

IMI STAKEHOLDER'S FORUM 2013 - BRUSSELS

**NEW TREATMENTS FOR
BRAIN DISORDERS –
NEEDS & CHALLENGES**

**HAS SYNDROMIC NEUROLOGY HAD ITS DAY?
TURNING NEUROLOGY ON ITS HEAD**

Richard Frackowiak (CHUV Lausanne)



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

HOW DO WE PREVENT IT? AND TREAT IT?

Can we diagnose it?

Do symptoms matter?

What weight to pathology?

What about "carriers"? - Can we compensate?

How do we compensate? – redundancy

Why don't the treatments work?

And what about preventive treatment

WHAT CAUSES IT?

What about mechanisms?

Role of genes?

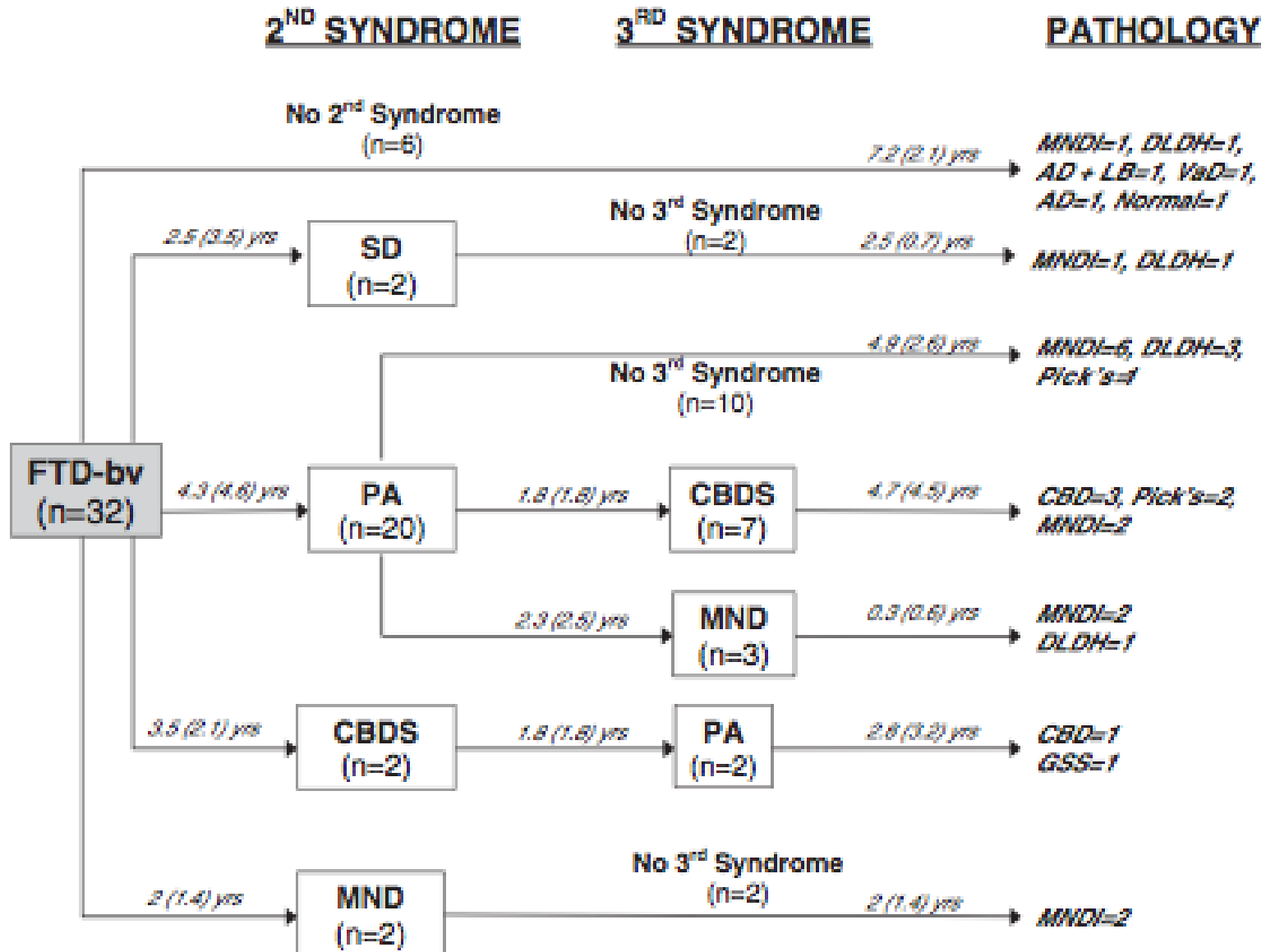
And abnormal proteins – amyloid?

But are they that abnormal?

Abnormal neurotransmission – Acetyl choline?

What abnormalities are causes and which effects?

CLINICAL SYNDROMES AND FINAL PATHOLOGY IN CASES PRESENTING WITH FTD



CLINICAL NEUROSCIENCE AT A TIPPING POINT



SYNDROMIC DIAGNOSIS

REACHED ITS LIMITS

HUMAN GENOME

MODERN NEUROIMAGING

MODERN NEUROSCIENCE

MODERN INFORMATION TECHNOLOGY

MODERN MATHEMATICS

MECHANISTIC/CAUSAL DIAGNOSIS

CLINICAL NEUROSCIENCE AT A TIPPING POINT



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BUILDING BLOCKS OF ORGANIC MATTER

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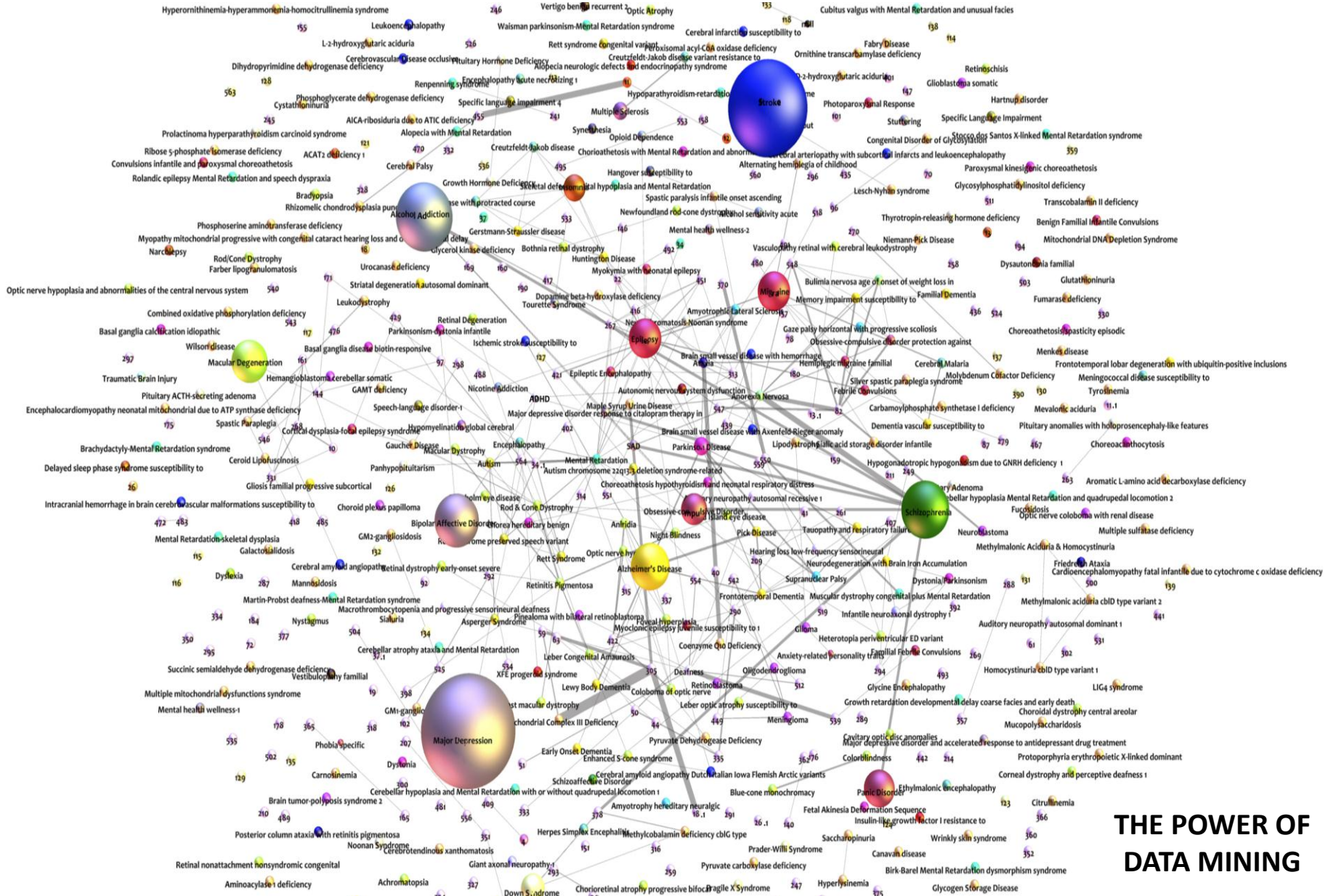
MODERN NEUROSCIENCE

MODERN INFORMATION TECHNOLOGY

MODERN MATHEMATICS

MECHANISTIC/CAUSAL DIAGNOSIS

HUMAN "NEURO-DISEASE" – DISEASE SPACE AS A FUNCTION OF GENETIC ASSOCIATIONS



THE POWER OF
DATA MINING

CLINICAL NEUROSCIENCE AT A TIPPING POINT



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INCREASINGLY SOPHISTICATED

MODERN NEUROSCIENCE

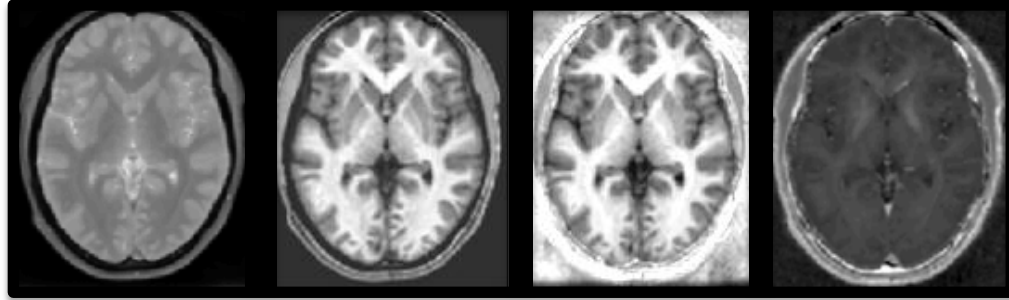
MODERN INFORMATION TECHNOLOGY

MODERN MATHEMATICS

MECHANISTIC/CAUSAL DIAGNOSIS

Amplitude Magnetization
 transfer

R1 (1/T1) R2* (1/T2*)



Water proton
density

Myelin

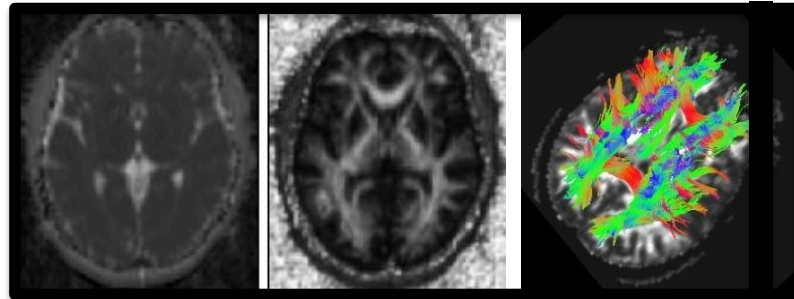
Water
motility

Iron

Mean
diffusivity

Fractional
anisotropy

Probabilistic
tractography



Fiber directionality & anatomical connectivity

COMPUTER-BASED 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

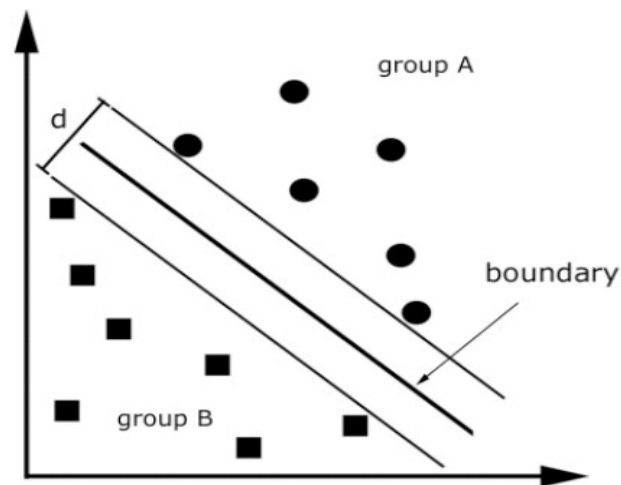
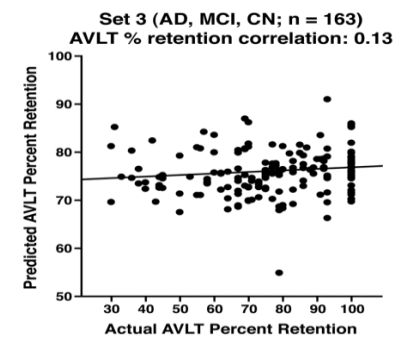
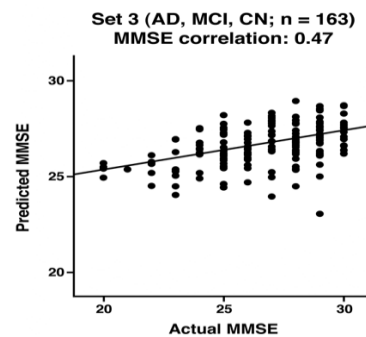
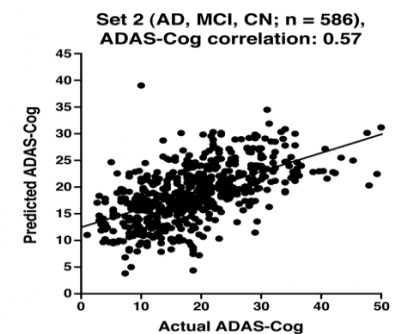
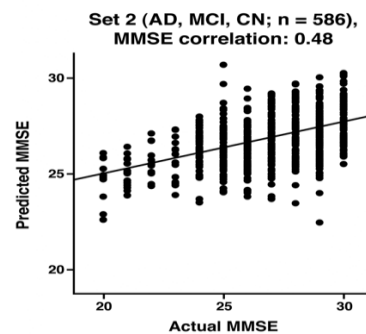
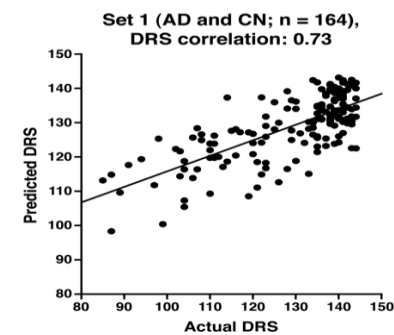
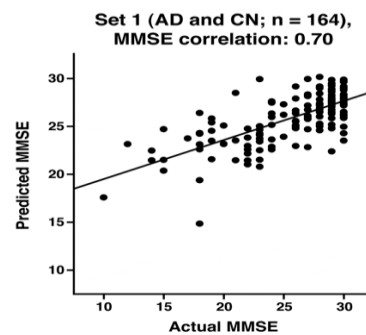
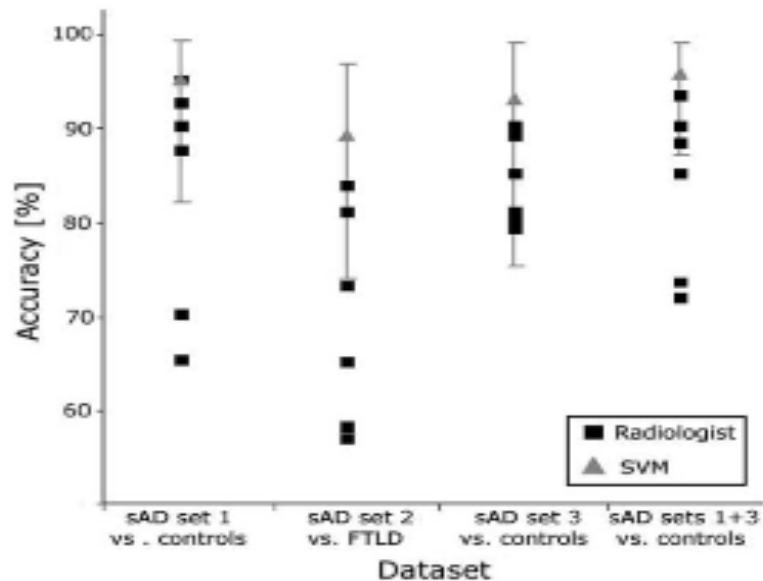
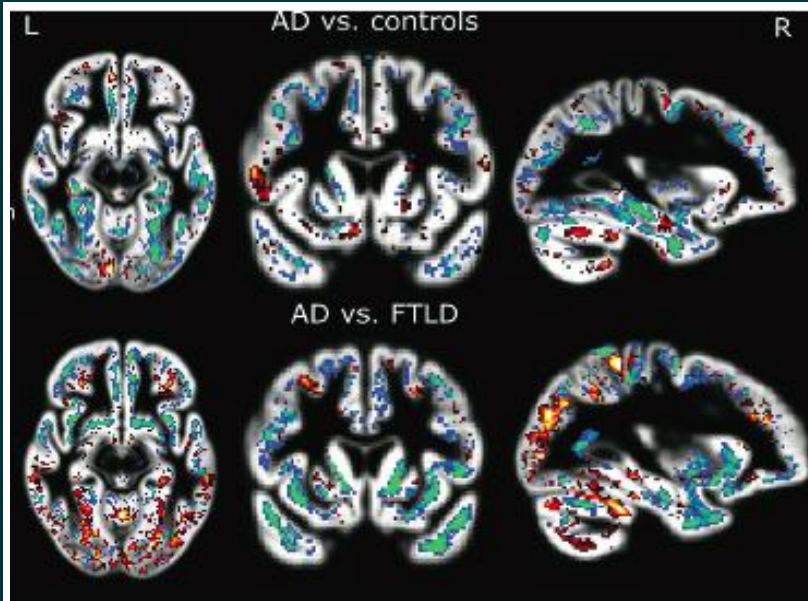


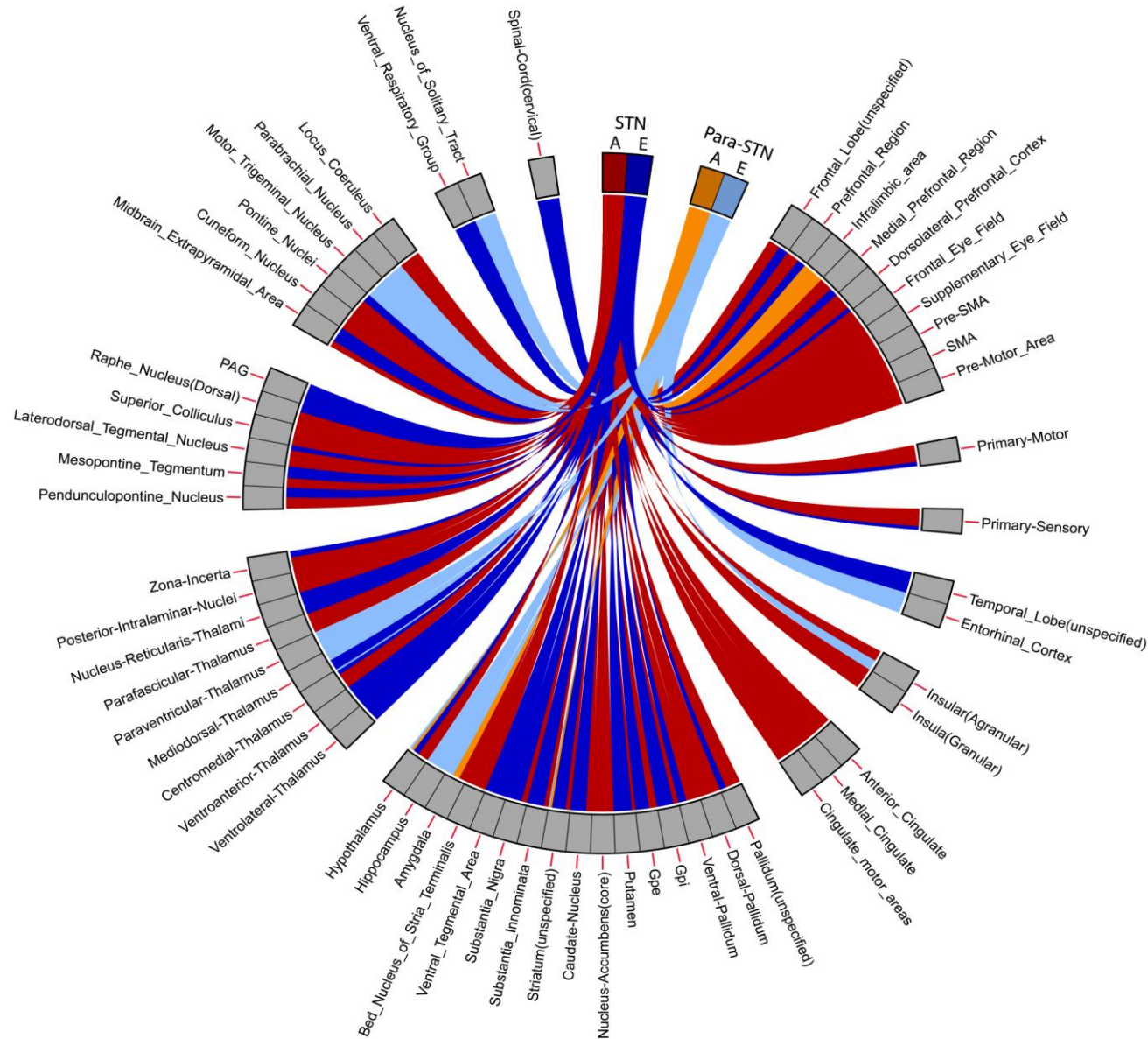
IMAGE CLASSIFICATION AND DIAGNOSIS - RADIOLOGY



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



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INCREASINGLY SOPHISTICATED

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FRAGMENTED AND ATHEORETIC

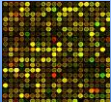
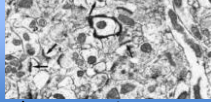
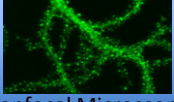
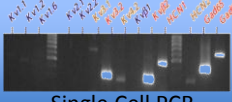
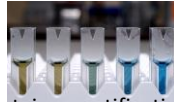
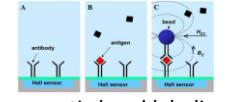
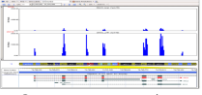
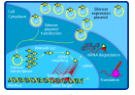
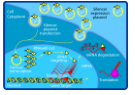
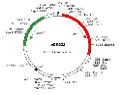


MODERN INFORMATION TECHNOLOGY

MODERN MATHEMATICS



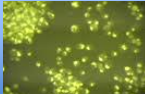
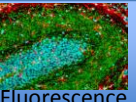

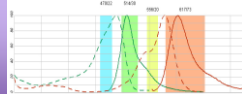
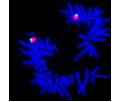
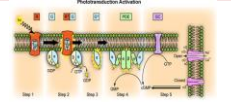

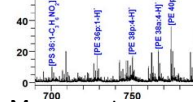

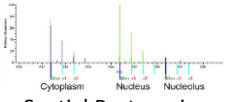
MECHANISTIC/CAUSATIVE DIAGNOSIS

MANY METHODS MUCH DATA – NO HOLISTIC CONCEPT

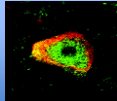
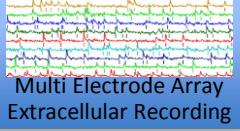
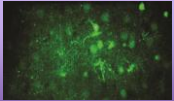



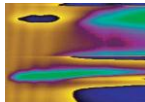
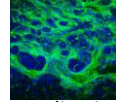
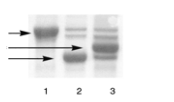
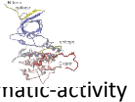
sub-cellular resolution

 microarrays	 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-spectrometry	 Organelle transfection	 Spatial Proteomics

tissue resolution

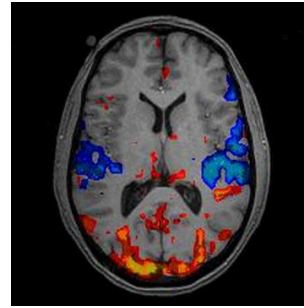
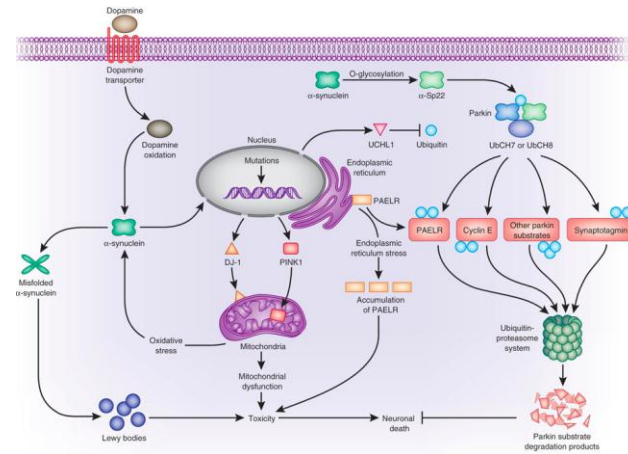
 Immunostaining	 Multi Electrode Array Extracellular Recording	 Dye Imaging	 2DE proteomics	 tissue transfection	Legend: <div style="border: 1px solid black; padding: 2px; margin-bottom: 2px;">Exploration</div> <div style="background-color: purple; color: white; padding: 2px; margin-bottom: 2px;">Research</div> <div style="background-color: blue; color: white; padding: 2px;">Prototype</div>
 HPLC	 voltammetry	 2-photon live imaging	 In vivo-binding studies	 enzymatic-activity measurement	

whole brain scale

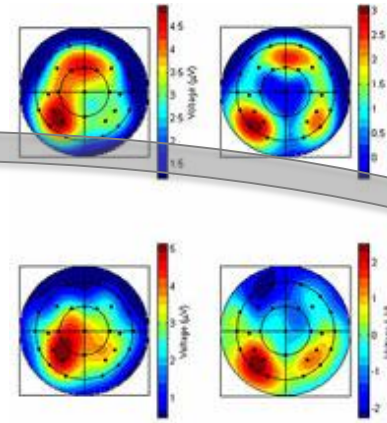
 Behavioral Studies	 ultramicroscopy	 Magnet Resonance Diffusion Imaging	 fMRI	 EEG	 Transgenic lines
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PERSPECTIVES

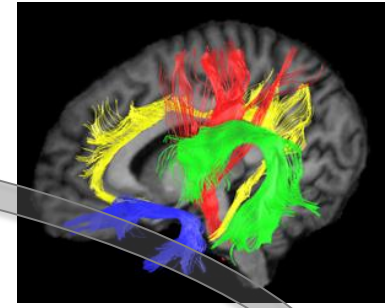
Integration of theoretical concepts from animal studies and human images by bridging between different scales of acquired data



MRI

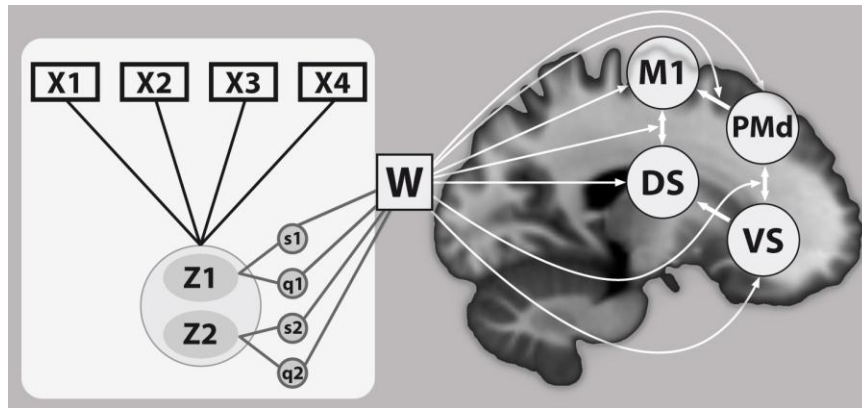


EEG

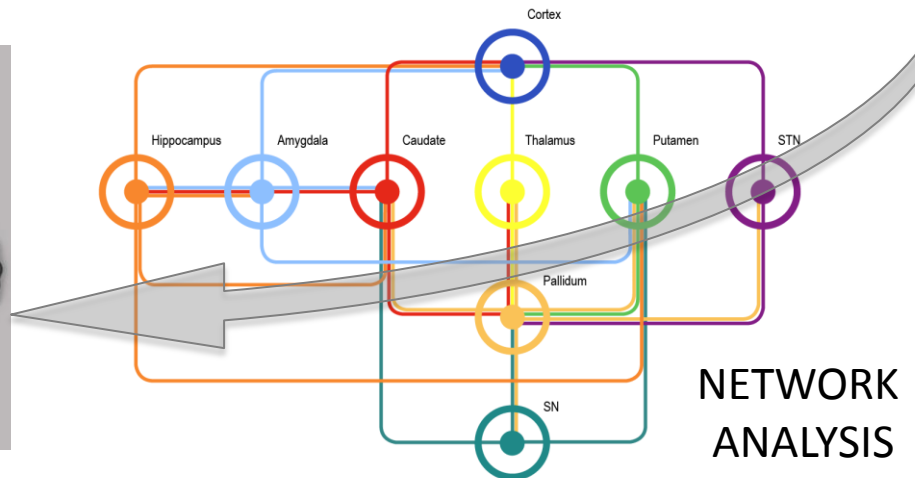


DTI

NEUROINFORMATICS



MEDICAL INFORMATICS



NETWORK ANALYSIS

CLINICAL NEUROSCIENCE AT A TIPPING POINT



SYNDROMIC DIAGNOSIS

REACHED ITS LIMITS

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MODERN INFORMATION TECHNOLOGY

EXPLOSIVE DEVELOPMENT

MODERN MATHEMATICS

MECHANISTIC/CAUSATIVE DIAGNOSIS

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

CLINICAL NEUROSCIENCE AT A TIPPING POINT



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FACILITATED BY CALCULATION POWER

MECHANISTIC/CAUSATIVE DIAGNOSIS

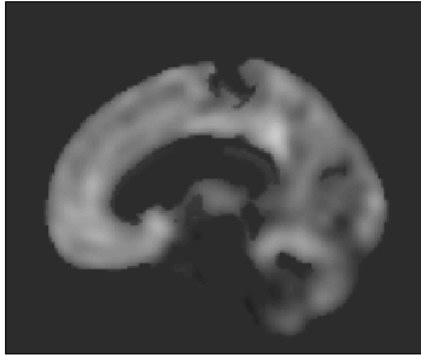
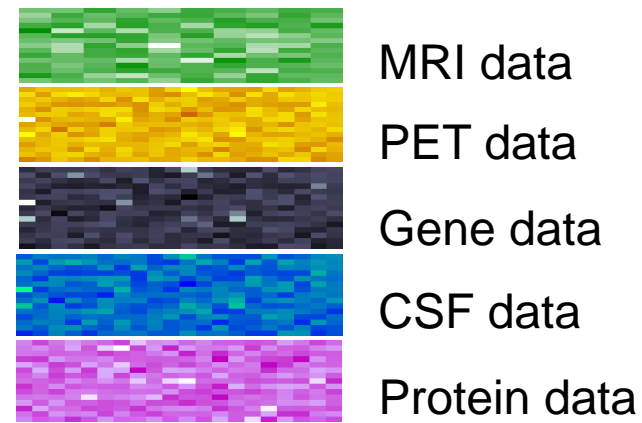
HIGH LEVEL GRAND CHALLENGE

A PARADIGM SHIFT:

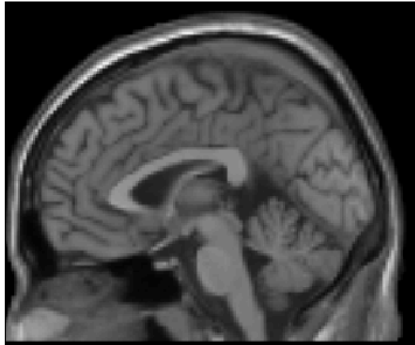
**FROM PHENOMENA TO BIOLOGY
IN DEFINING DISEASE**

912 Alzheimer's patients
5566 Healthy controls

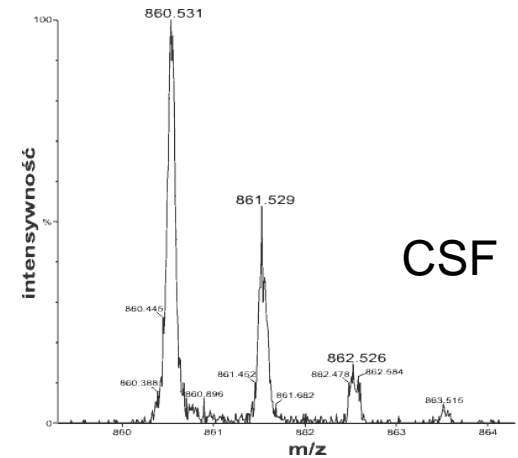
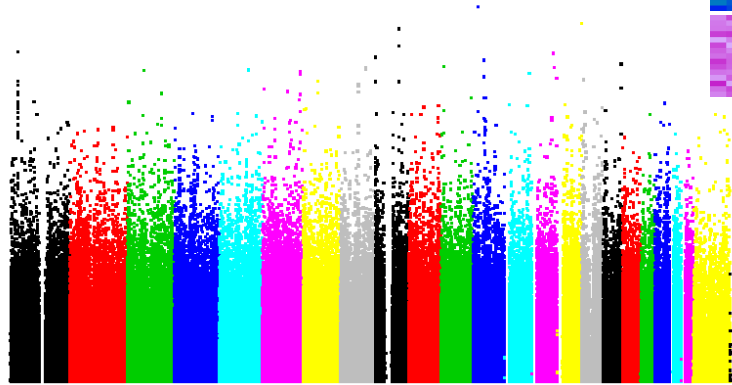
MoAE MODALITIES



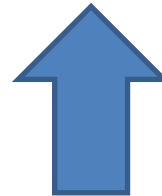
PET



MRI



Organising
Tabulating



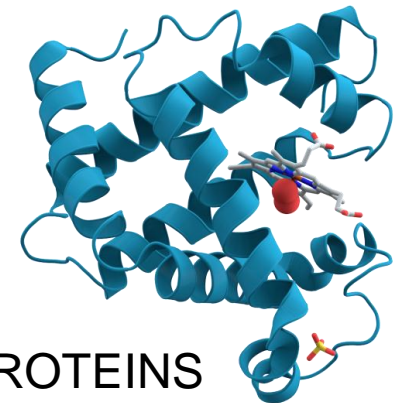
Processing...

... — GTGCATCTGACTCCTGAGGAGAAG — ...
... — CACGTAGACTGAGGACTCCTCTTC — ...



... — GUGCAUCUGACUCCUGAGGAGAAG — ...
... — V H L T P E E K — ...

Genes



CLINICAL SCALES
& MEASUREMENTS

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
- ...



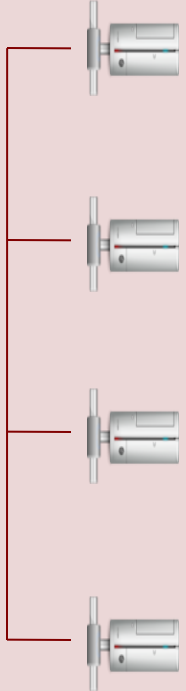
- Data Audit
- Correlations
- Rule Builder

- Rule management
- Scenario simulation

Set of rules

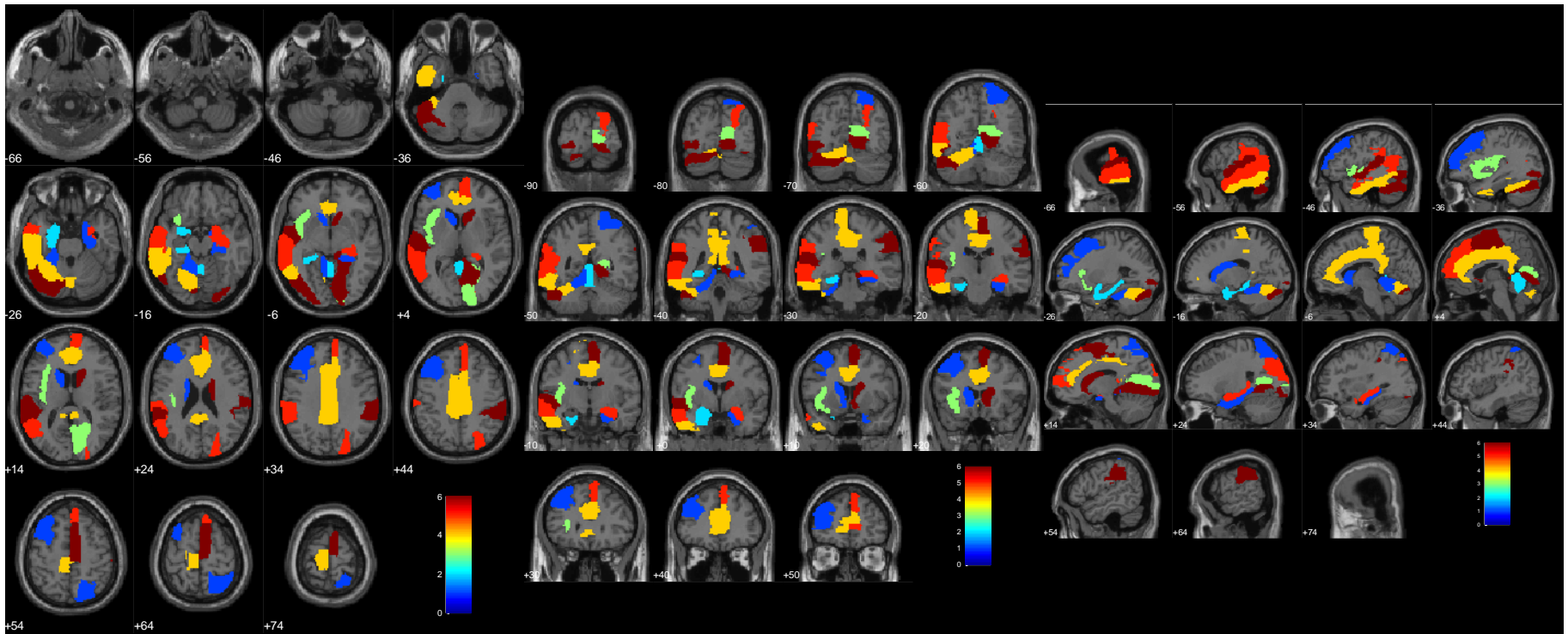


HyperCube interface



Automatic rule recovery

A pilot study that used human imaging data and rudimentary demographics was carried out on 200 subjects MRI scans from the ADNI database. Hypercube identified 6 sub-groups and formal rules that explained 100% of the differential patterns between AD and healthy controls – a highly satisfactory result



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DISEASE SIGNATURES

MECHANISTIC/CAUSATIVE DIAGNOSIS

MEDICAL INFORMATICS

DATA INTEGRATION AND CAUSAL ANALYSIS

DATA FEDERATION

DATA INTEGRATION

DATA MINING

CAUSAL MODELING

BIOLOGICAL SIGNATURES OF DISEASE

GENETIC –OMICS SYSTEM DYSFUNCTION

DEEP HUMAN PHENOTYPING

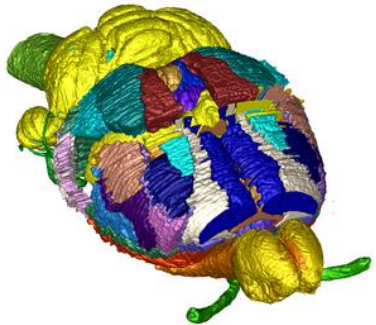
PHARMACOLOGY

TARGET IDENTIFICATION

CLINICAL TRIALS

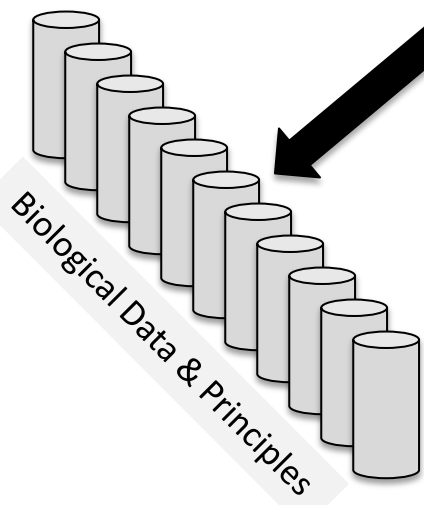
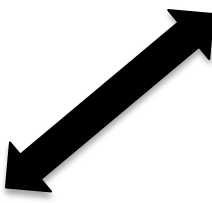
Principles of Reconstructing and Simulating the Brain

Brain Atlases
Data source

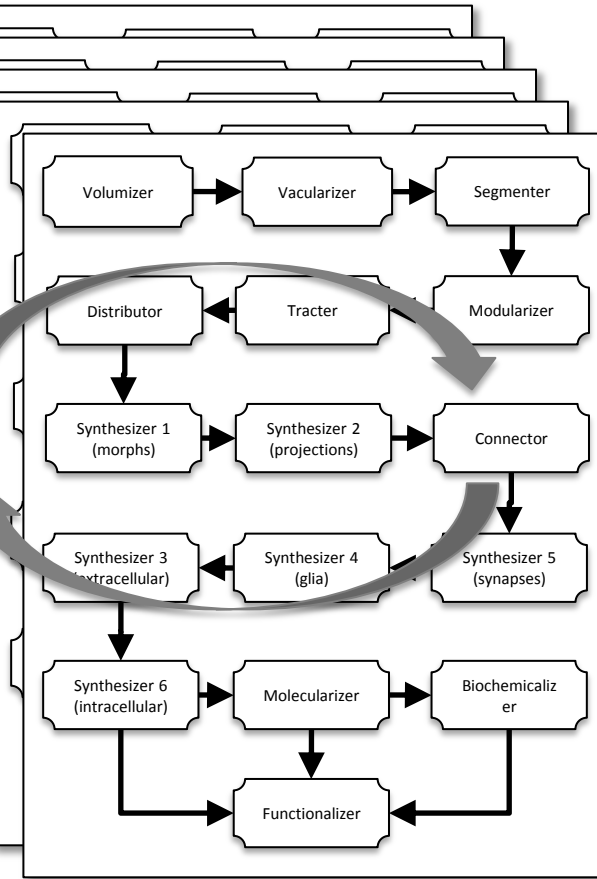


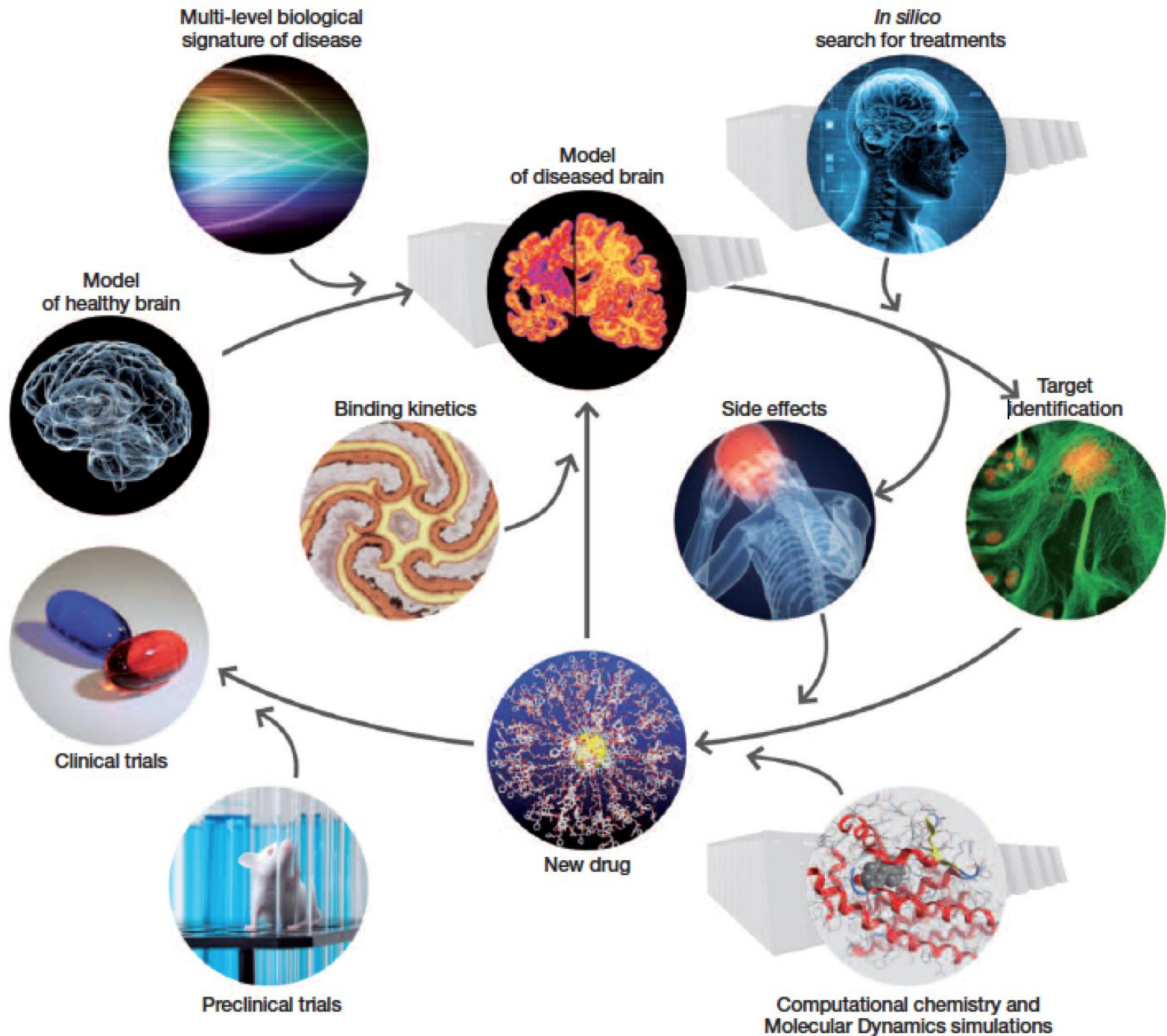
Biological Parameter Constraints & Biological Principles
Configurations

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	...



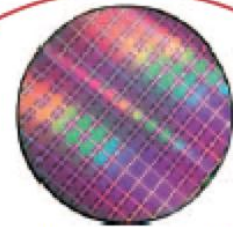


Future Medicine



- from symptom-based to biologically-based classifications
- unique biological signatures of diseases
- early diagnosis & preventive medicine
 - optimised clinical trials
- efficient drug and other treatment
- personalised medicine

Future Computing



- supercomputing as a scientific instrument
- supercomputing as a commodity
 - new software for multiscale and interactive supercomputing
 - new hardware from neuromorphic computing
- intelligent tools for managing and mining massive data
- human-like intelligence!

Future Neuroscience



- multi-level view of the brain
- causal chain of events from genes to cognition
- uniqueness of the human brain
- body ownership, language, emotions, consciousness
 - theory of mind

Accelerated Medicine

Accelerated Neuroscience

Accelerated Future Computing



THANK YOU



Unil

UNIL | Université de Lausanne

Faculté de biologie
et de médecine

FIL, London

John Ashburner

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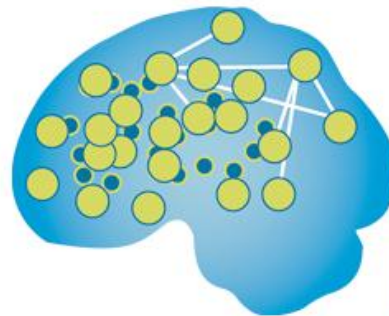
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