GridKa course – Karlsruhe 2014

BRAIN PATHOLOGY & BIG DATA

Richard Frackowiak (CHUV & EPFL Lausanne)

MOTIVATION 1

Alzheimer's disease: **2 people out of 10** 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 **2 out of 1,000** people.

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

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

WHAT CAUSES IT?

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

What pathophysiological abnormalities are causes and which effects?

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?	- **???**

HISTORY from the patient

Always interrogate the partner, a close friend, or a nurse who knows the patient

- **US President 1981-1989**
- **Oldest US President on record**
- **Public announcement that the President was suffering from AD**

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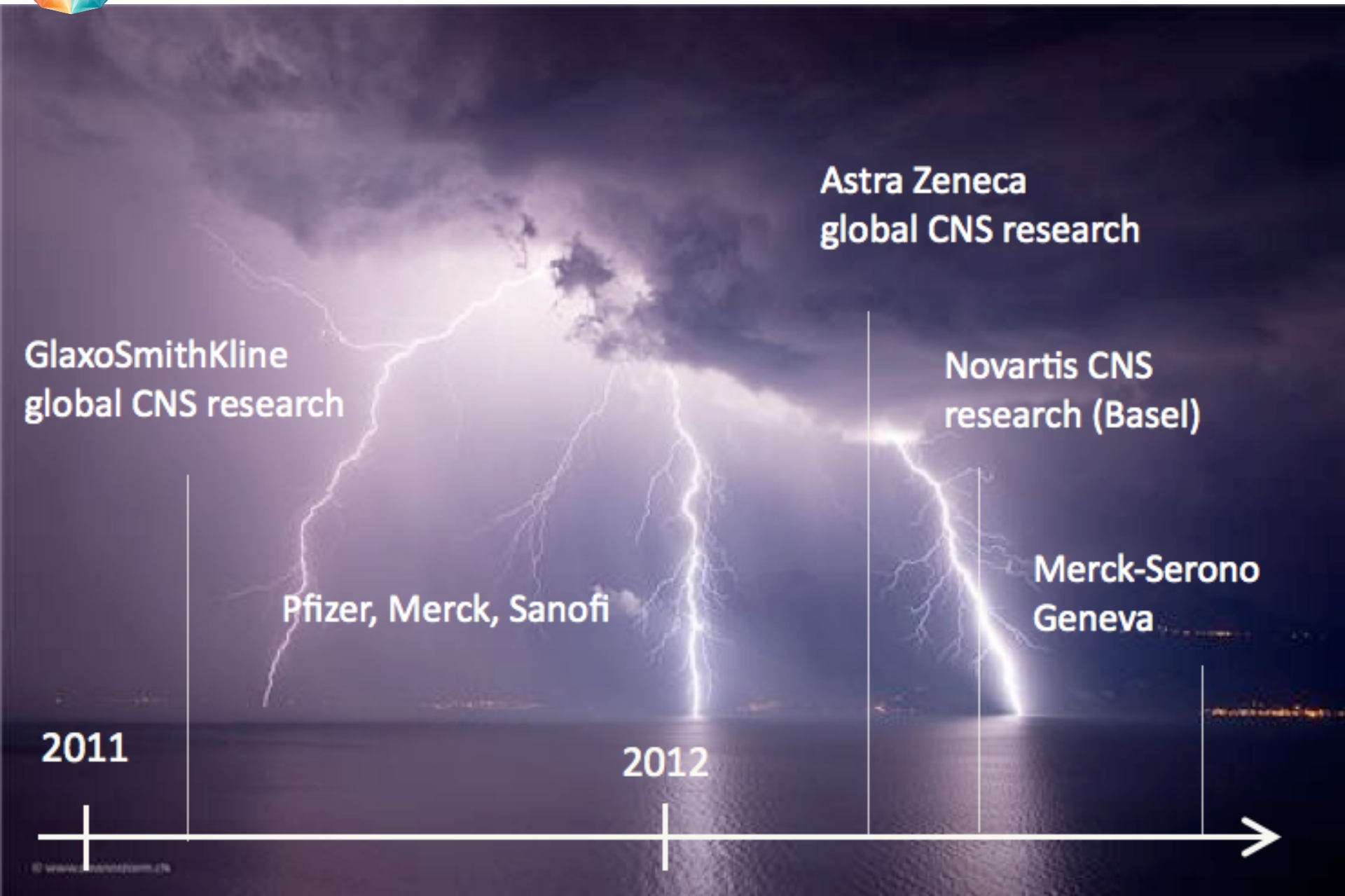
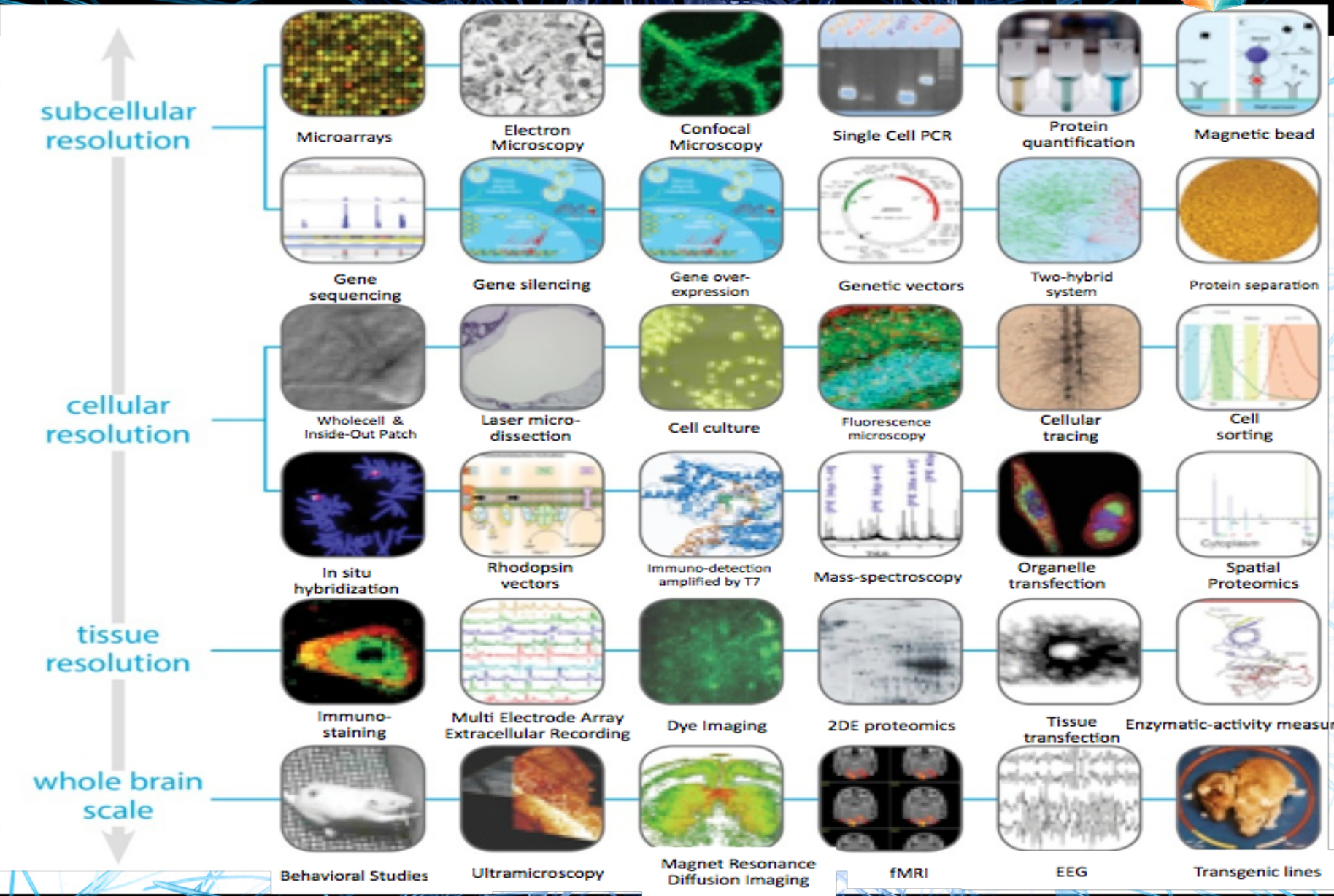
And what about preventive treatment?	- **???**

HBP
The Human Brain Project

THE DECLINING INTEREST OF PHARMA



NEUROSCIENCE METHODS



HBP
The Human Brain Project

MOTIVATION 2 - DATA FEDERATION & INTEGRATION

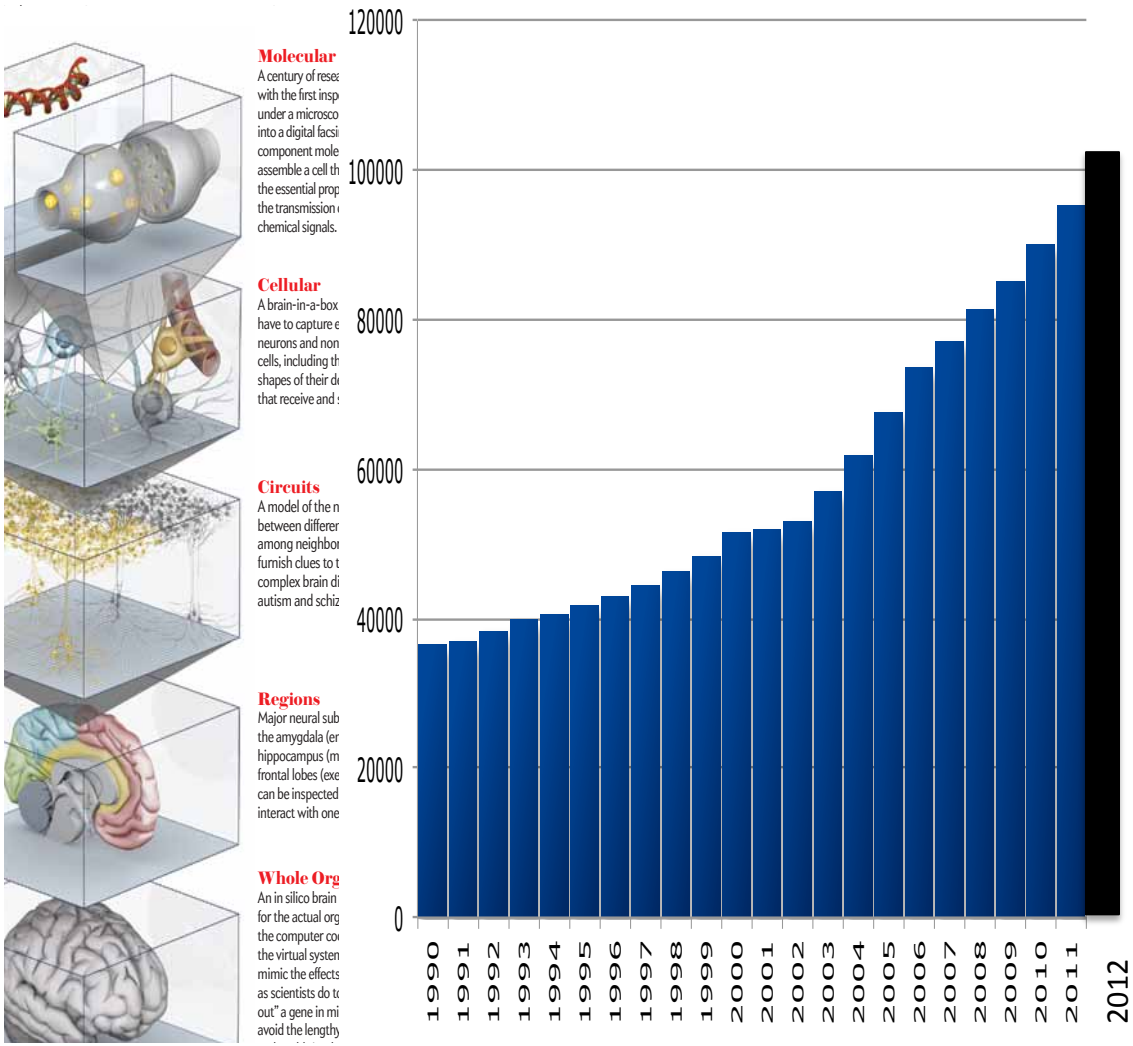
Reality check

1. Data and knowledge is growing **exponentially**
2. Data and knowledge is increasingly **fragmented**
3. Benefits for society seem to be **decreasing** (diagnostic accuracy, treatments, drugs)
4. Economic burden increasing rapidly to **unsustainable** levels

What we lack

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

Number of Peer Reviewed Publications on the Brain /yr



MOTIVATION 3 - INFORMATION TECHNOLOGY

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

What is a FET Flagship?

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

GOAL

Develop informatics technology
to unify our understanding of the human brain

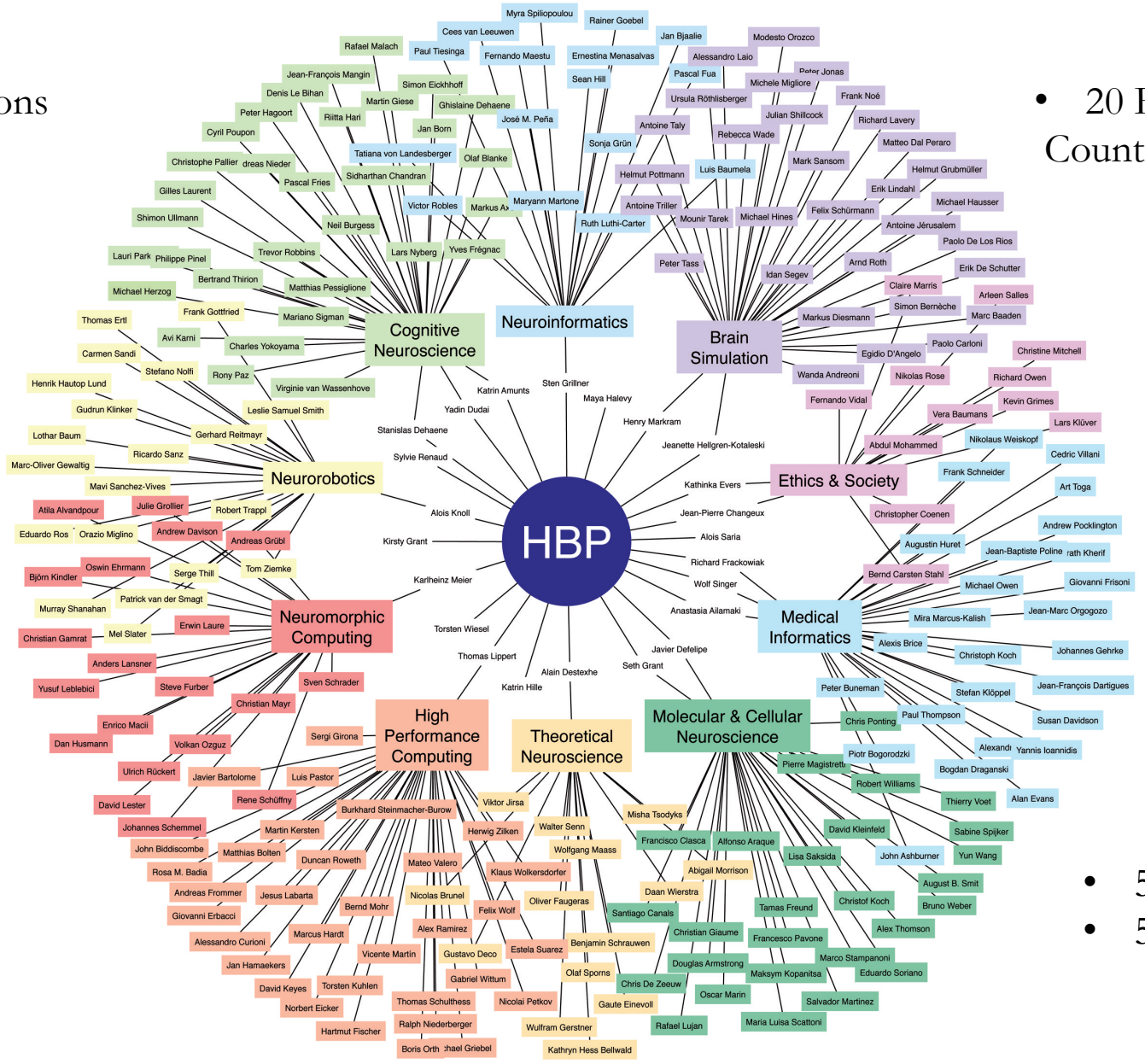
HBP is NOT primarily a data generation project

It IS a data integration project.

The Consortium

- 80 Institutions
- 150 PIs
- 2000 PhDs

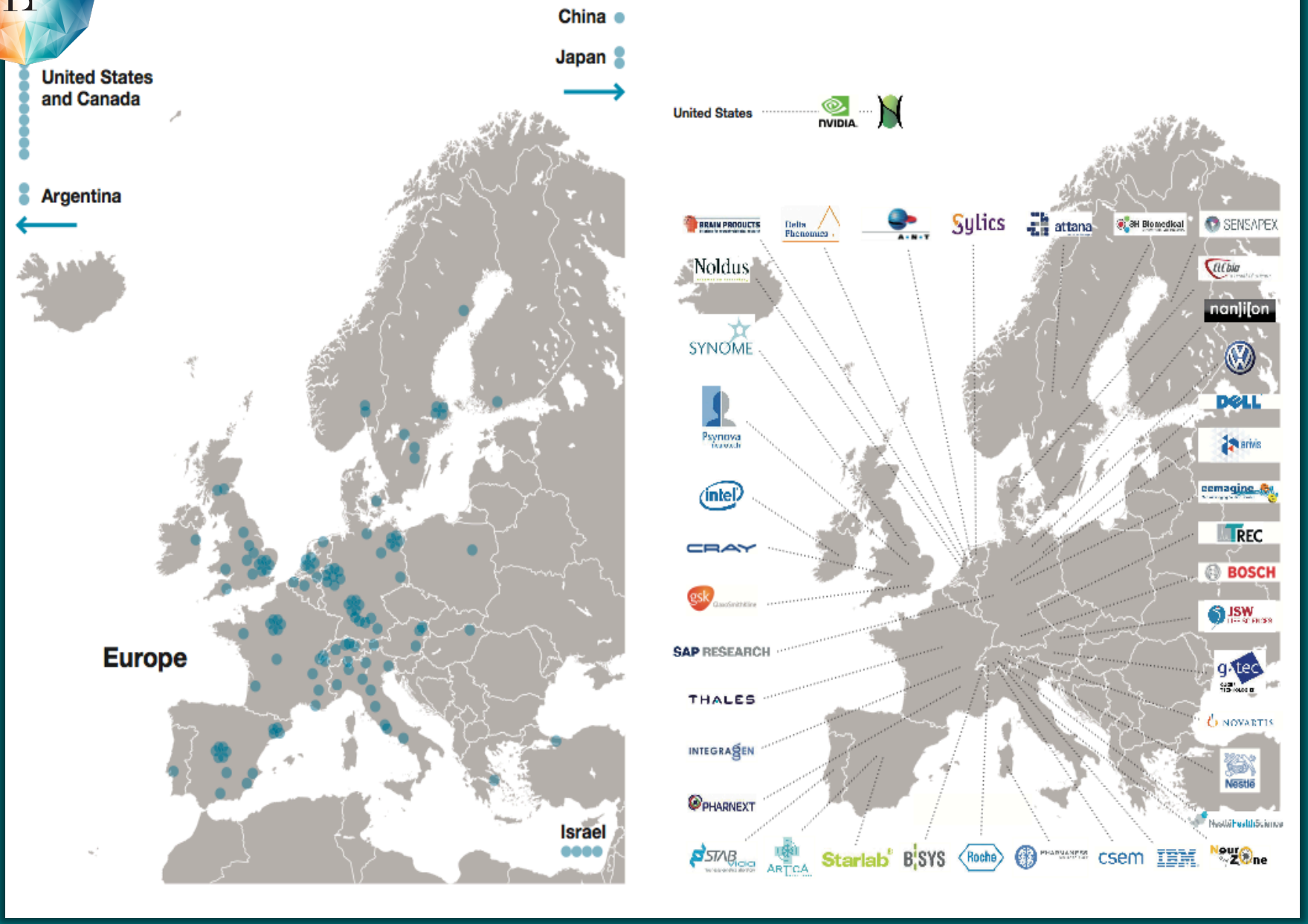
- 20 European Countries

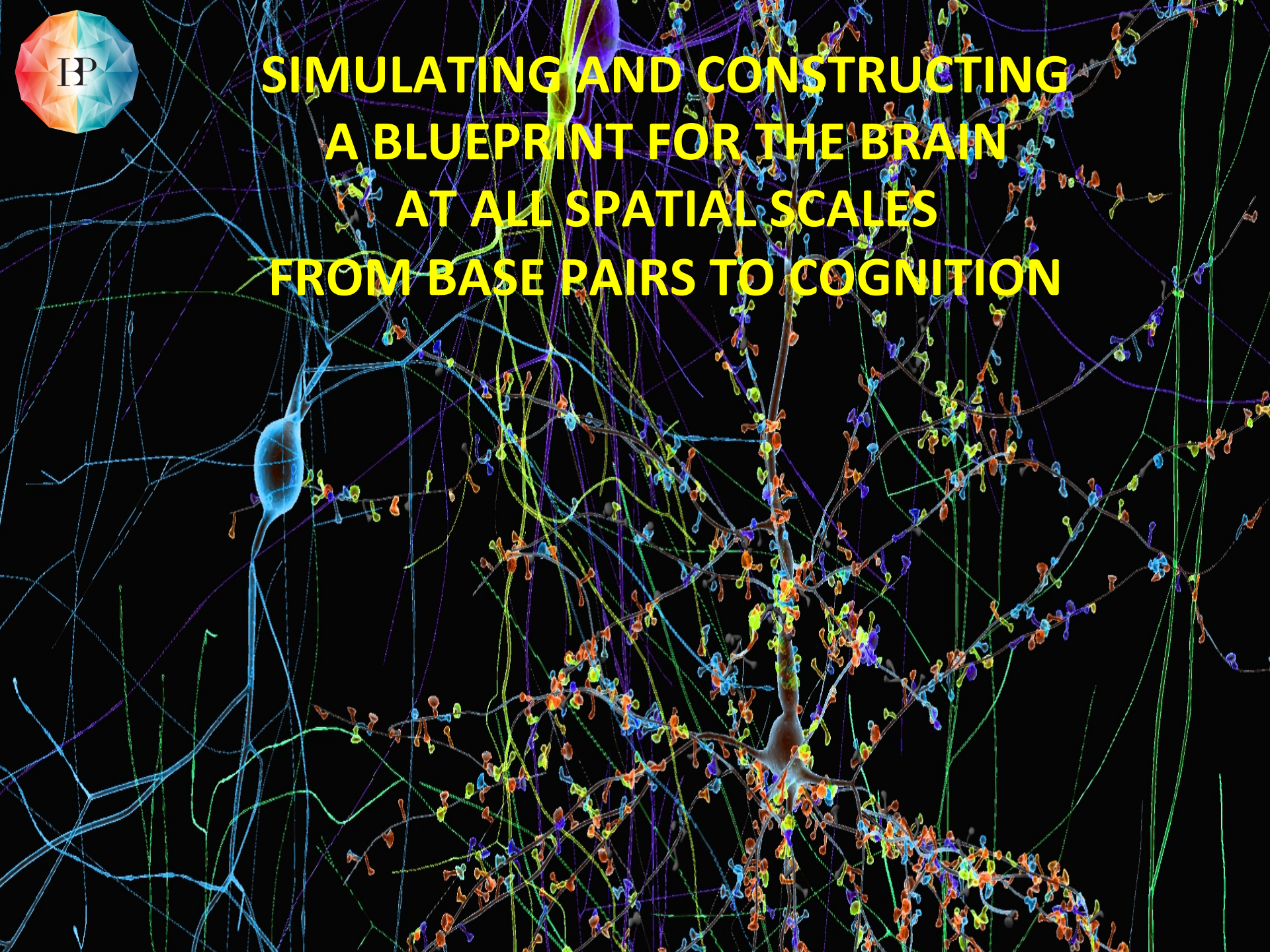


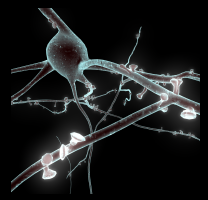
- USA
- Israel
- Japan
- China
- Canada

- 50% Core
- 50% Grants

THE CORE CONSORTIUM & INDUSTRIAL PARTNERS




SIMULATING AND CONSTRUCTING
A BLUEPRINT FOR THE BRAIN
AT ALL SPATIAL SCALES
FROM BASE PAIRS TO COGNITION

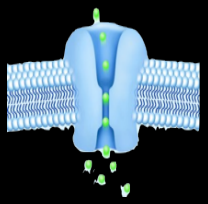


NEURONS

$$\frac{C_m dV_m}{dt} = \frac{E_m - V_m}{R_m} + I_{channels} \ldots + I_{synapses}$$
$$+ \frac{2(V_{m_{i+1}} - V_{m_i})}{R_{a_{i+1}} + R_a} + \frac{2(V_{m_{i-1}} - V_{m_i})}{R_{a_{i-1}} + R_a}$$

10,000 neurons

~ 4,000,000 Electrical compartments (Rall Equations)



ION CHANNELS

$$\frac{dm}{dt} = \alpha_m(V_m)(1-m) - \beta_m(V_m)m$$
$$\frac{dh}{dt} = \alpha_h(V_m)(1-h) - \beta_h(V_m)h$$
$$I_{channel} = m^n h g_{channel}(V_m - E_{channel})$$

80,000,000 Ion Channels

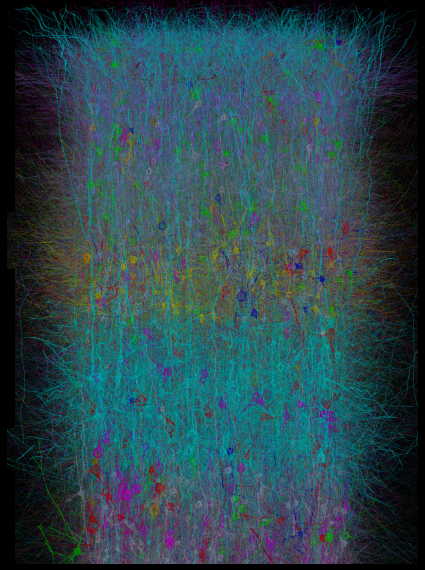
(Hodgkin-Huxley Equations)

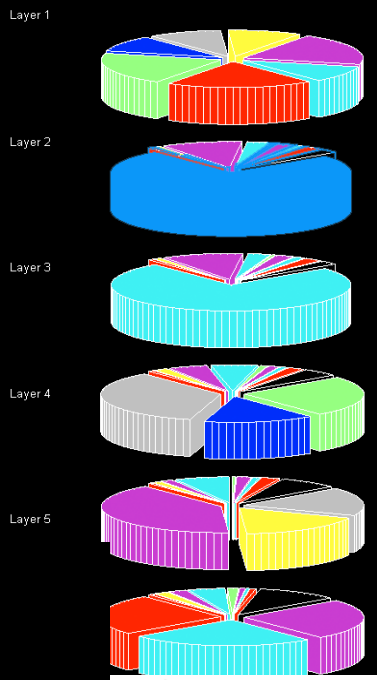
SYNAPSES

$$\frac{dx}{dt} = \frac{z}{\tau_{rec}} - ux\delta(t - t_{sp})$$
$$\frac{dy}{dt} = -\frac{y}{\tau_1} - ux\delta(t - t_{sp})$$
$$\frac{dz}{dt} = \frac{y}{\tau_1} - \frac{z}{\tau_{rec}}$$
$$\frac{du}{dt} = \frac{u}{\tau_{facil}} + U(1-u)\delta(t - \ldots$$
$$I_{synapse}(i) = \sum_j A_{ij} y_{ij}(t)$$

10,000,000 Synapses

(Tsodyks-Markram Equations)





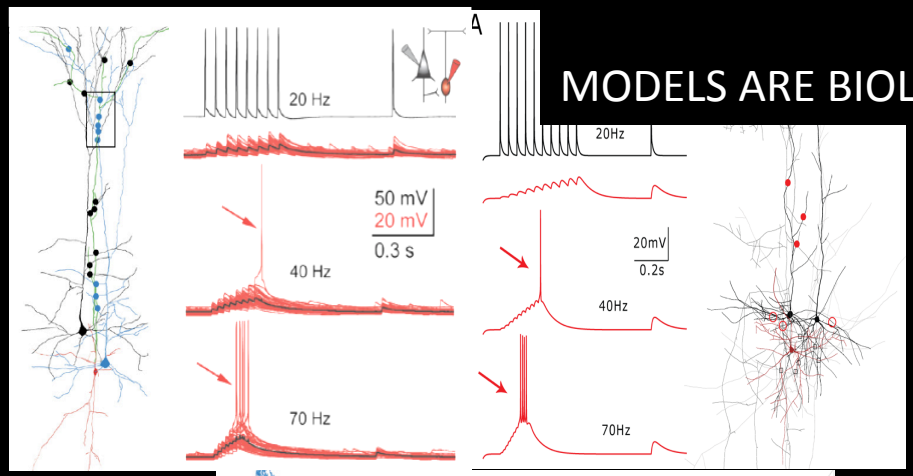
Markram et

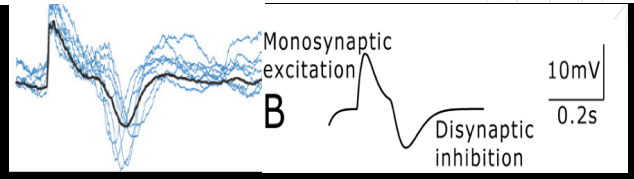
MODELS ARE DATA DRIVEN

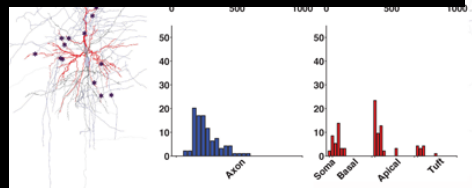
MODELS ARE MATHEMATICALLY EXPRESSED

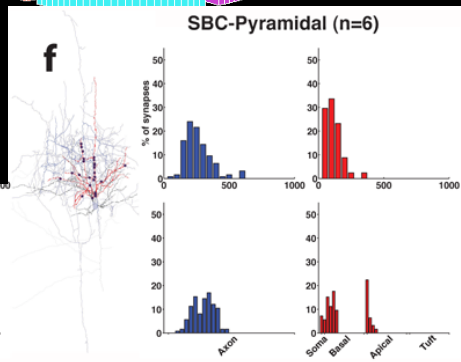
MODELS ARE BIOLOGICALLY VALIDATED

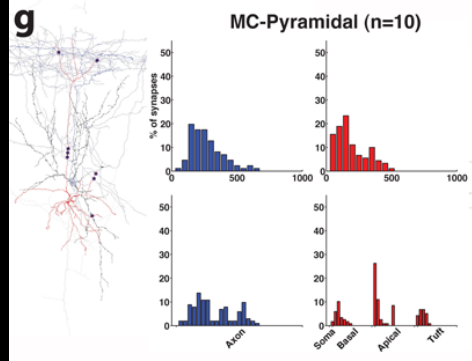
In vitro

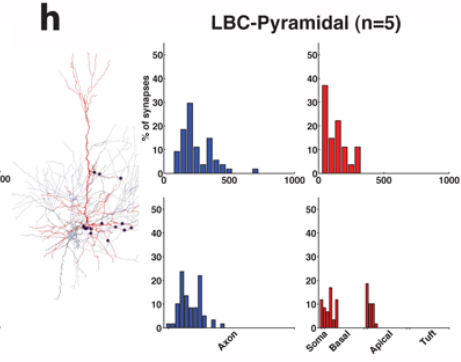






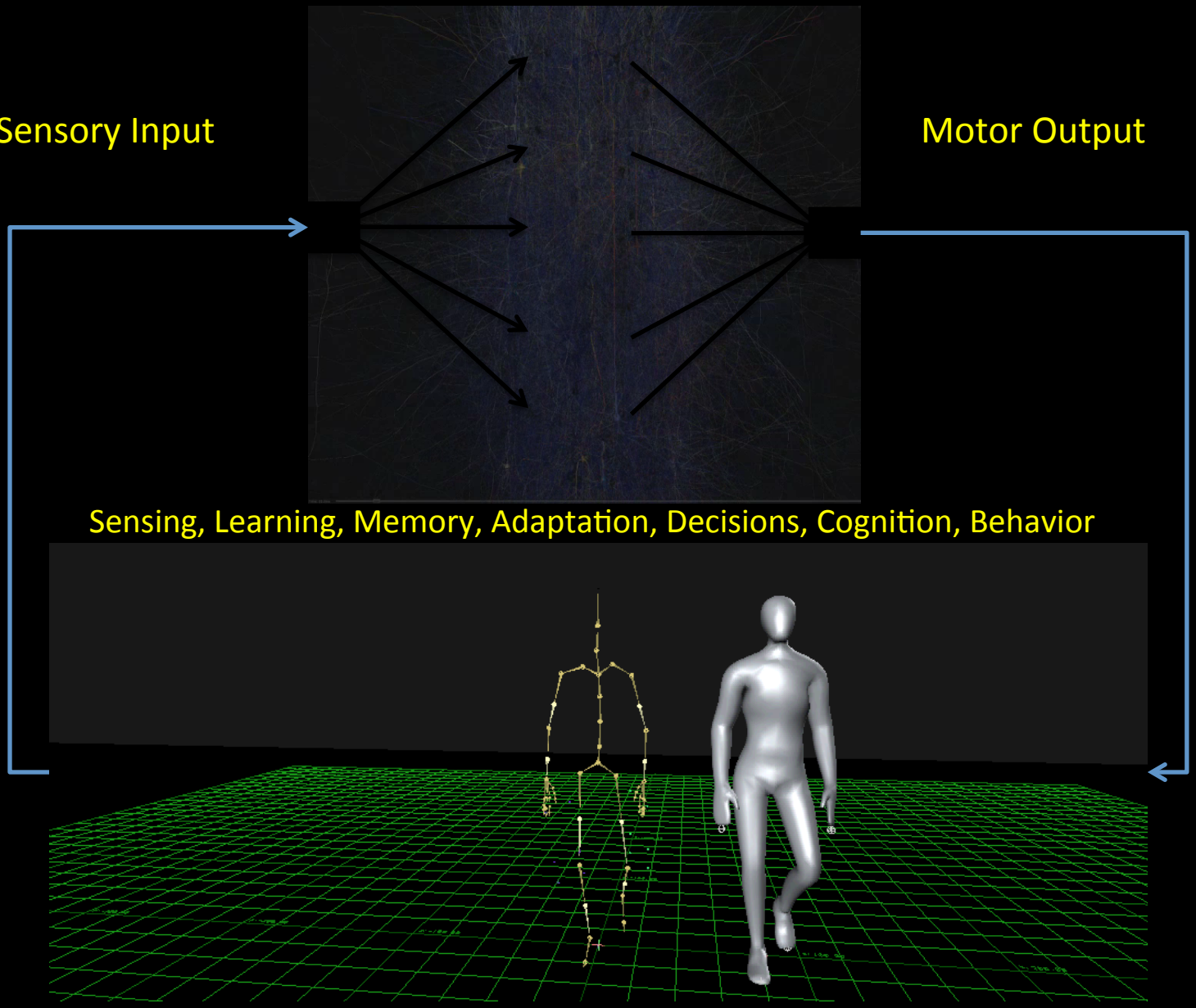







A SIMULATED PYRAMIDAL NEURON

NEURAL COMPUTATION:
CAUSAL CHAIN OF EVENTS LEADING TO COGNITION



MEDICINE AT A TIPPING POINT

SYNDROMIC DIAGNOSIS

REACHED ITS LIMITS

HUMAN GENOME

BUILDING BLOCKS OF ORGANIC MATTER

MODERN NEUROSCIENCE

FRAGMENTED AND ATHEORETIC

MODERN CLINICAL NEUROSCIENCE

INCREASINGLY SOPHISTICATED

MODERN INFORMATION TECHNOLOGY

MOORE'S LAW BUT ENERGY LIMITED

MODERN MATHEMATICS

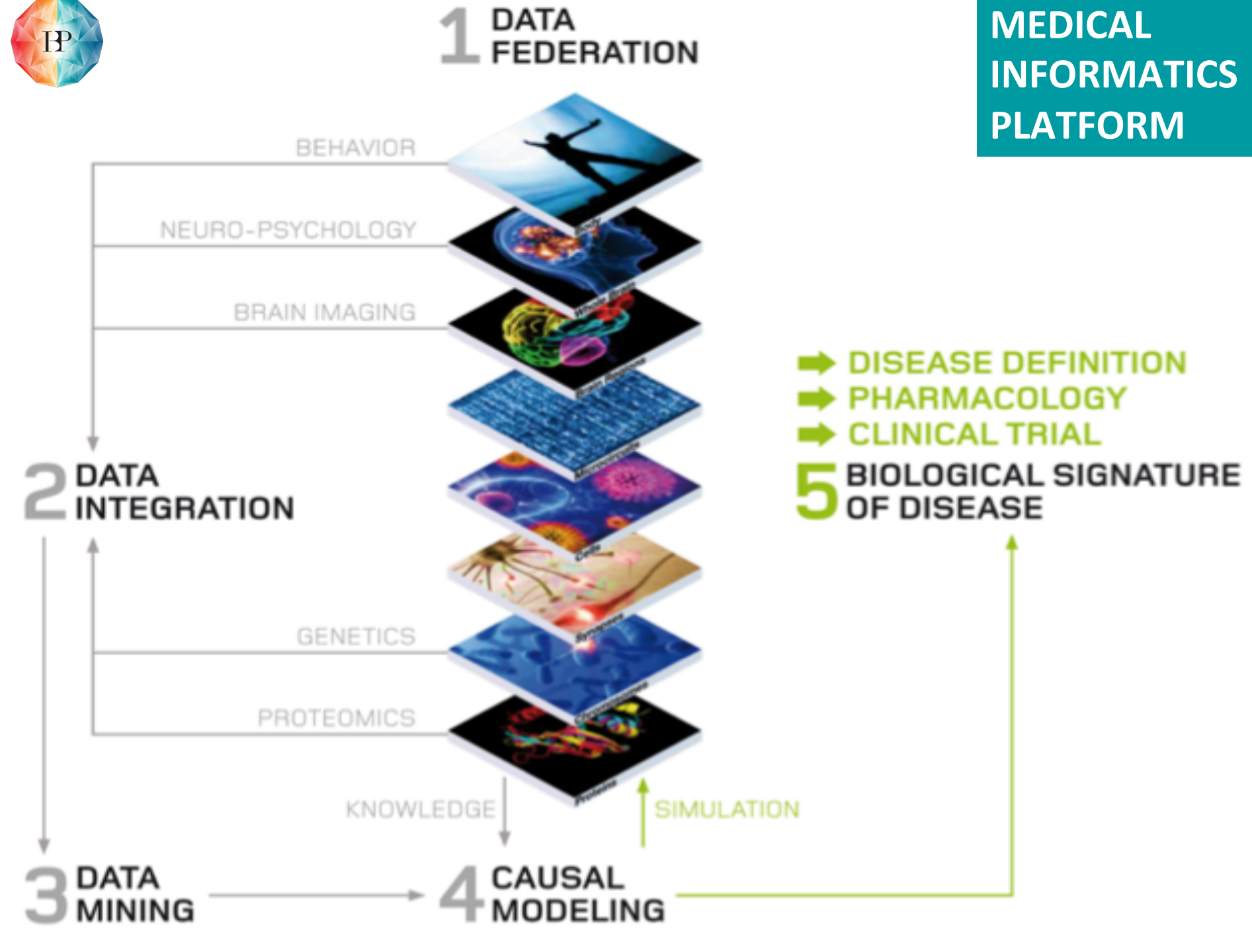
FACILITATED BY CALCULATION POWER

DISEASE SIGNATURES

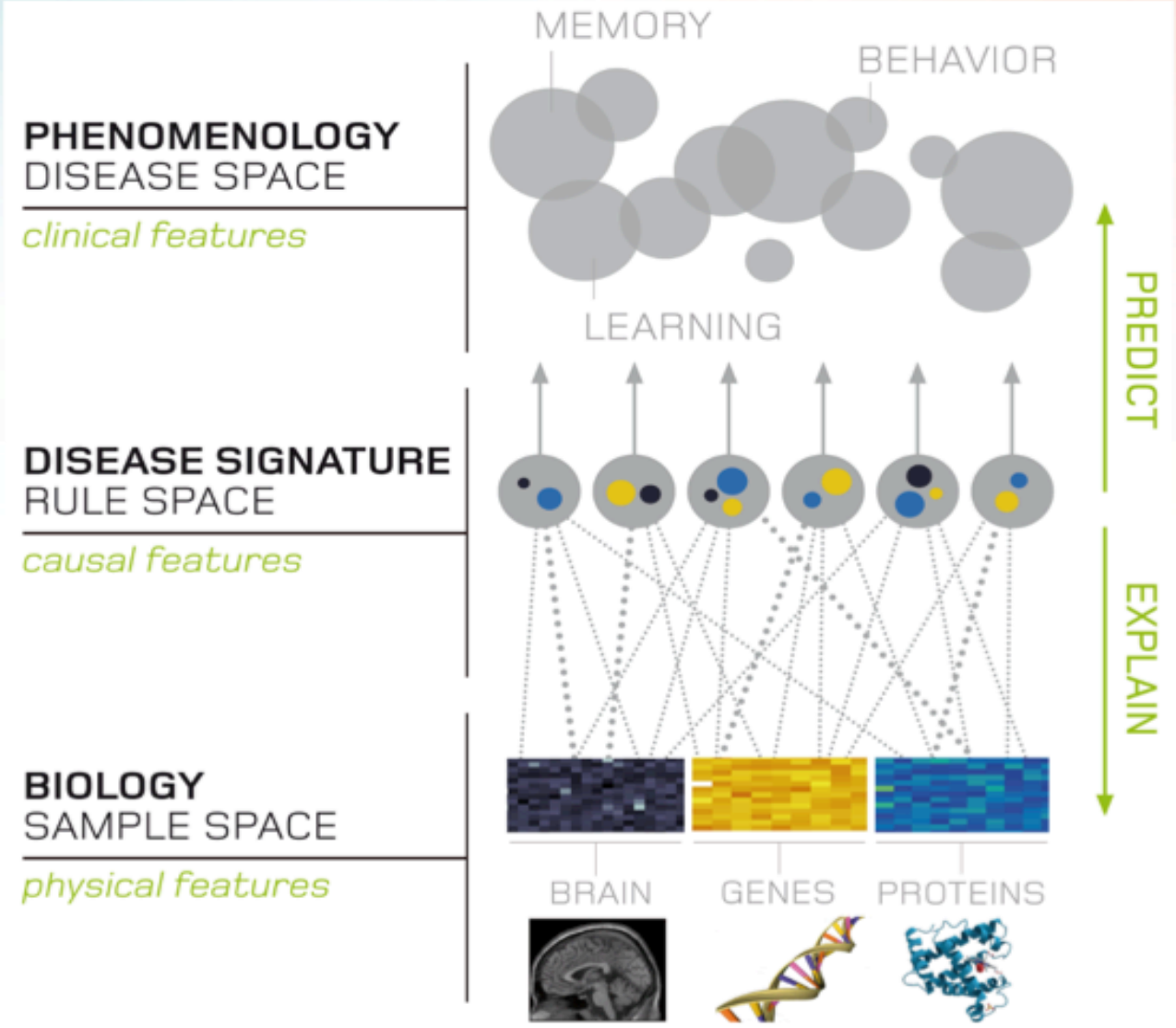
MECHANISTIC DIAGNOSIS

THE HUMAN BRAIN PROJECT

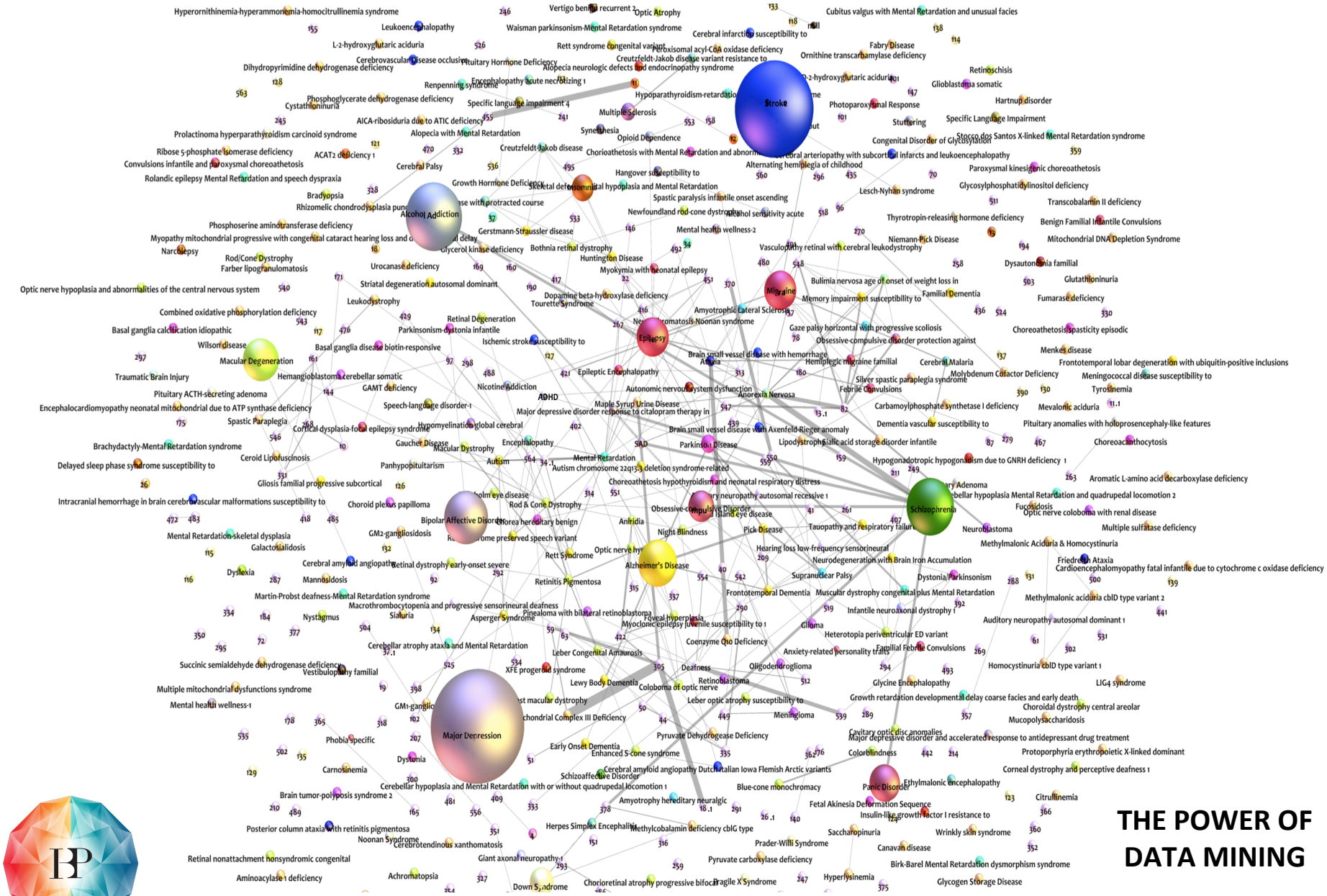
MEDICAL INFORMATICS PLATFORM



Disease signatures

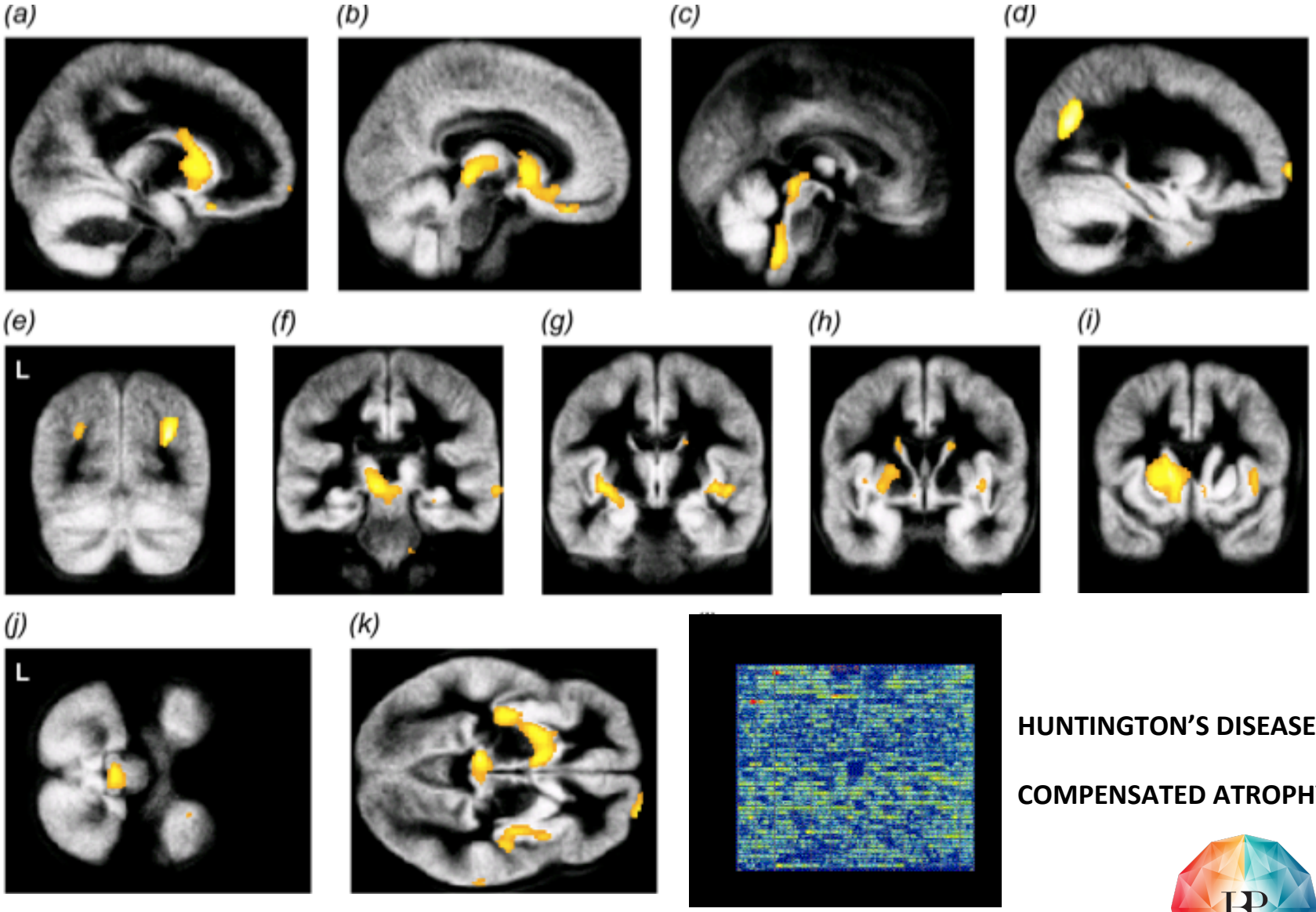


HUMAN “NEURO-DISEASOME” – DISEASE SPACE AS A FUNCTION OF GENETIC ASSOCIATIONS



THE POWER OF DATA MINING

PRE-SYMPTOMATIC DIAGNOSIS - BRAIN RESERVE



HUNTINGTON'S DISEASE

COMPENSATED ATROPHY

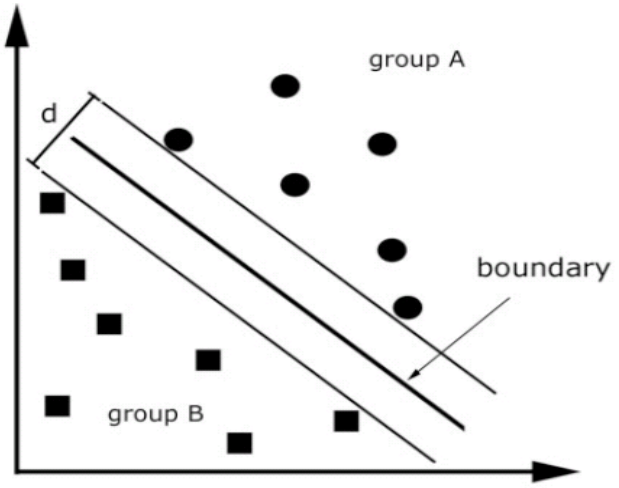
ESSENTIALS OF TRANSLATION

GROUP STUDIES	INDIVIDUAL STUDIES
Samples	**Single subjects**
Averaging	Classification
Contrasting	Binary or probabilistic
Univariate statistics	Potentially multivariate
Generalisation	Diagnosis &/or prognosis
KNOWLEDGE	**MEDICINE**

COMPUTER ASSISTED IMAGE CLASSIFICATION

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



TESTING CLINICAL VS IMAGING BIOMARKER DIAGNOSIS

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

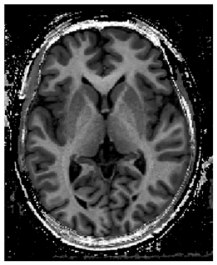
Sensitivity 75%

Specificity 85%

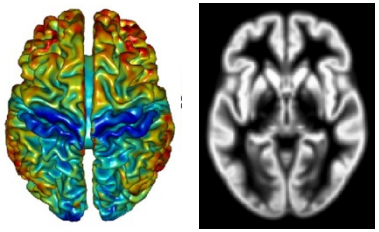
SVM trained on pathologically proven AD

PARADIGM SHIFT – BRAIN TISSUE CHARACTERISATION (VBQ)

T1-weighted



Thickness/Volume



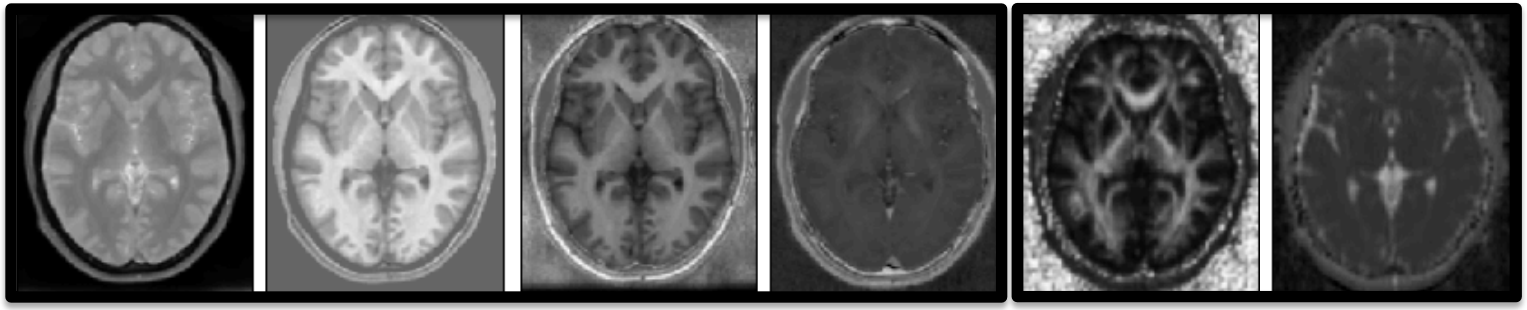
Statistical inferences

?

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 »

!

Interpretation

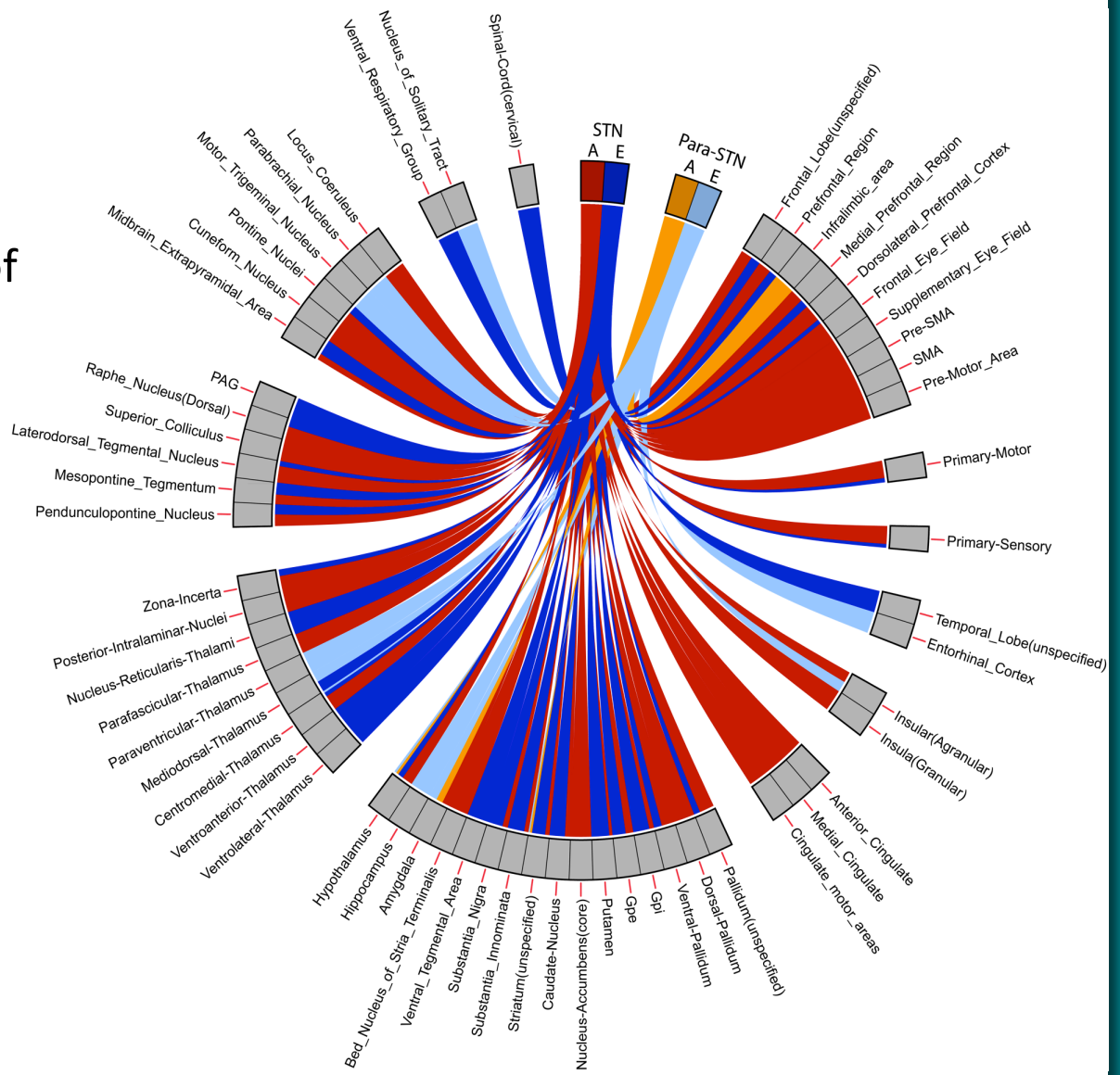
by A. Ruef

BASAL GANGLIA ARCHITECTURE

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.

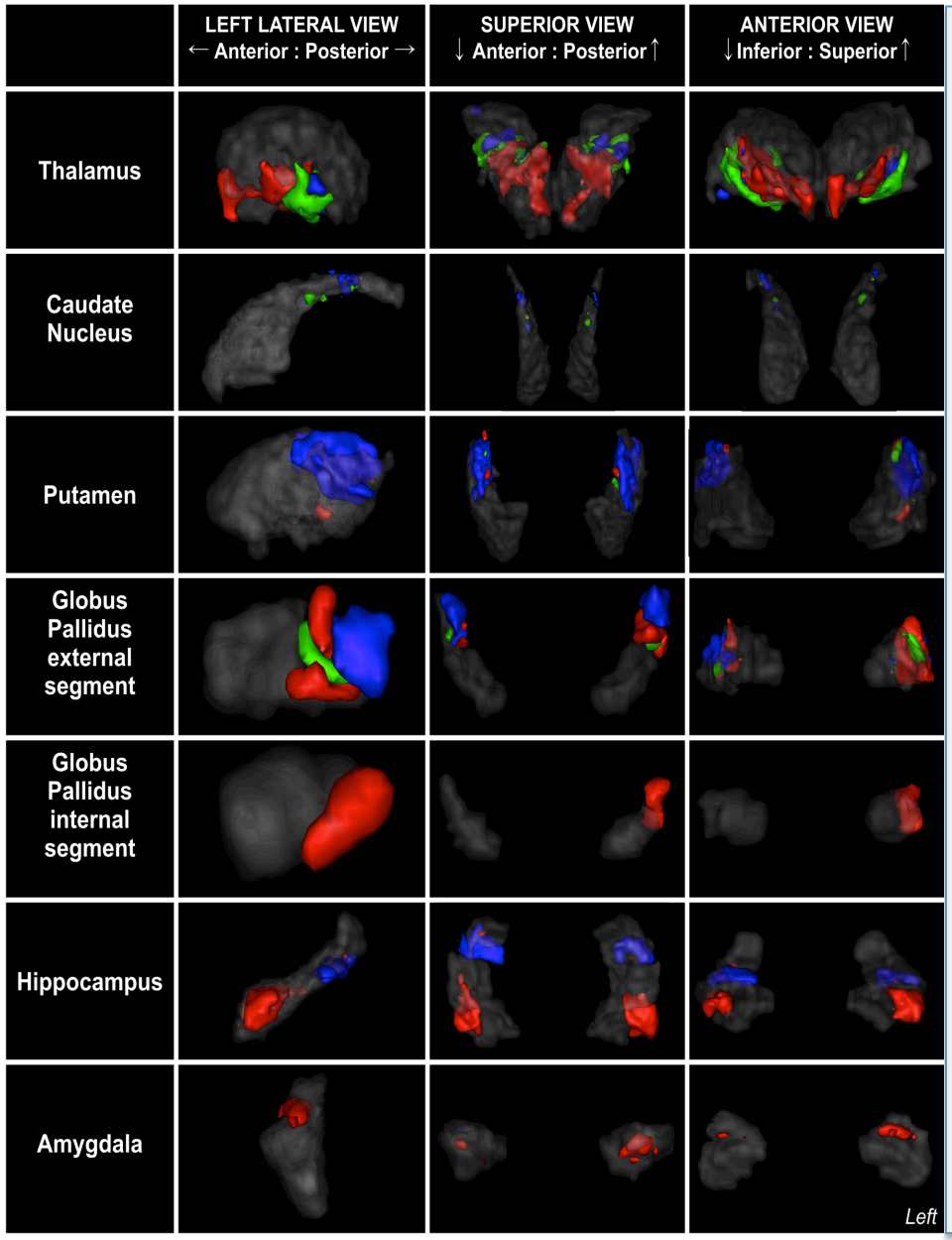
BLUE = EFFERENT

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 [illegible]

FUNCTIONAL IMPLICATIONS

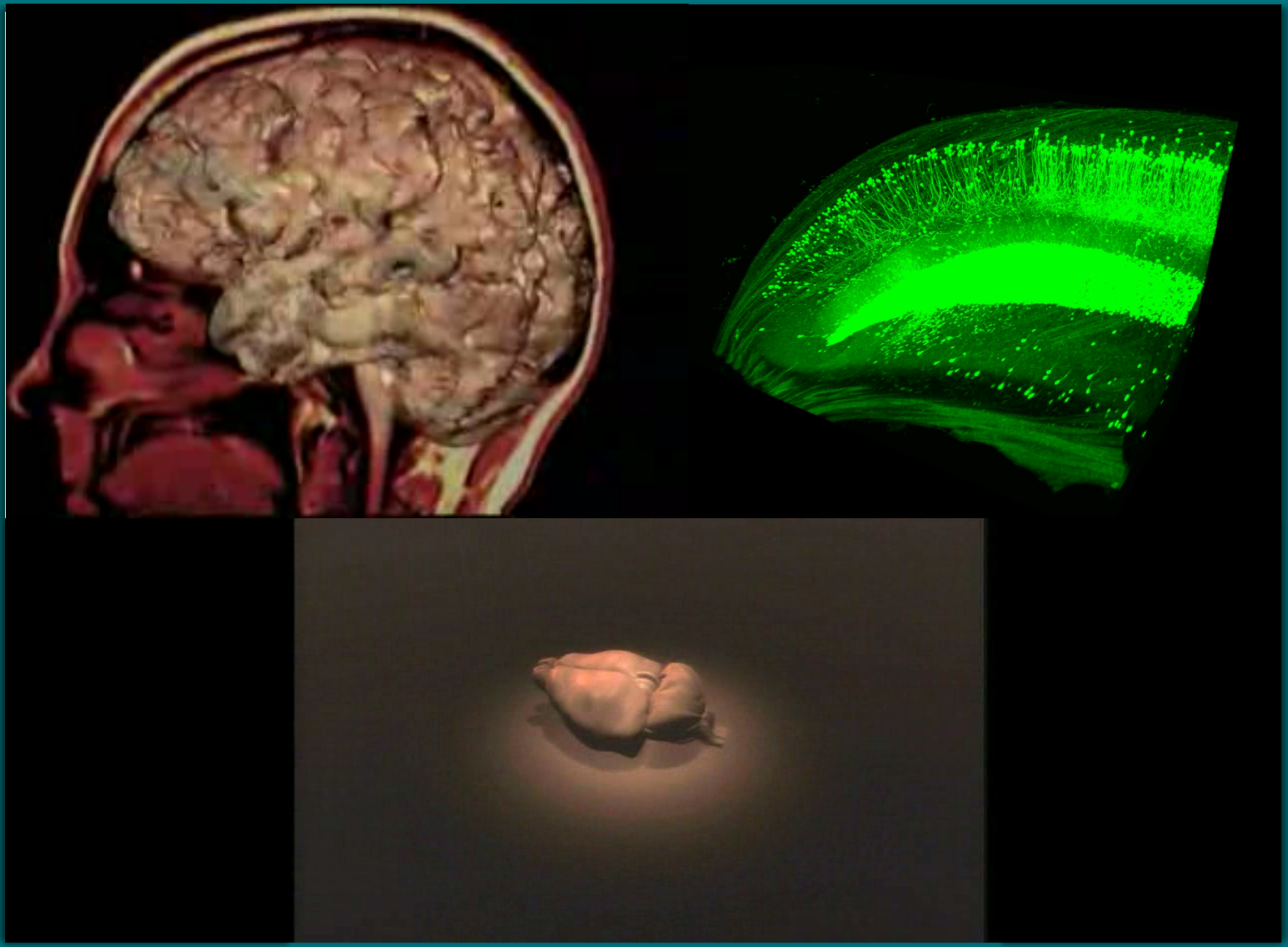


The posterior aspect of the STN projects to structures consistent with a motor structure:
Posterior putamen
Posterior GPe
Mid caudate nucleus
Ventro-lateral thalamic nuclei
Posterior Insula
Posterior hippocampus

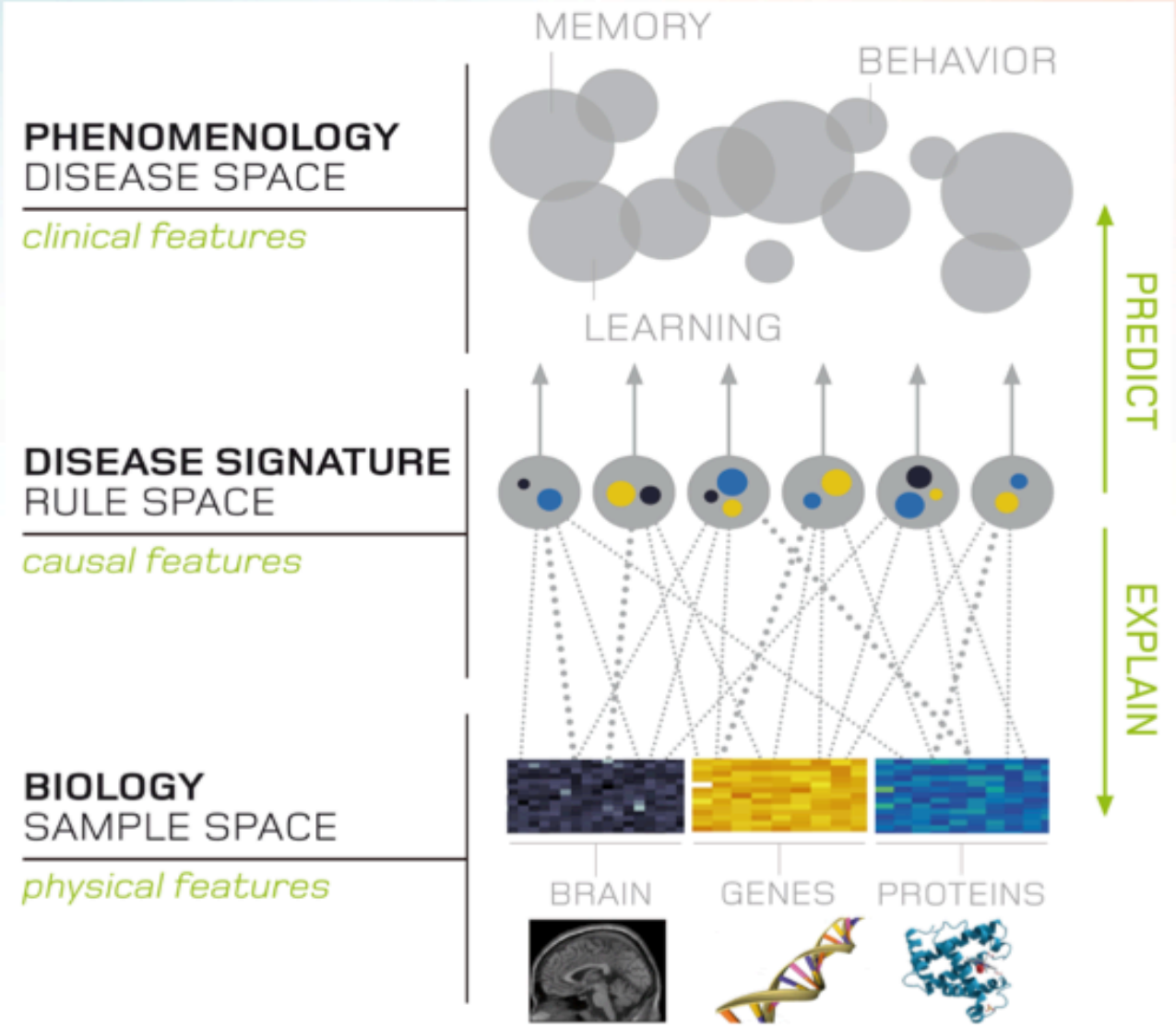
The anterior aspect of the STN projects to structures consistent with a limbic structure:
Baso-lateral amygdala
Posterio-medial GPi
Inferio-mid putamen
Mid-GPe
Ventral-anterior and ventral-lateral thalamus
Anterior Insula
Anterior hippocampus

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

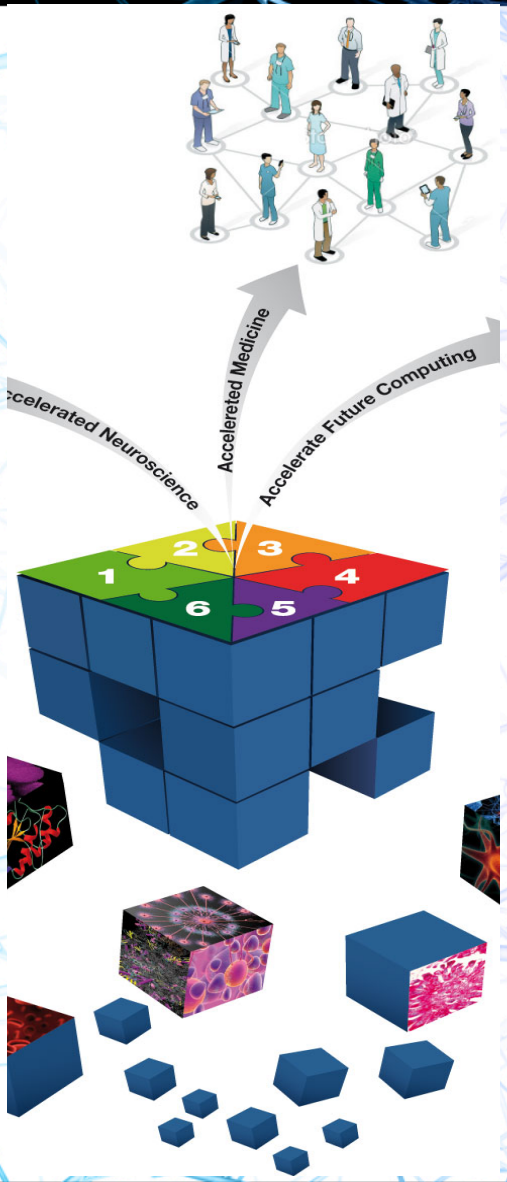
IMAGES – IMAGES - IMAGES



Disease signatures



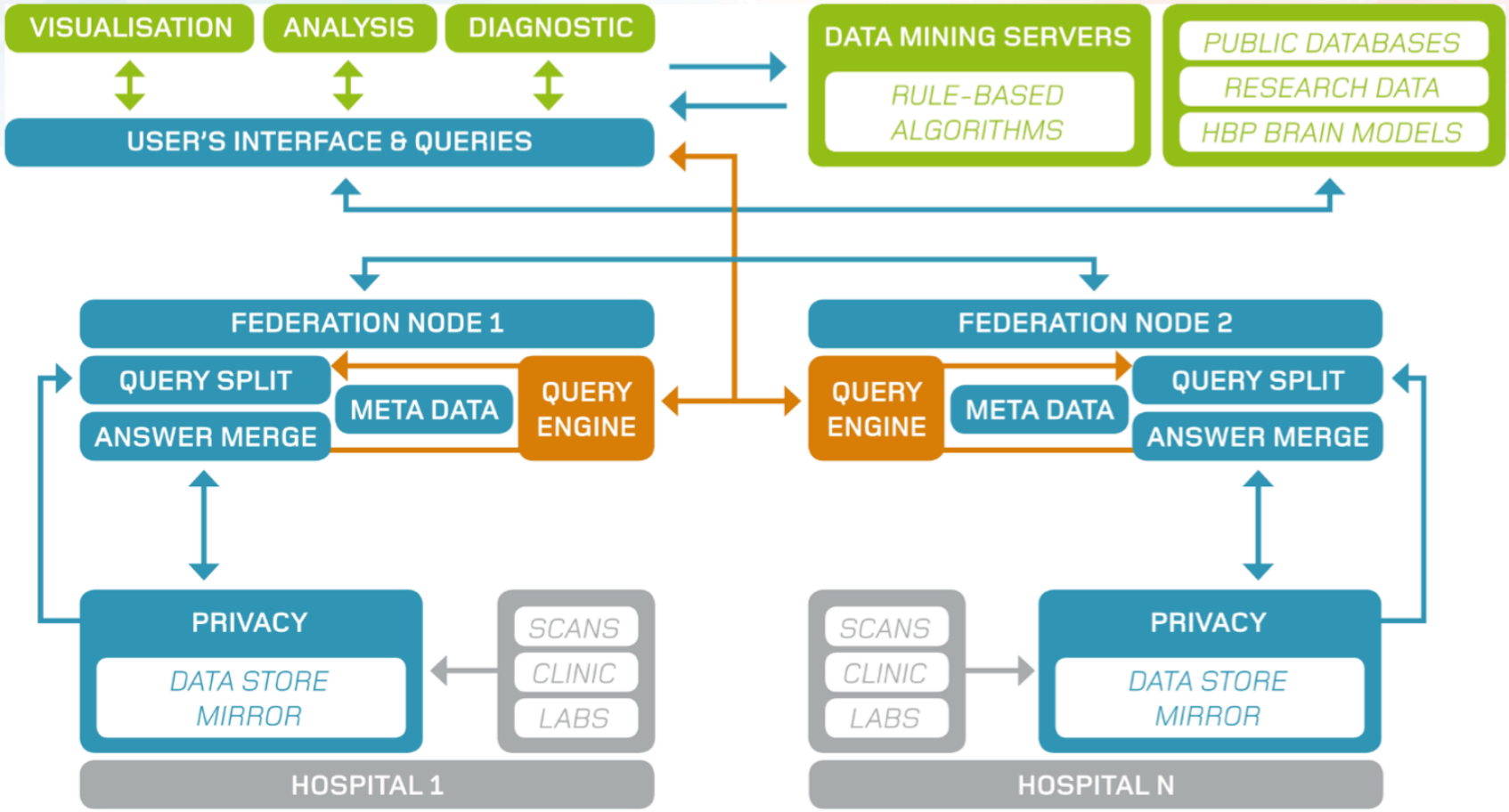
MEDICAL INFORMATICS



INFORMATICS-BASED DIAGNOSIS AND TREATMENT OF BRAIN DISEASES

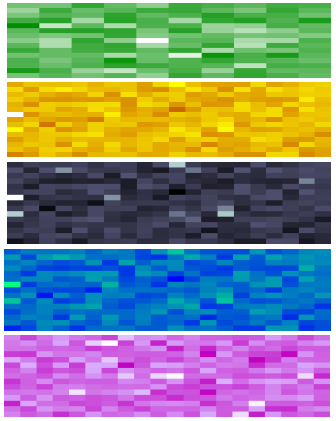
1. **Increase the value of clinical records & data**
2. **Catalyse a massive collaboration of hospitals**
3. Federate and integrate knowledge and data about human diseases – **IT based atlas-encyclopaedia**
4. **Derive biologically-grounded brain disease signatures** for novel diagnostic methods
5. Understand the biological similarities and differences between brain diseases
6. **Provide new discovery pipelines** for therapy to prevent, diagnose and treat brain disorders

Disease signatures



912 Alzheimer's patients
5566 Healthy controls

COMPONENTS
MODALITIES



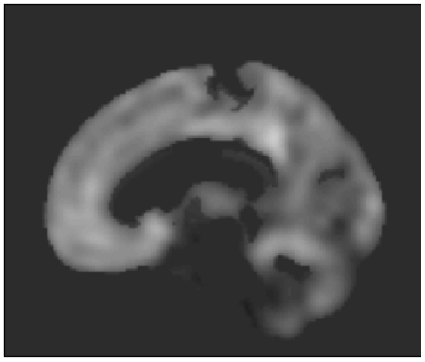
MRI data

PET data

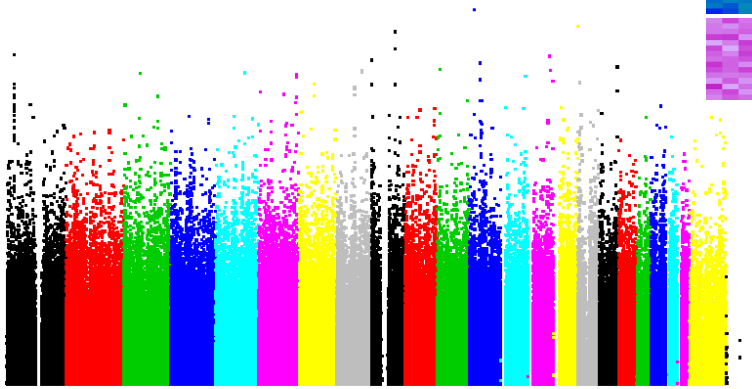
Gene data

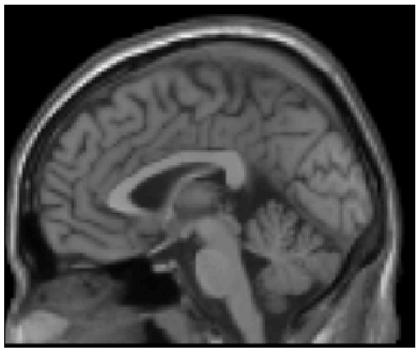
CSF data

Protein data



PET

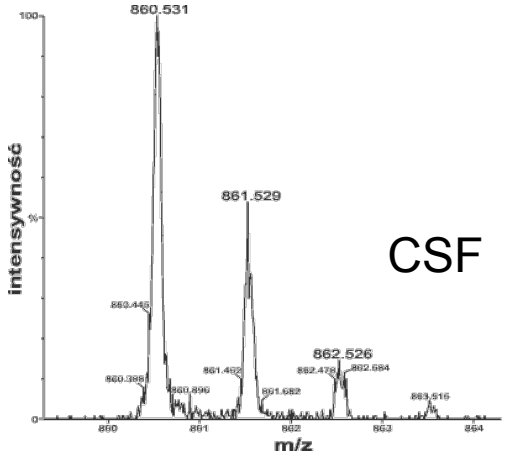




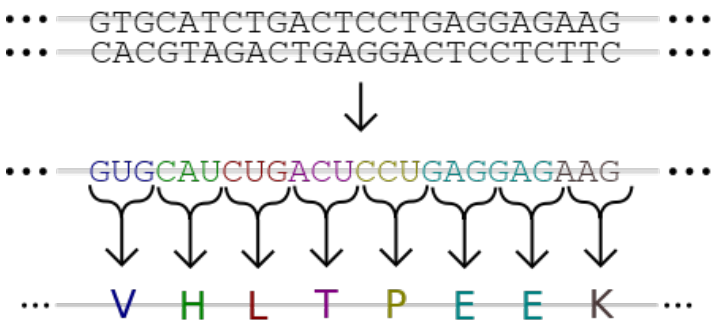
MRI

Organising
Tabulating

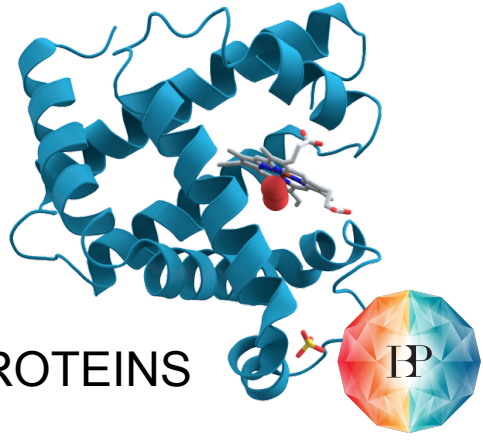
Processing…



CSF



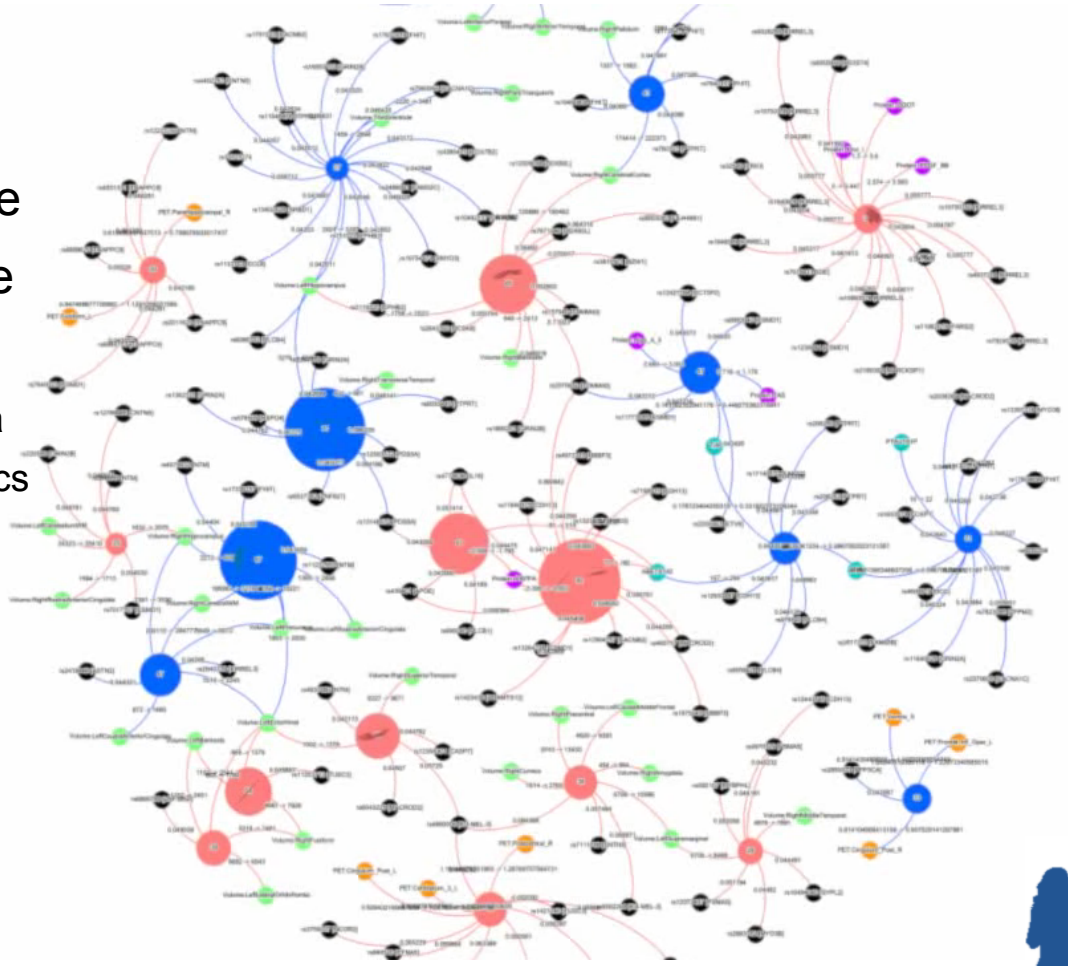
Genes



PROTEINS

CLINICAL SCALES & MEASUREMENTS

- AD Rule
- NL Rule
- MRI Data
- PET Data
- Proteomics
- CSF
- Genetics



Establish a framework for federating clinical data – all diseases, many hospitals

Develop federated query technology that respect anonymity requirements

Develop rule-based clustering algorithms

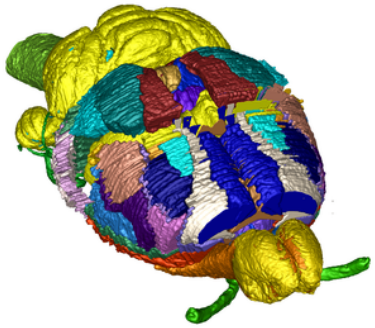
Derive biological signatures of brain disease

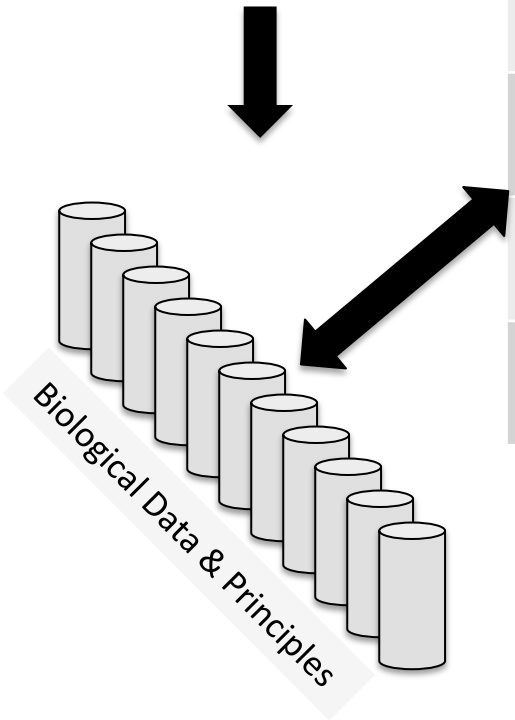
PRINCIPLES OF RECONSTRUCTING SIMULATING AND REVERSE ENGINEERING THE HUMAN BRAIN

Brain Atlases
Data source

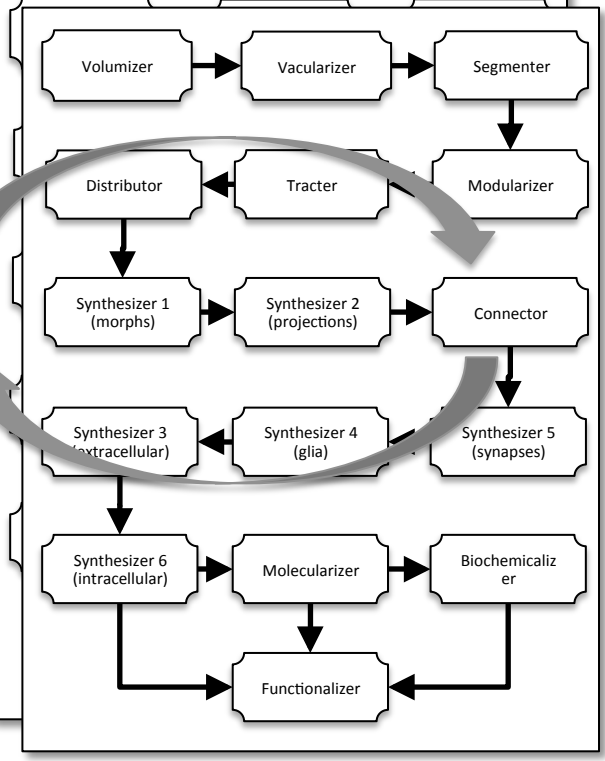
Biological Parameter Constraints & Biological Principles
Configurations

Multi-constraint Algorithms
Brain Reconstruction Workflows



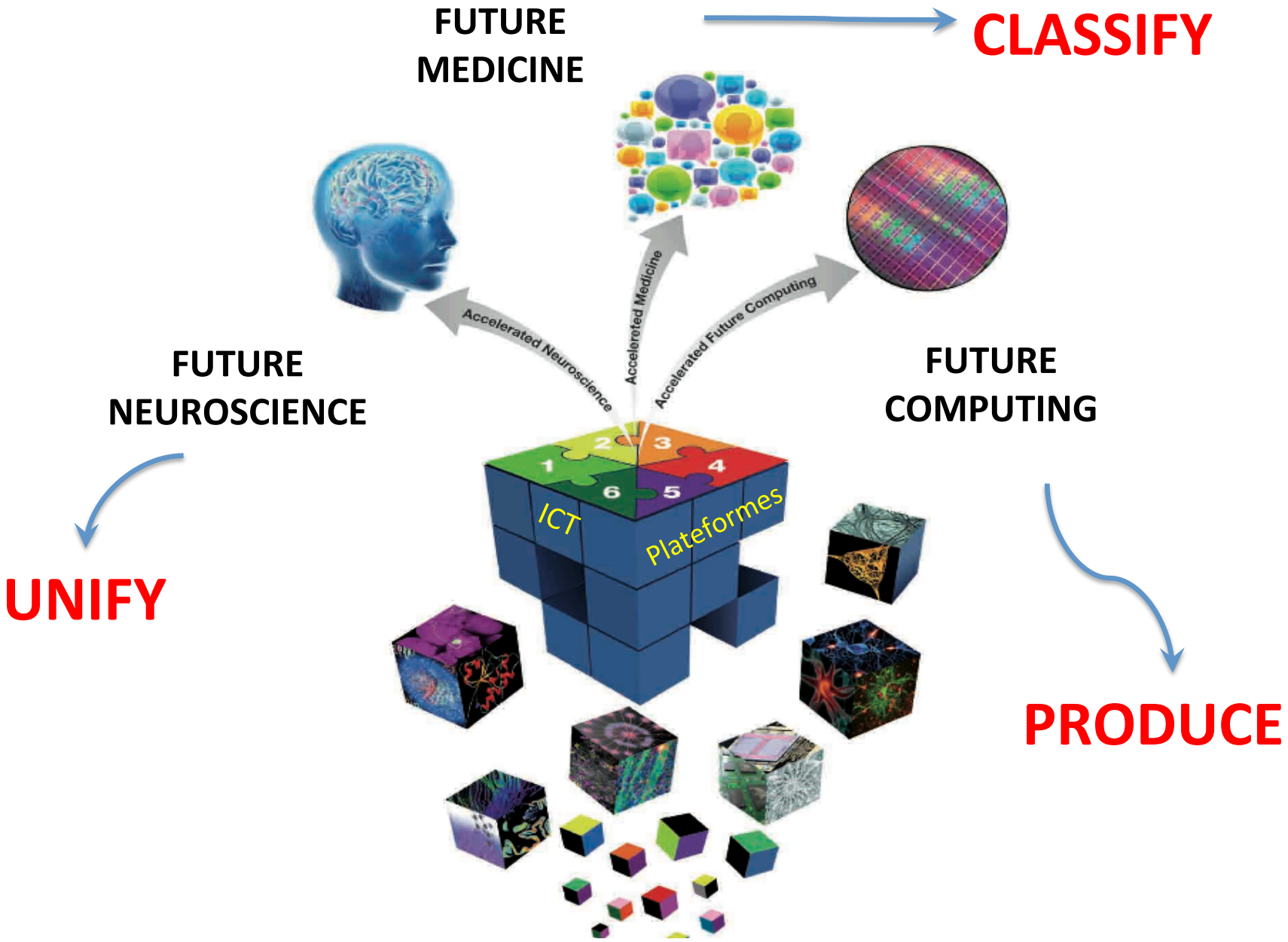


	Data	Principles	Disease Data	Disease Principles
Bouton density	A	AA	A	AA
Synapse density	B	BB	B	BB
Syns/ connect	C		C	CC
P Connect			D	...
Synaptic Response			E	...



HBP
The Human Brain Project

THREE RESEARCH DOMAINS



THANKS FOR LISTENING

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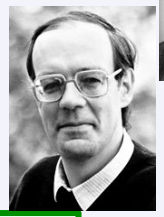
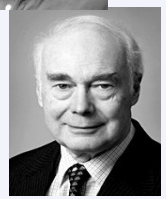
EUROPEAN NOBEL CONTRIBUTIONS TO NEUROSCIENCE 1900-2012

NEUROANATOMY	Golgi & Ramon y Cajal
NEUROPHYSIOLOGY	Pavlov
	Barany
	Sherrington & Adrian
	Von Bekesy
	Eccles, Hodgkin & Huxley
	Wiesel
	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





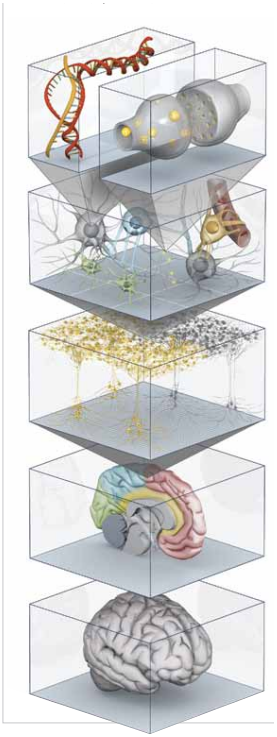


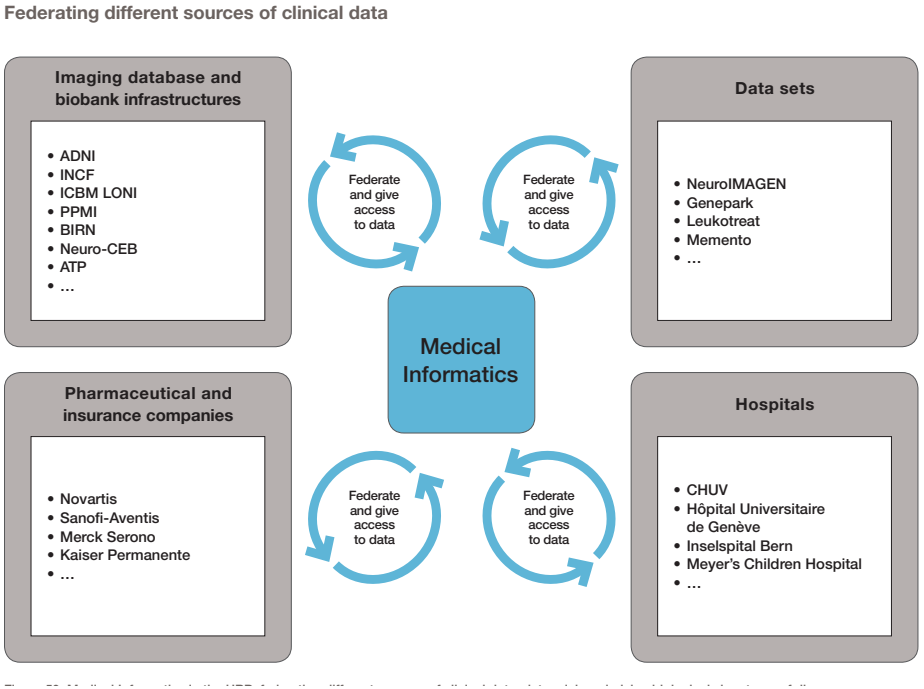



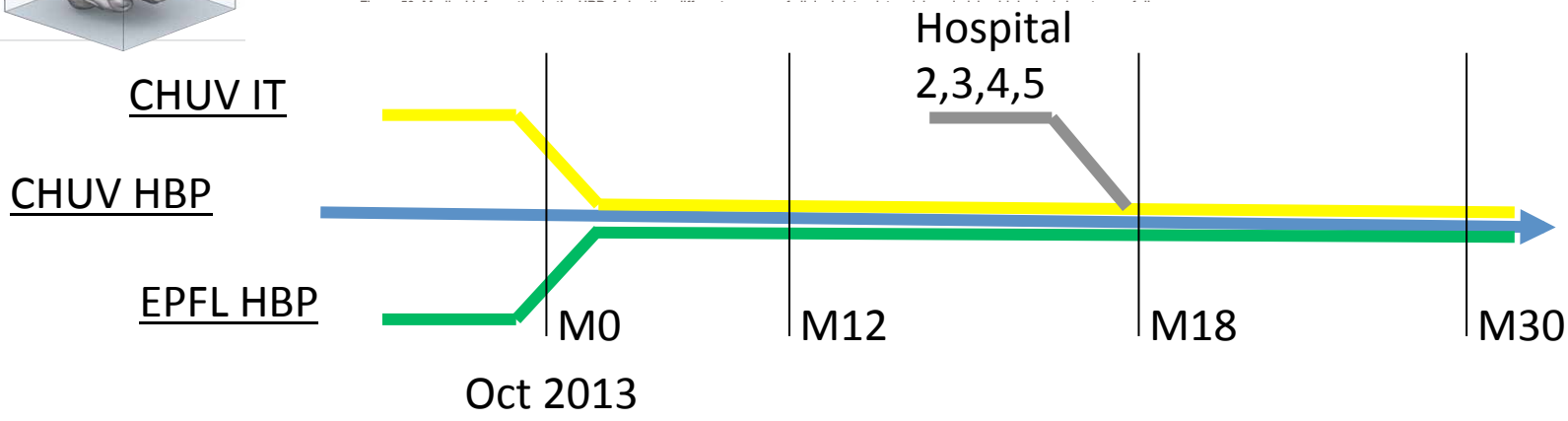
CEA CHRU CNRS CPU INRA INRIA INSERM INSTITUT PASTEUR IRD

aviesan

DATA & TIMELINE







The Medical Platform will build on existing work to establish what will ultimately become a completely new, information- and simulation-based approach to brain disease.

1. Create a Facility for Medical ICT
2. Federate very large volumes of data about diseases of the brain (imaging, data from tissue and blood samples, clinical data, medical histories, genomic data, etc.)
3. Use this data to discover meaningful correlations within and between etiological, diagnostic, pathogenic, treatment, and prognostic parameters
4. Analyze similarities and differences between brain disorders and across individual patients;
5. Use this knowledge to build and constrain models of the healthy brain
6. Simulate disorders of the brain and test hypotheses of causation
7. Develop novel diagnostic tools, exploiting new screening, data analysis, informatics and modeling techniques to diagnose disease at the pre-symptomatic stage;
8. Simulate beneficial and undesirable effects of proposed treatments.