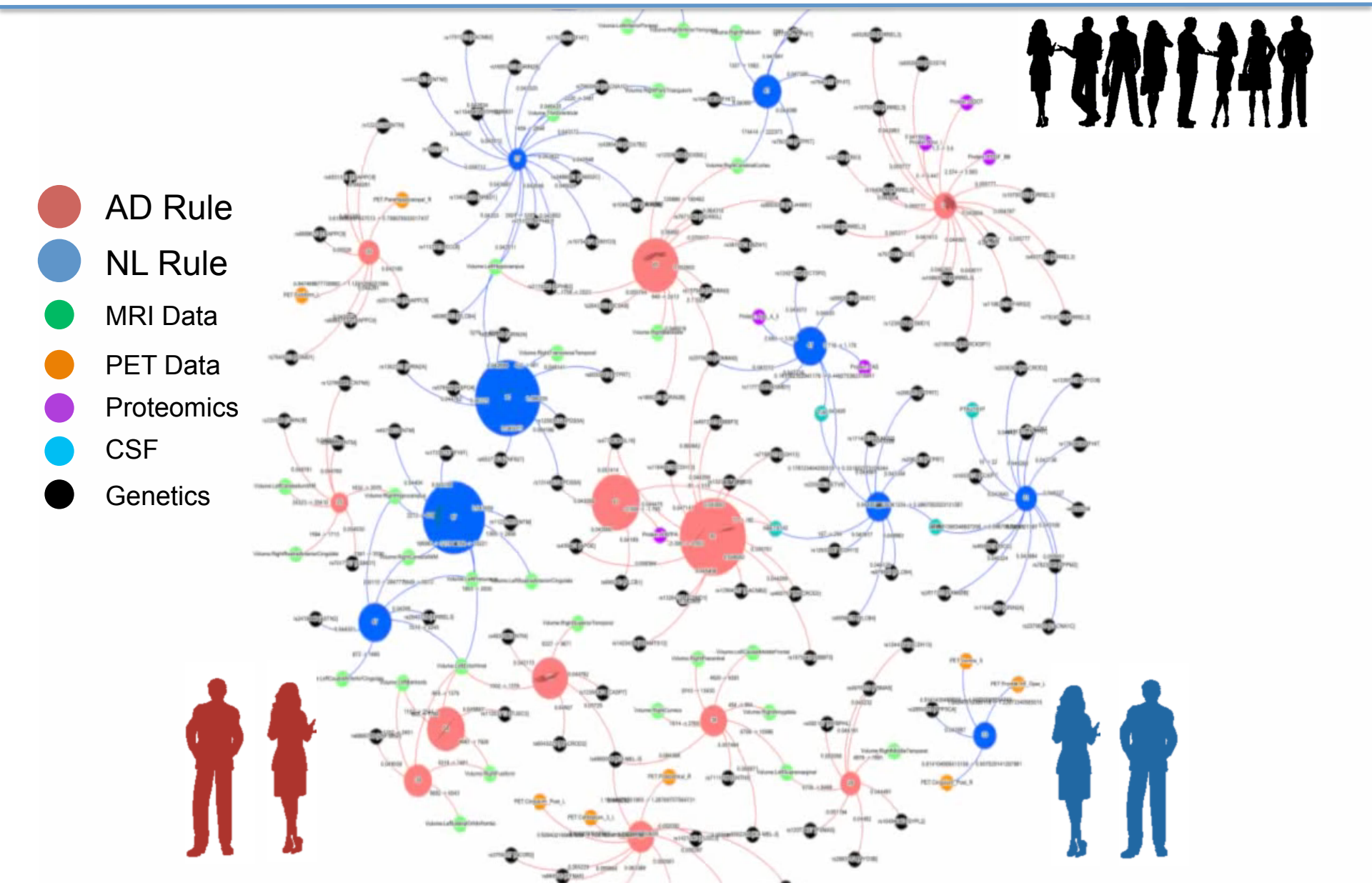
CSF data

Protein data

912 Alzheimer's patients
5566 Healthy controls

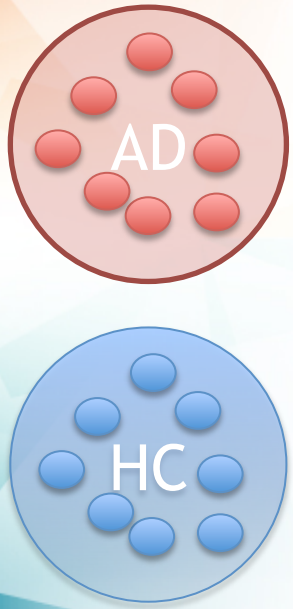
- **Phenotype led semi-supervised clustering**
- **Biologically led classification**
- **High dimension and feature learning**

LINKS BETWEEN PHENOMENOLOGY & BIOLOGY

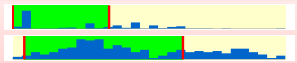


FINDING CAUSAL RULES

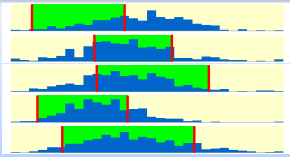
- Phenotype-led semi-supervised clustering



• AD RULES

1	ABETA142 Protein: PAPPA	
2	Protein: PAPPA ABETA142	
3	Volume:LeftHippocampus Volume:RightCerebralCortex Volume:RightBankssts	
4	Volume:LeftEntorhinal Volume:RightFusiform Volume:LeftBankssts	

• HC RULES

PET:Cingulum_Post_L PET:Cerebelum_3_L PET:Postcentral_R	
Volume:RightAmygdala Volume:LeftCaudalMiddleFrontal Volume:RightPrecentral Volume:RightCuneus Volume:LeftSupramarginal	
Protein: Prol_I Protein: SGOT Protein: PDGF_BB	
PET:ParaHippocampal_R PET:Fusiform_L	

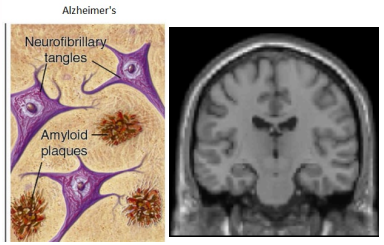
- New disease classification.
- Standard Format

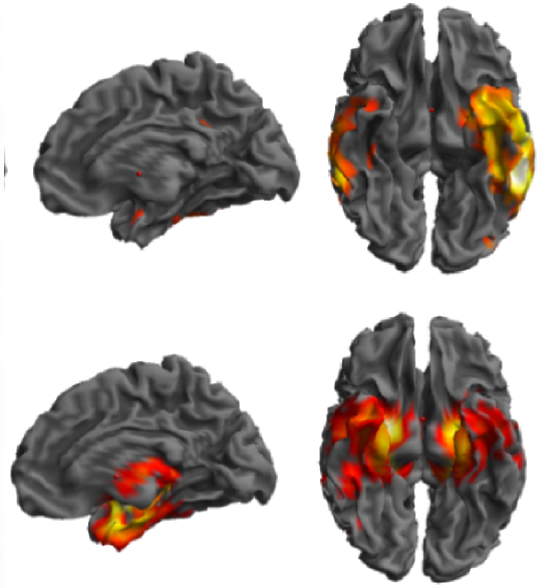
FINDING CAUSAL RULES 2

- Biologically-led classification

AD

HC



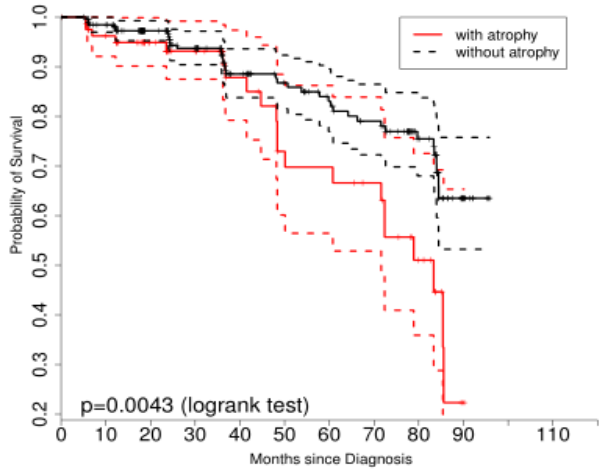


AD + Symptoms + Pathology

AD - Symptoms NO Pathology

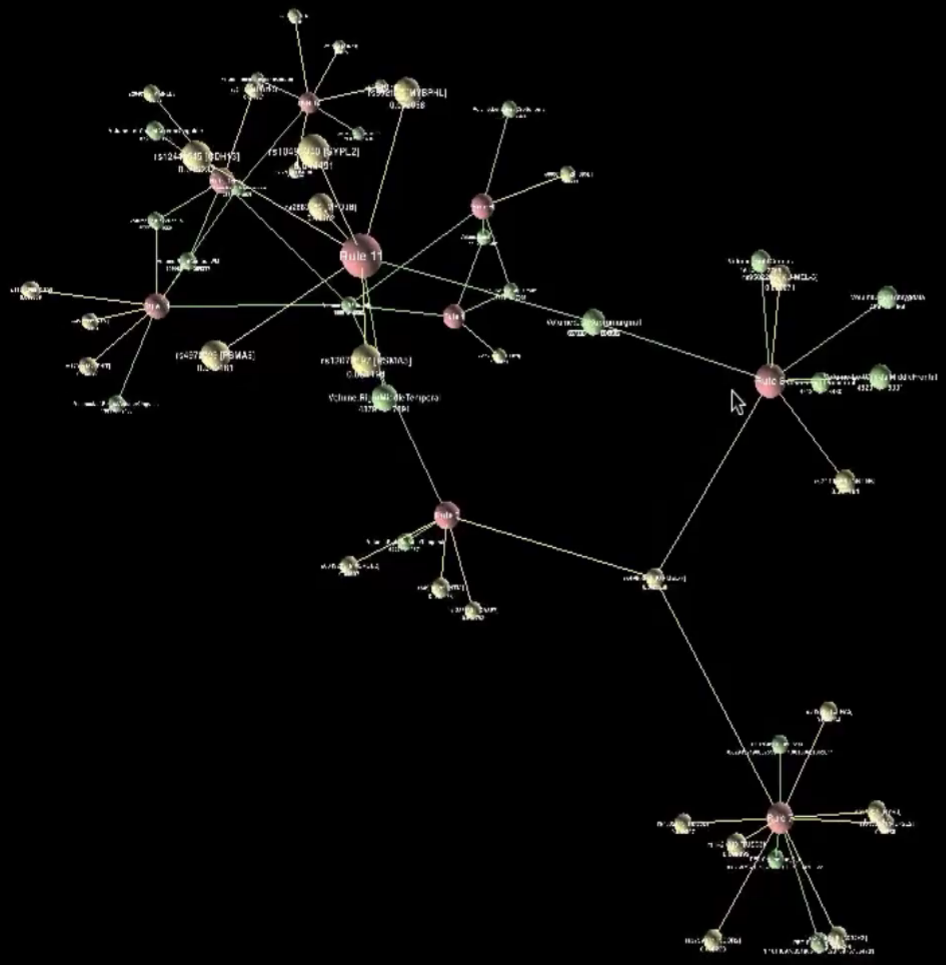
HC + NO Symptoms + Pathology

HC - NO Symptoms NO Pathology



- Intermediate phenotype of disease
- Automated diagnosis based on pathology

LINKS BETWEEN PHENOMENOLOGY & BIOLOGY

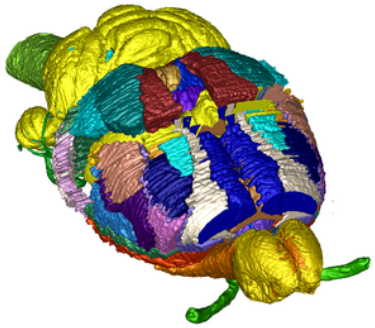


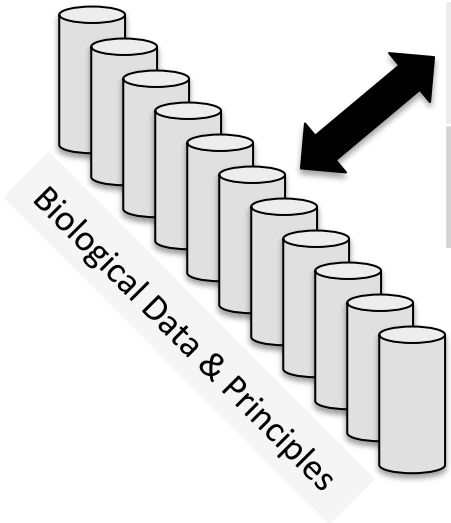
REVERSE ENGINEERING – TO VALIDATE

Brain Atlases
Data source

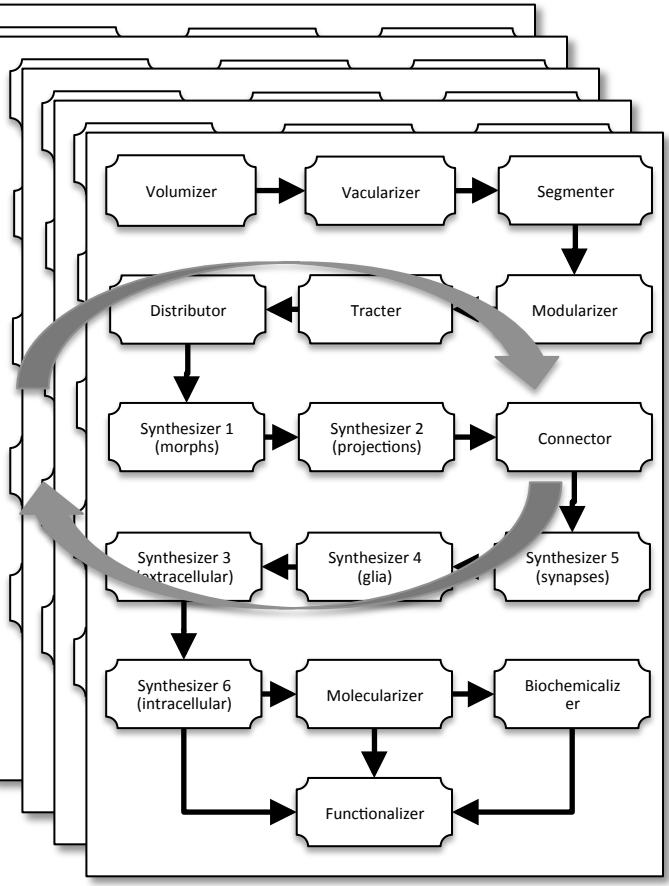
Biological Parameter Constraints & Biological Principles
Configurations

Multi-constraint Algorithms
Brain Reconstruction Workflows





	Data	Principles	Disease Data	Disease Principles
Bouton density	A	AA	A	AA
Synapse density	B	BB	B	BB
Syns/ connect	C		C	CC
P Connect			D	...
Synaptic Response			E	...



NORMAL

DISEASE

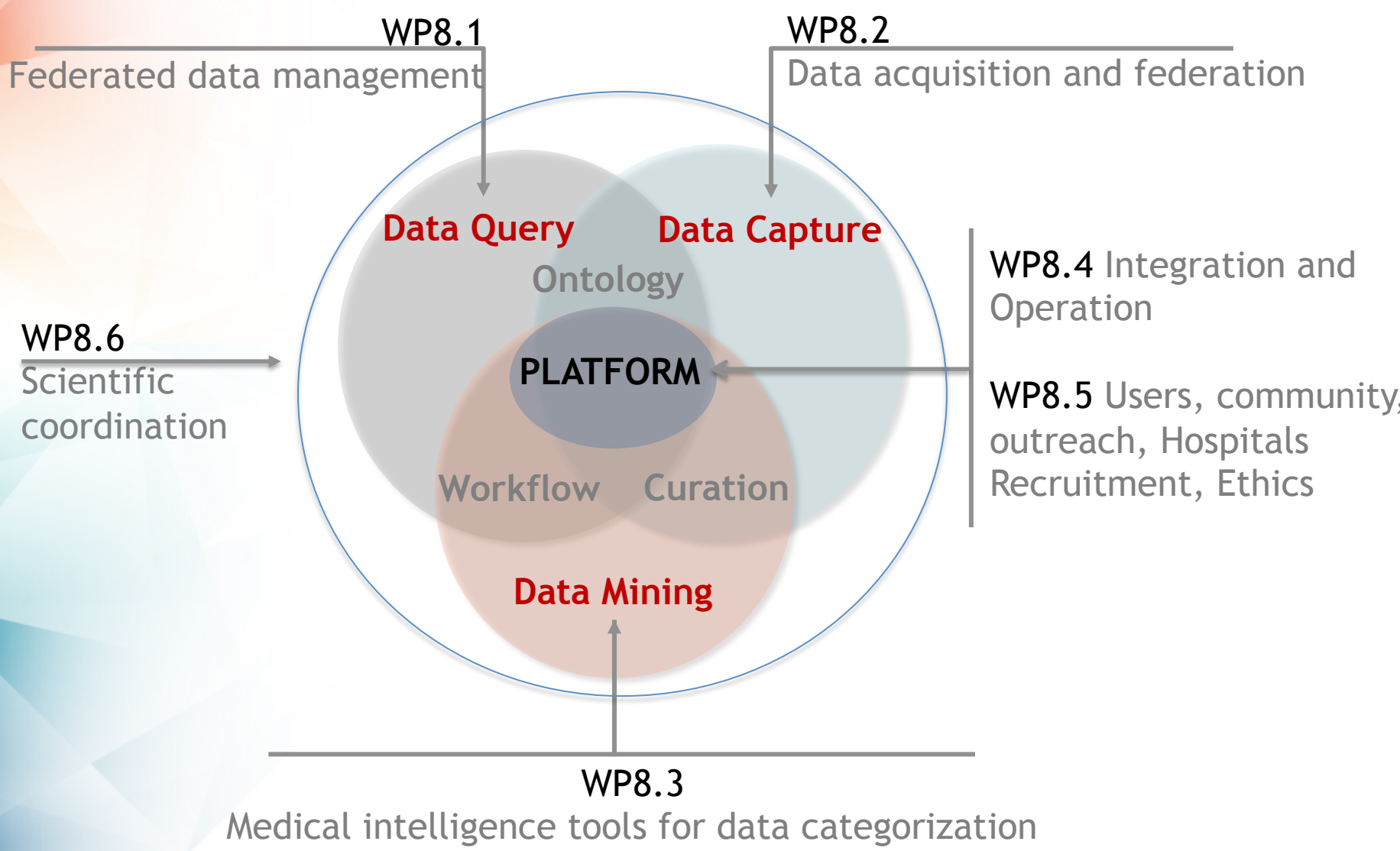
INFORMATICS BASED APPROACH

Informatics-based characterisation of brain diseases

- **Unlocks** added value of clinical records & data
- **Catalyses** a major collaboration of hospitals
- **Federates and integrates** knowledge and data about human diseases – IT based atlas-encyclopedia
- **Analyses and Derives** biologically-grounded brain disease signatures for new diagnostic classification

- **Understanding** biological similarities and differences between brain diseases
- Providing **new discovery** pipelines to prevent, diagnose and treat brain disorders

MIP INTEGRATED VIEW



THANKS FOR LISTENING

MIP HBP

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www.humanbrainproject.org

www.unil.ch/lren