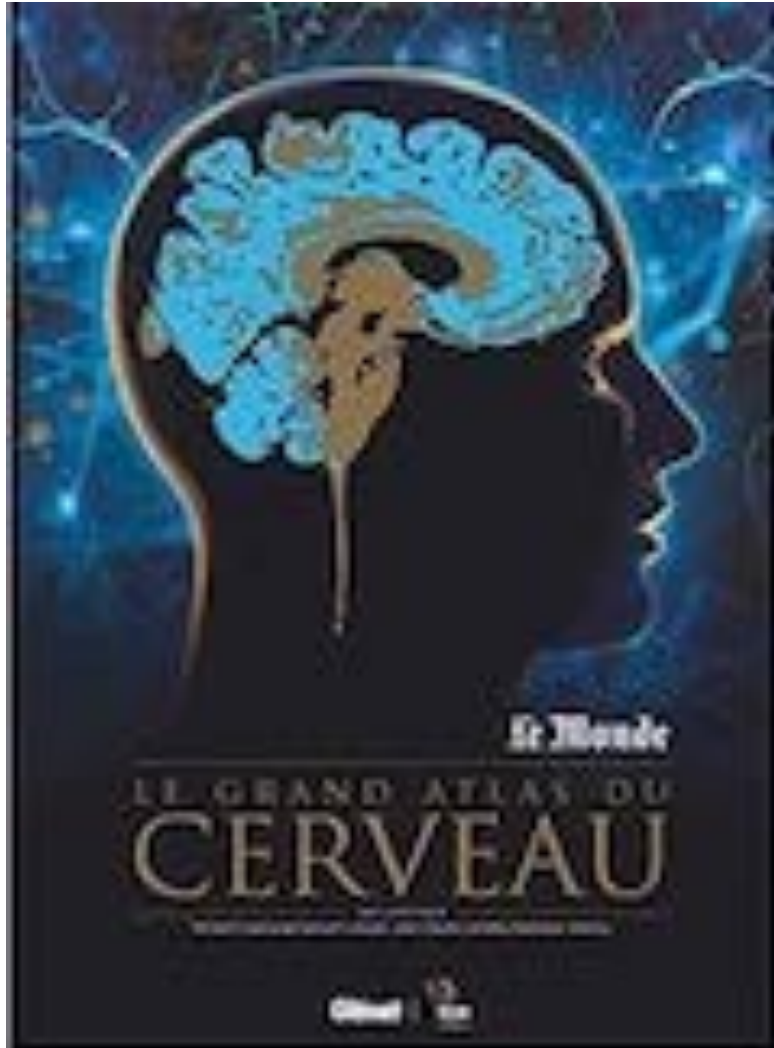
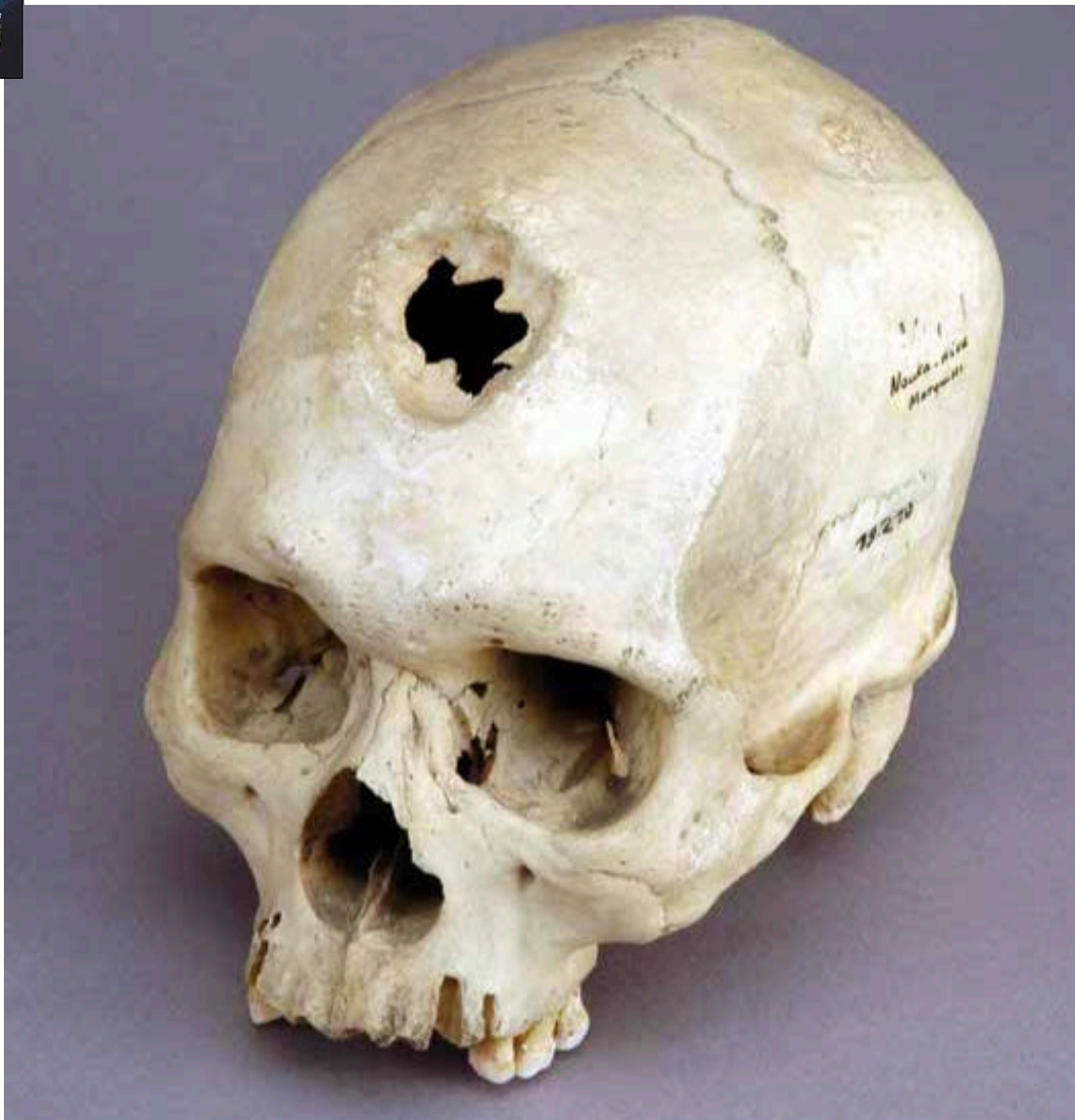




Geneeskundige Stichting Koningin Elisabeth
Fondation Médicale Reine Elisabeth
Königin-Elisabeth-Stiftung für Medizin

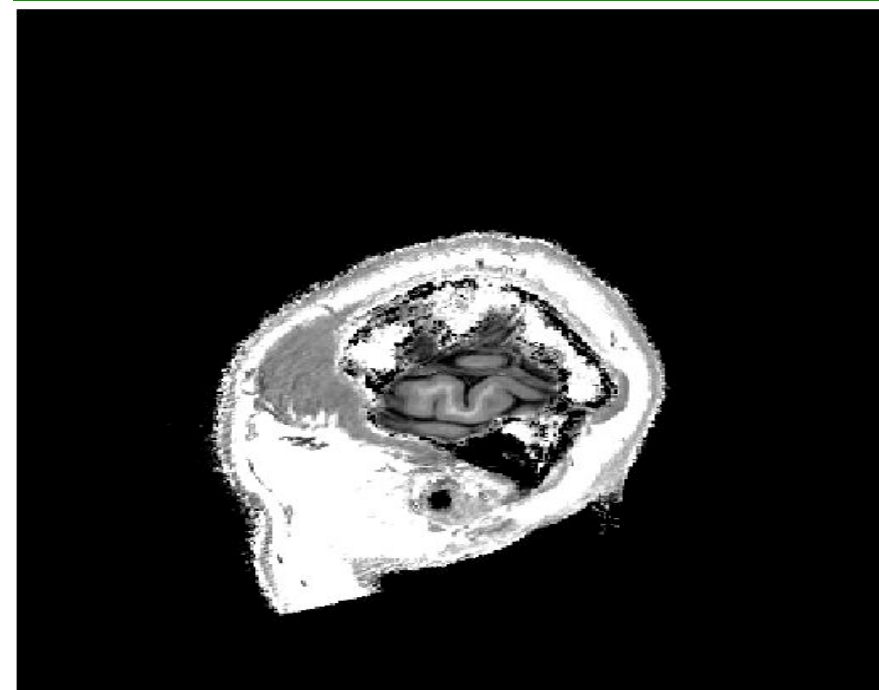
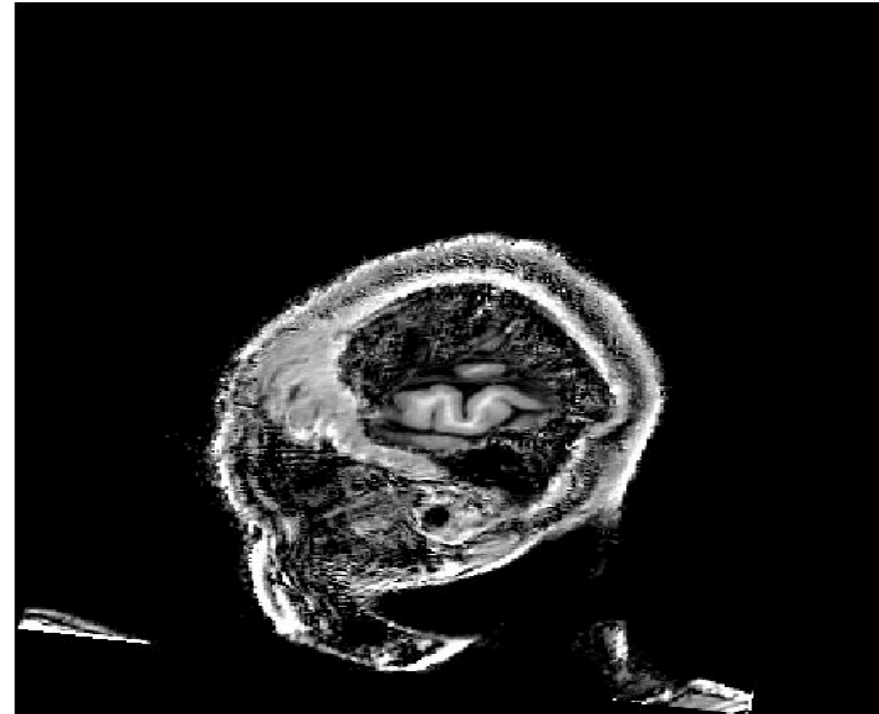
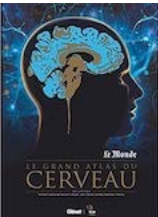
ADVANCES IN HUMAN BRAIN STUDIES WITH NEUROIMAGING

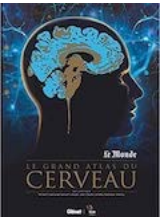


Neolithic skull (6500 years BC)

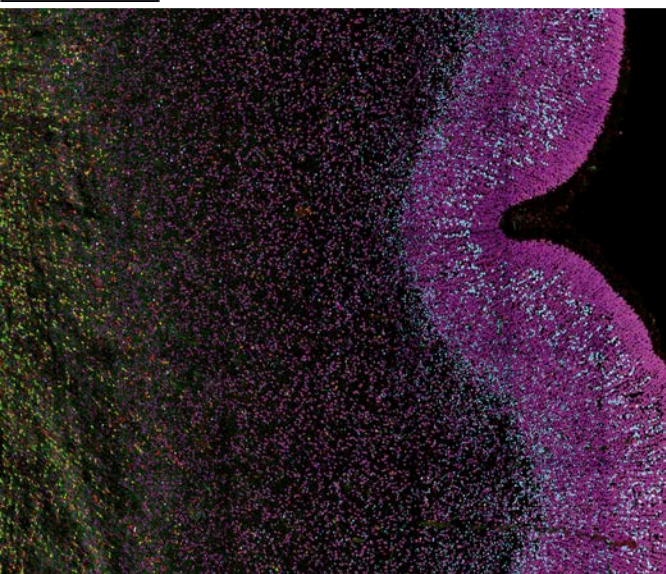


VESALIUS 16th century AD

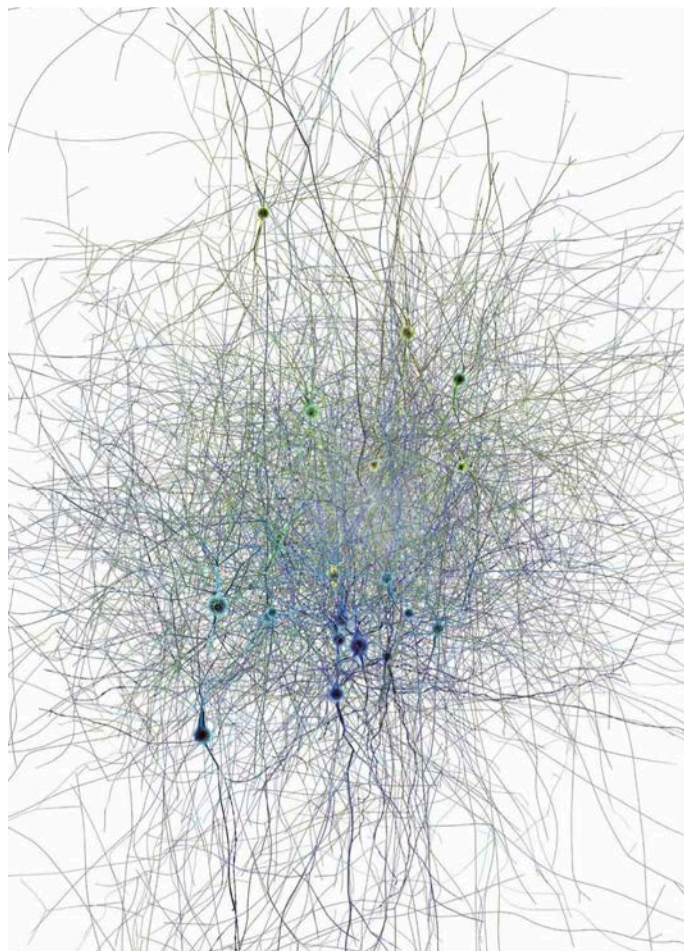




LEVELS OF RESOLUTION

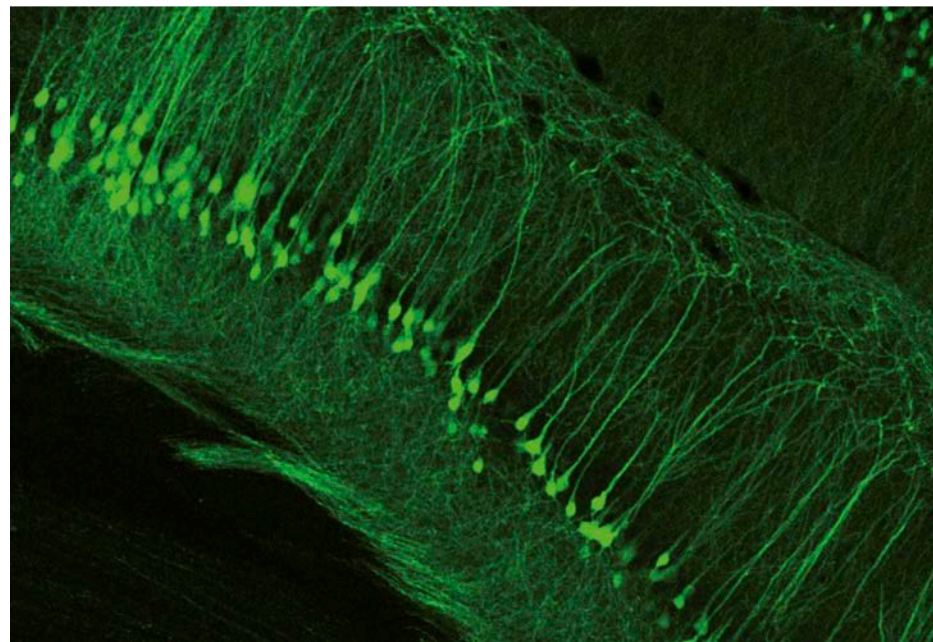


Cortex

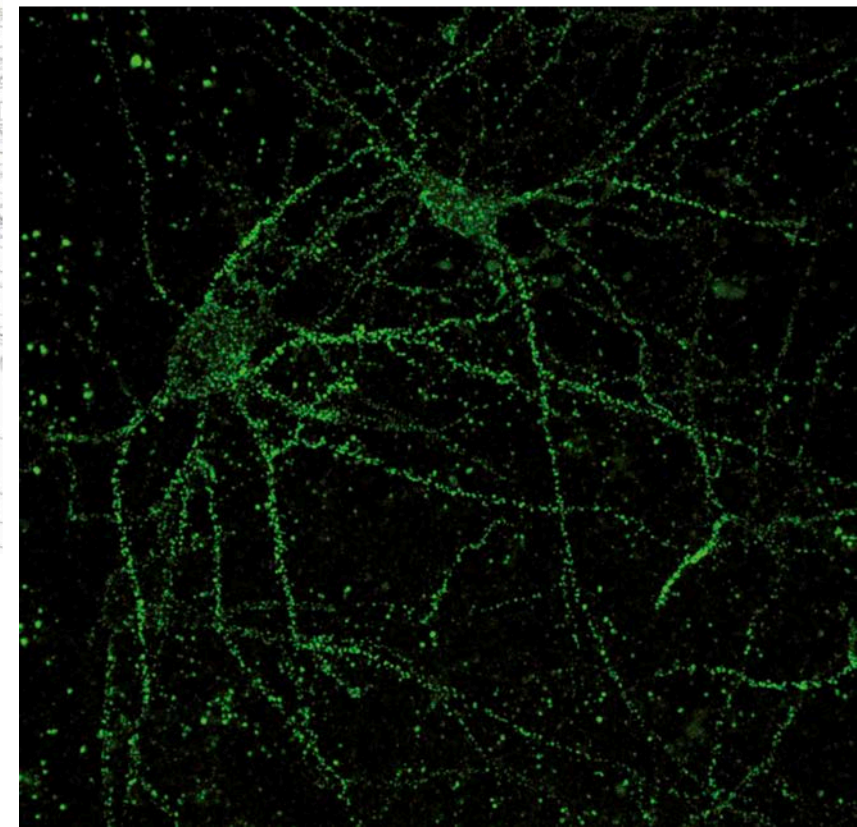


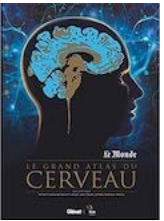
Cell clusters

Synapses

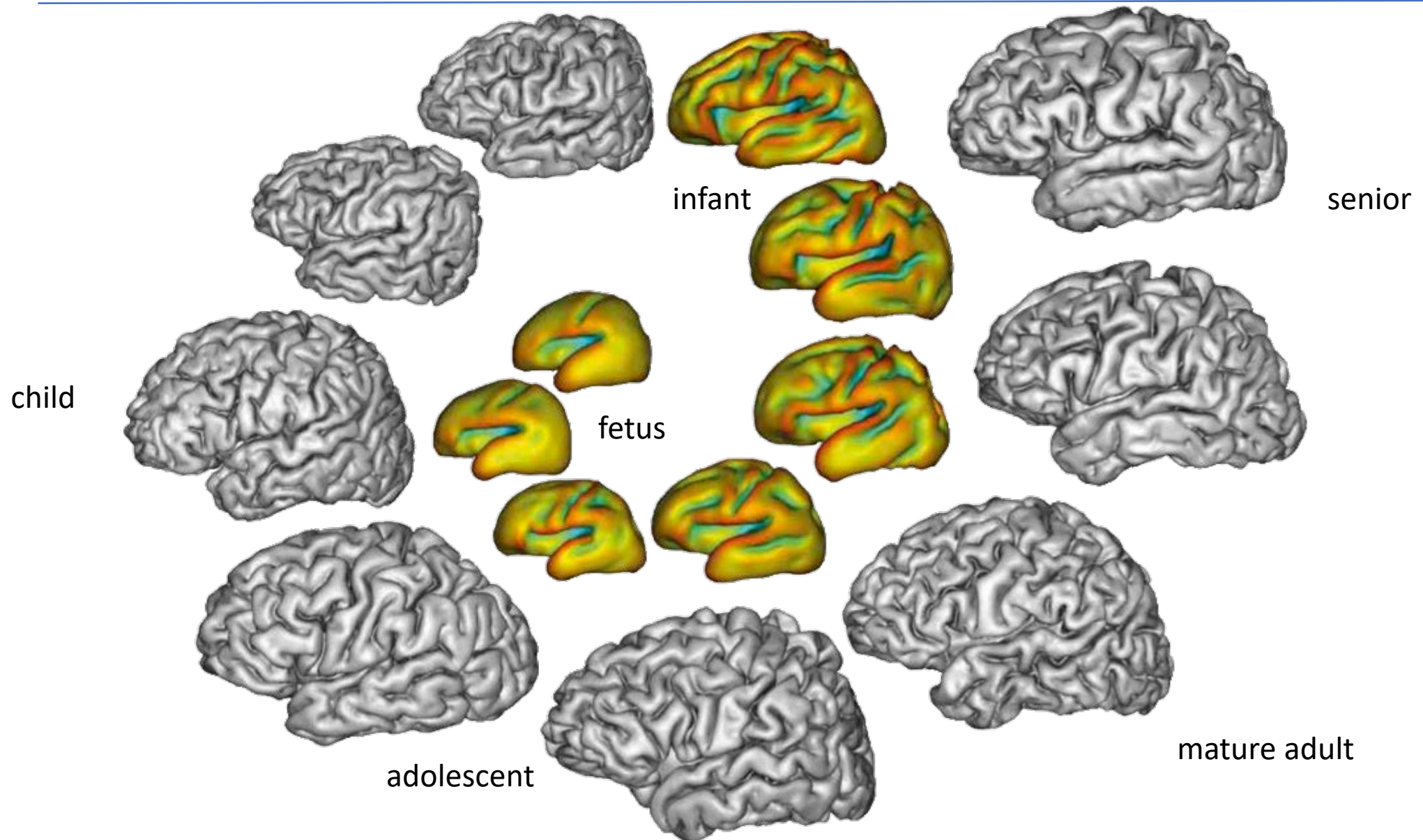


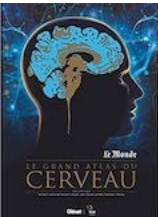
Cells in layers



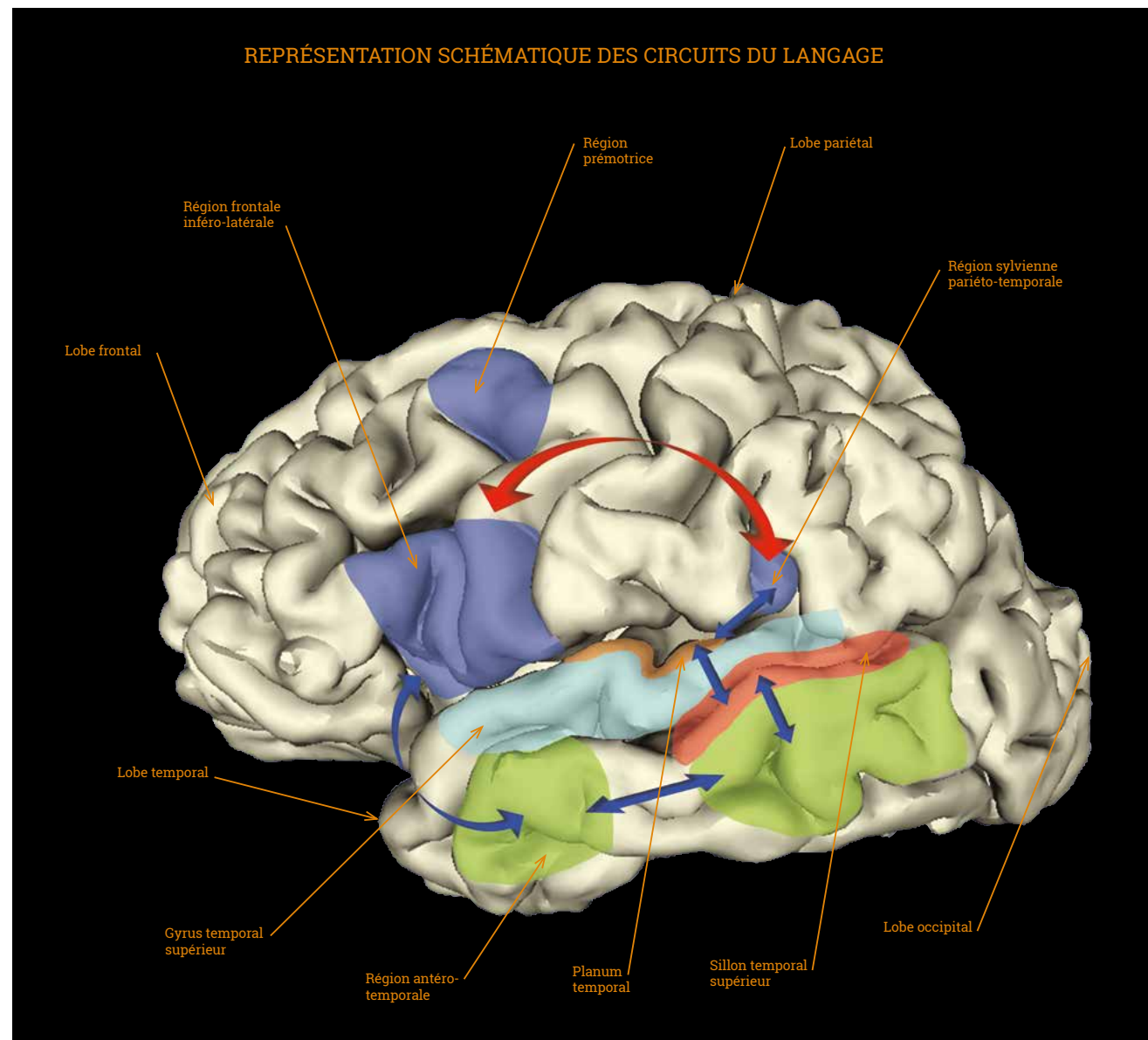
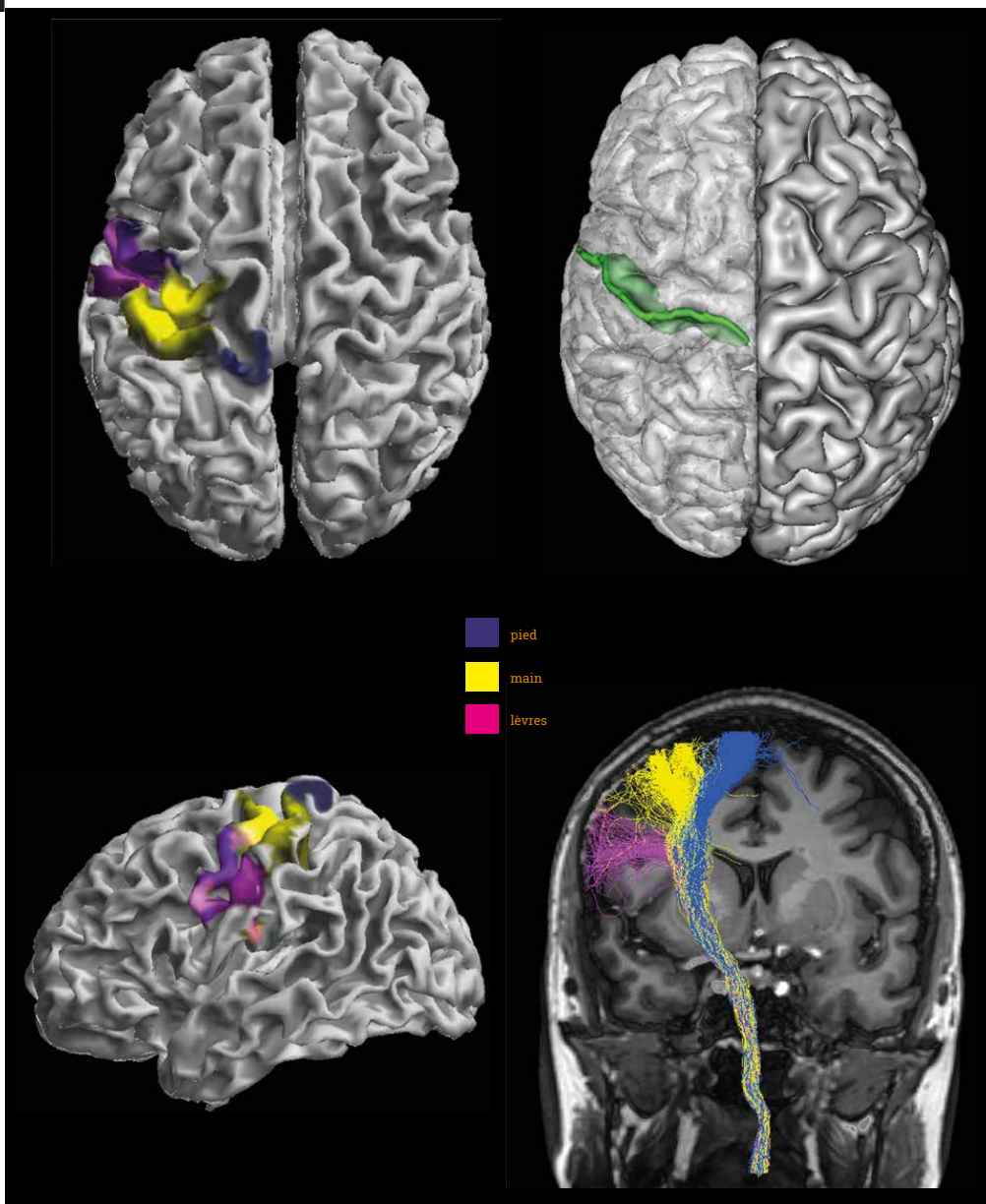


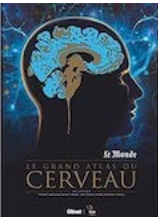
DEVELOPMENT AND PLASTICITY



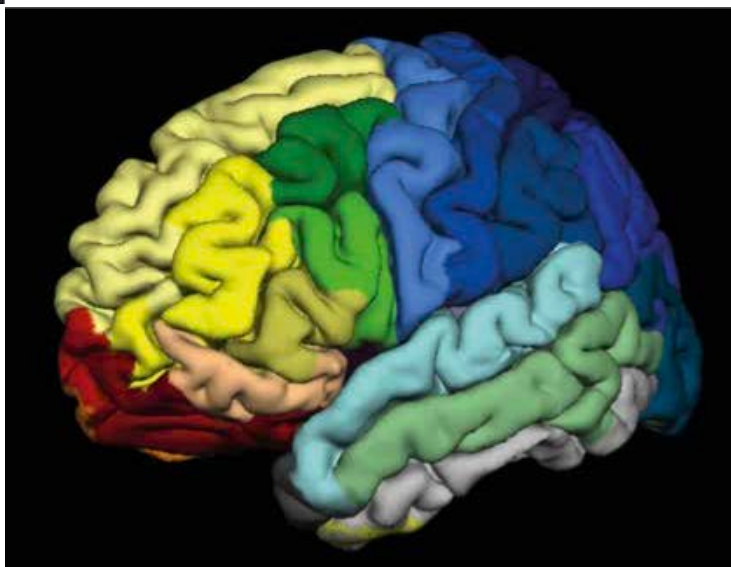


CONNECTIONISM 1

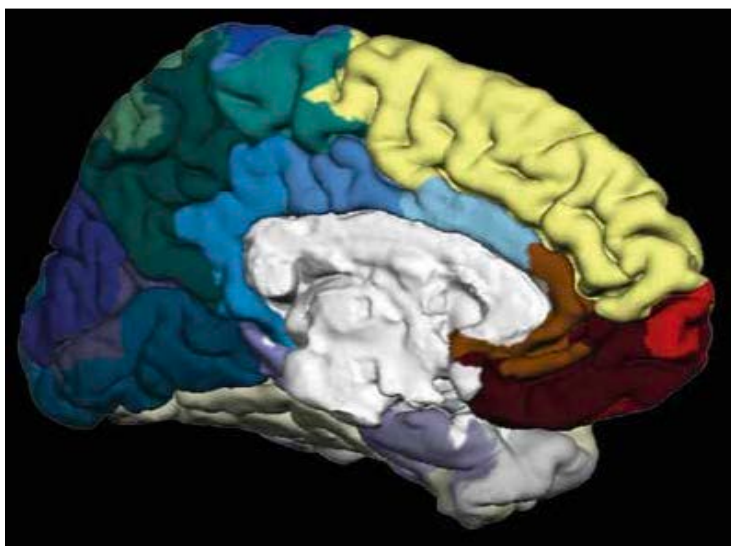




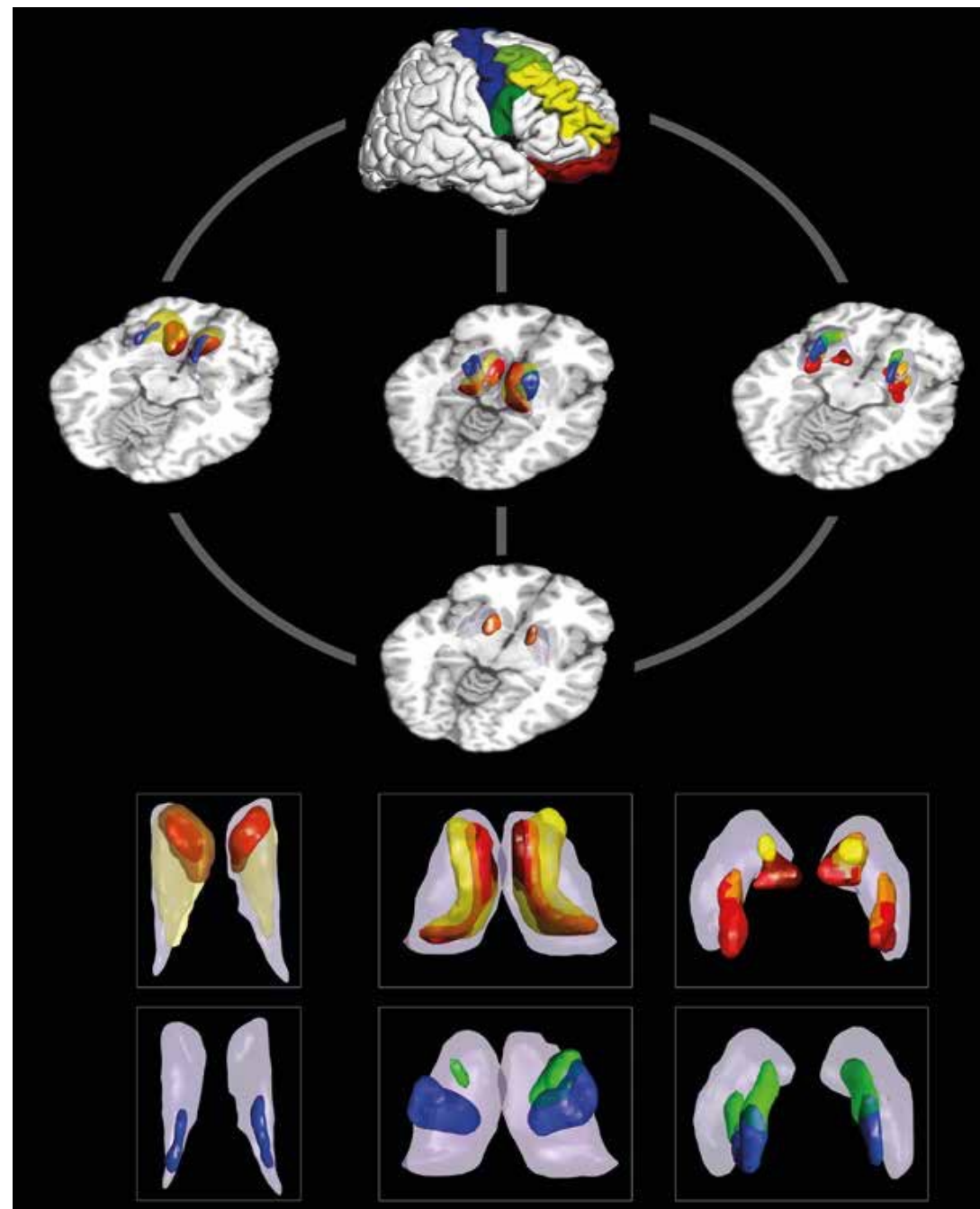
CONNECTIONISM 2

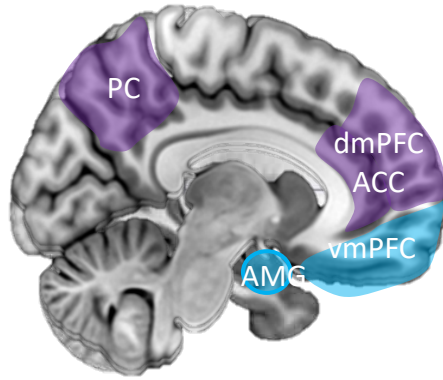
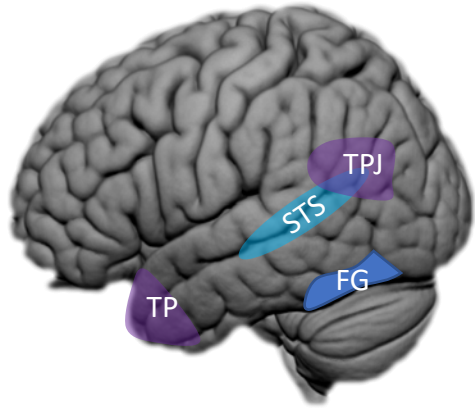
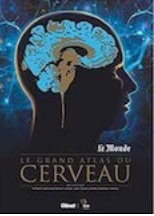


**CORTICO-
SUBCORTICAL
CONNECTIONS**



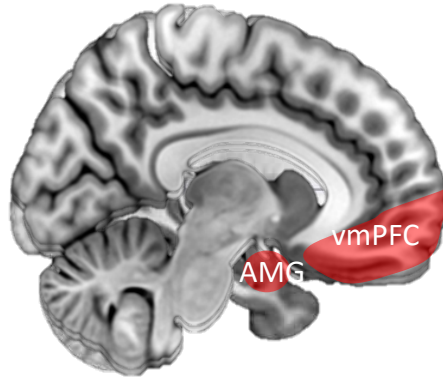
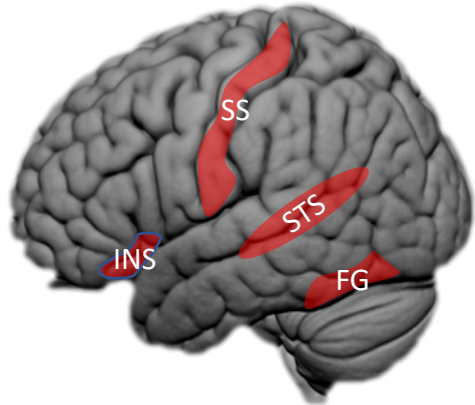
**SPECIALISATION
AND
INTEGRATION**





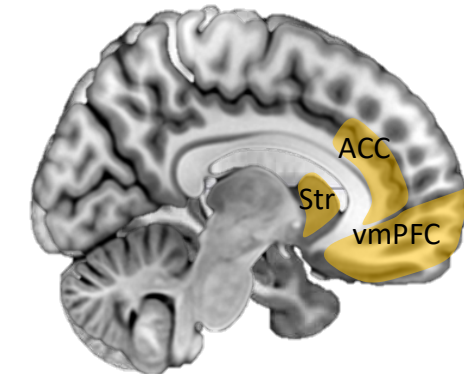
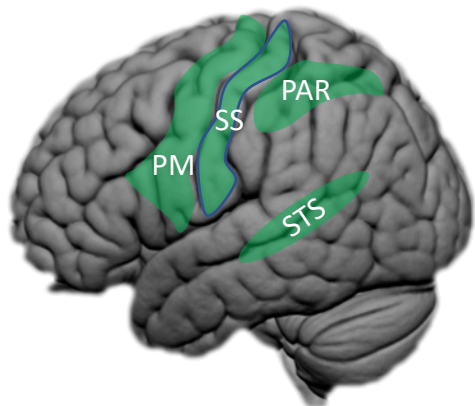
Face

Gyrus fusiforme (FG)
Sillon temporal supérieur (STS)
Amygdale (AMG) et Cortex préfrontal ventro-médian (vmPFC).



Emotion

Gyrus fusiforme (FG)
Sillon temporal supérieur (STS)
Amygdale (AMG), Insula (INS), Cortex préfrontal ventro-médian (vmPFC) et Cortex somatosensoriel (SS).



Perception of action:

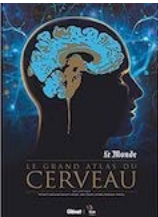
Sillon temporal supérieur (STS)
+ Réseau moteur: Cortex pariétal (PAR), Cortex somatosensoriel (SS) et Cortex Prémoteur (PM).

Theory of Mind

Jonction temporo-pariétale (TPJ), Pôle temporal (TP), Précuneus (PC), Cortex cingulaire antérieur (ACC) et Cortex préfrontal dorso-médian(dmPFC).

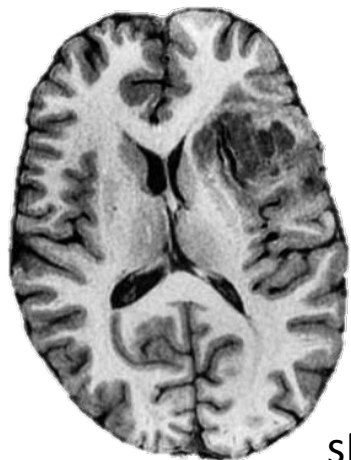
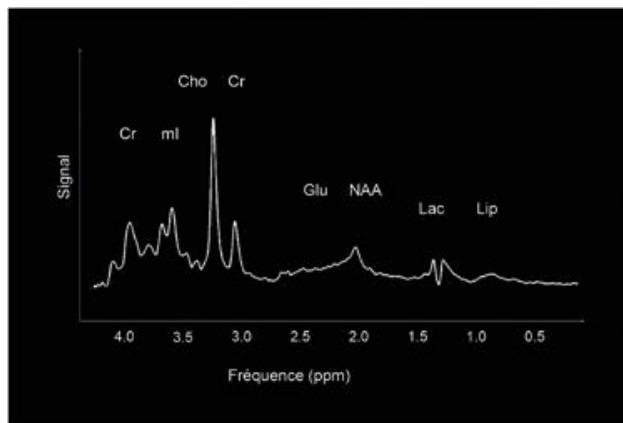
Value and reward

Striatum (Str dont Noyau accumbens NAcc), Cortex cingulaire antérieur (ACC), et Cortex préfrontal ventro-médian (vmPFC).

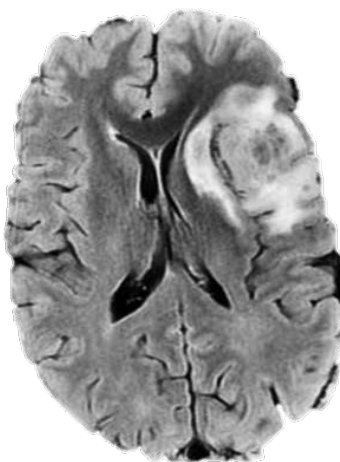


MAGNETIC RESONANCES

MRS



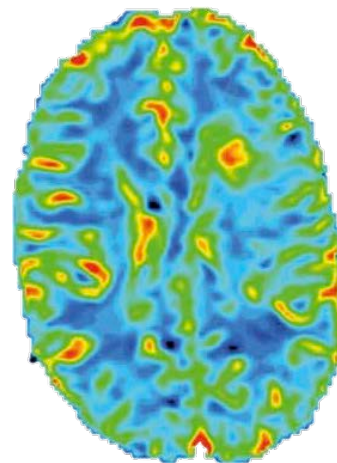
sMRI T1



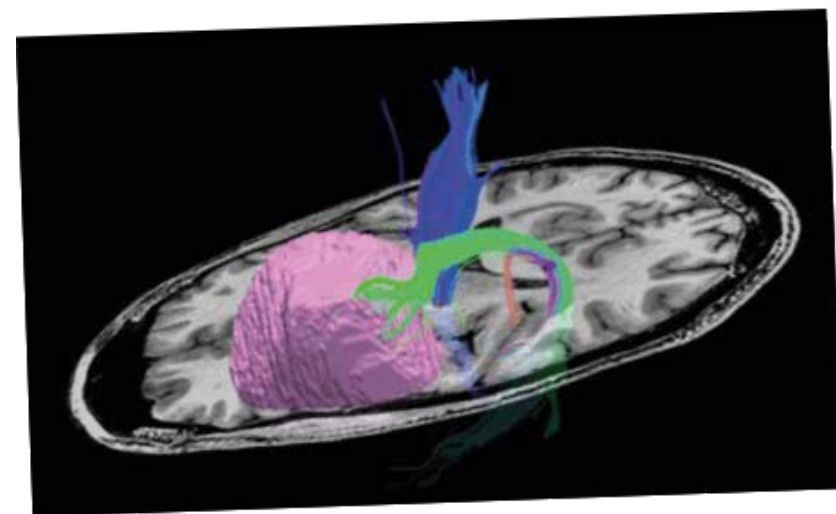
sMRI T2



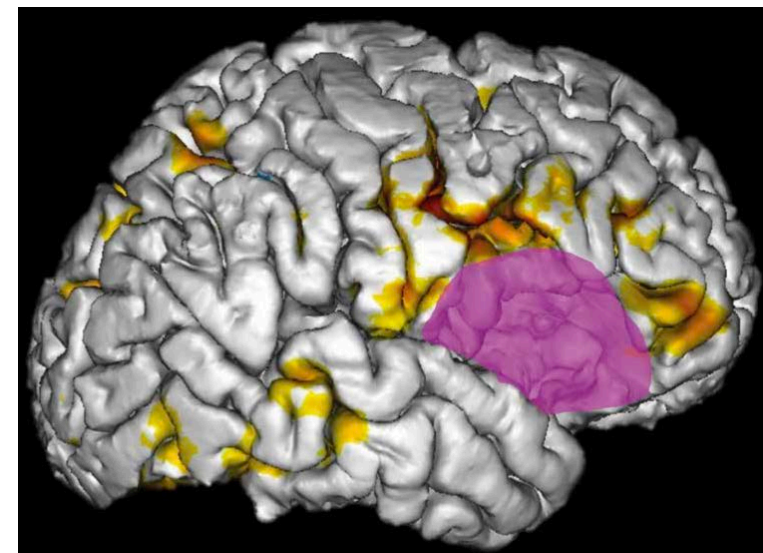
cMRI



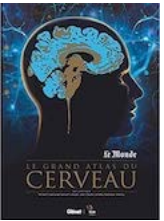
pMRI



MRt



fMRI



GRAND MEDICO-SOCIAL CHALLENGES



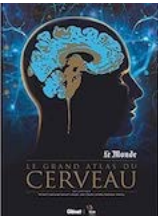
Alzheimer's disease: 20 per cent beyond the age of 80; dependent within 3-5 years of onset.



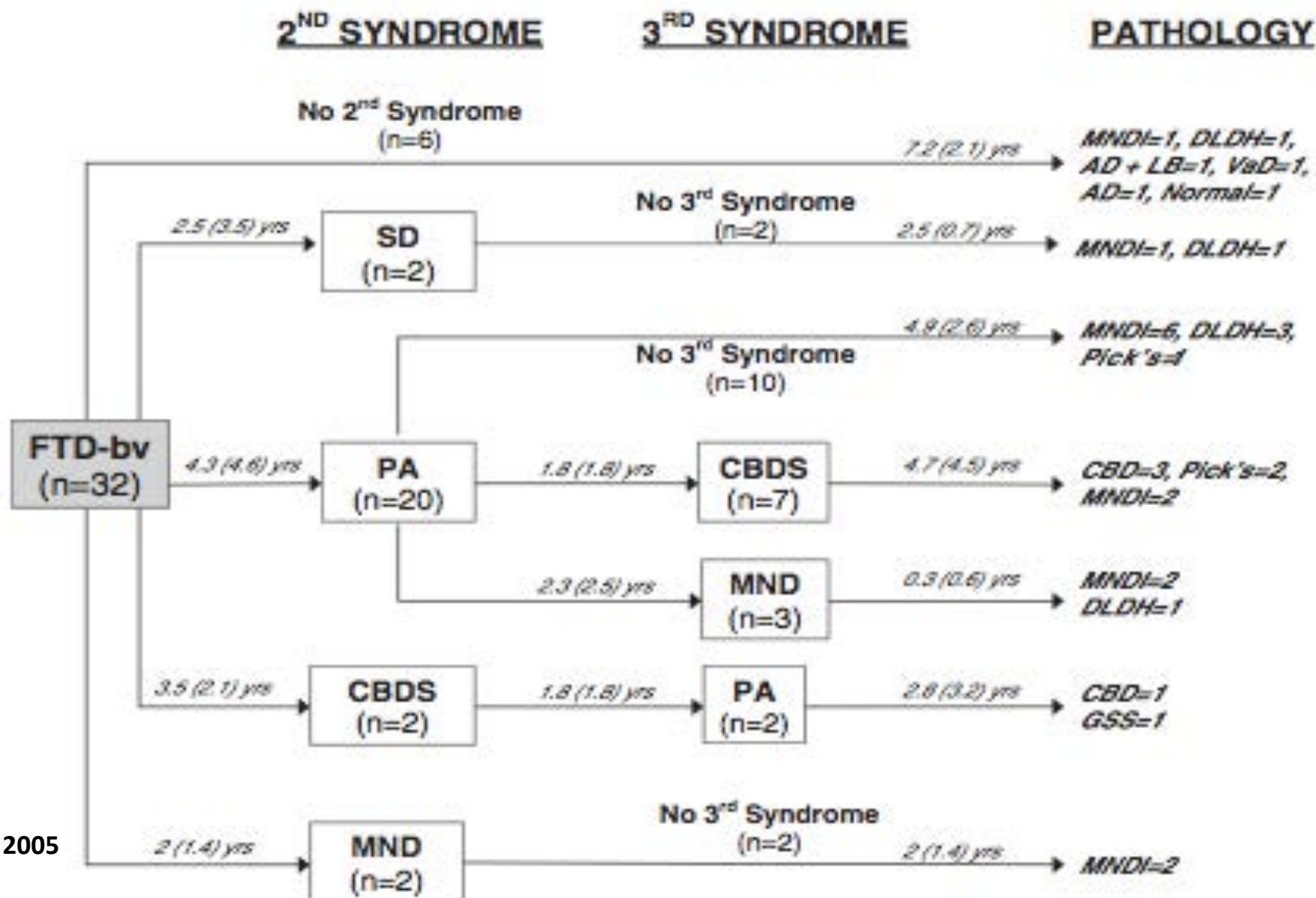
Depression: the second most common condition in the world (WHO):
6 per cent of the population in the Western world.

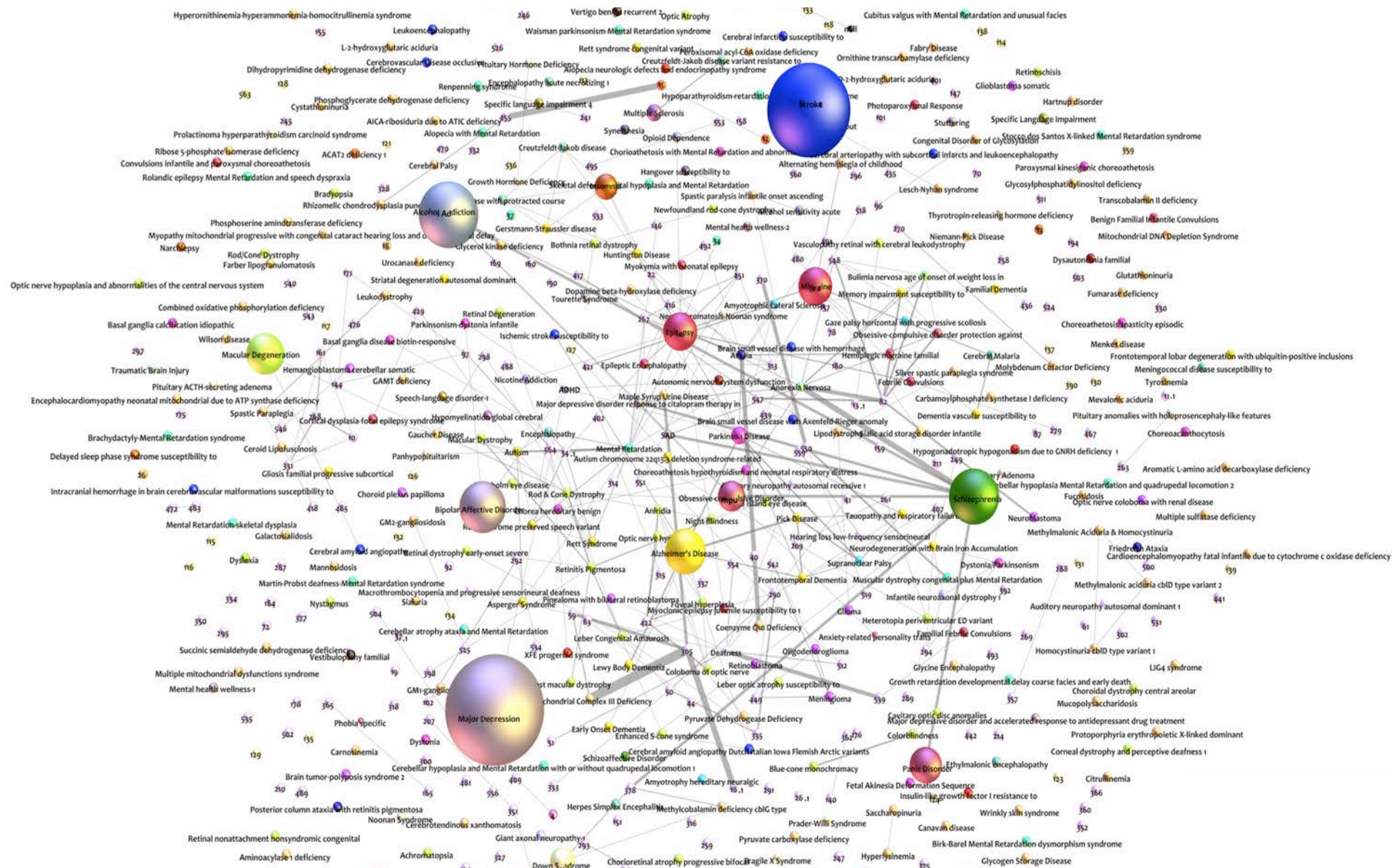


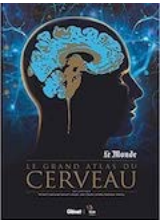
Parkinson's disease: second cause of motor disability. Affects **0.2 per cent** of the population.



HAVE WE REACHED A DEAD END CLINICALLY?







THE HERE AND NOW

**Phenomenology alone
is insufficiently discriminative
for diagnosis and prognosis**

**Genotyping does not
replace descriptive medicine**

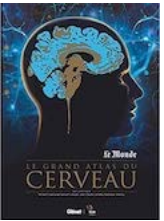
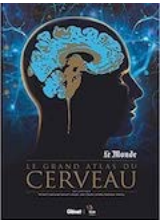


IMAGE PATTERNS – A LINK FROM BIOLOGY TO PHENOMENOLOGY

ARE **PATTERNS** OF PIXEL ABNORMALITIES
OF DIAGNOSTIC
and/or
PROGNOSTIC SIGNIFICANCE?

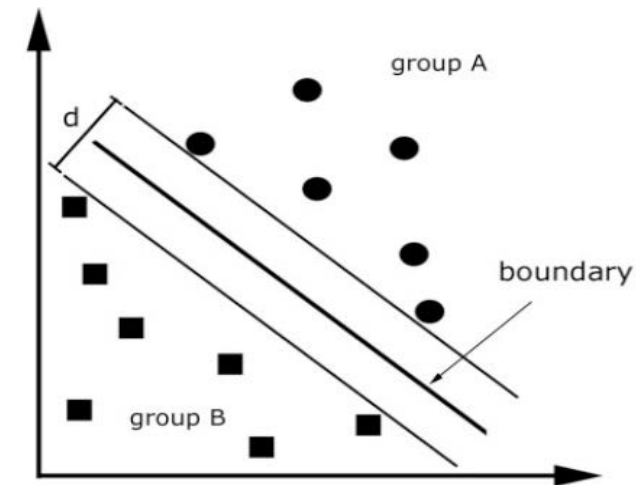
INFORMATICS MEETS MEDICINE

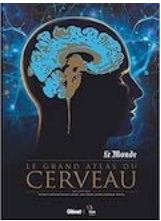


INFORMATICS CLASSIFY PATTERNS

	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

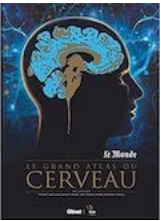




INFORMATICS REFINE DIAGNOSIS

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

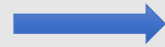
SVM ANALYSIS



BIG DATA & INFORMATICS

RUBBISH IN  RUBBISH OUT

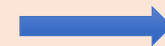
Signal additive
Noise suppressed
Avoids myth of perfect controls – whither RCTs?



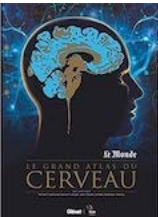
GENERATES HYPOTHESES

How big data can help: Bradford Hill (1965)

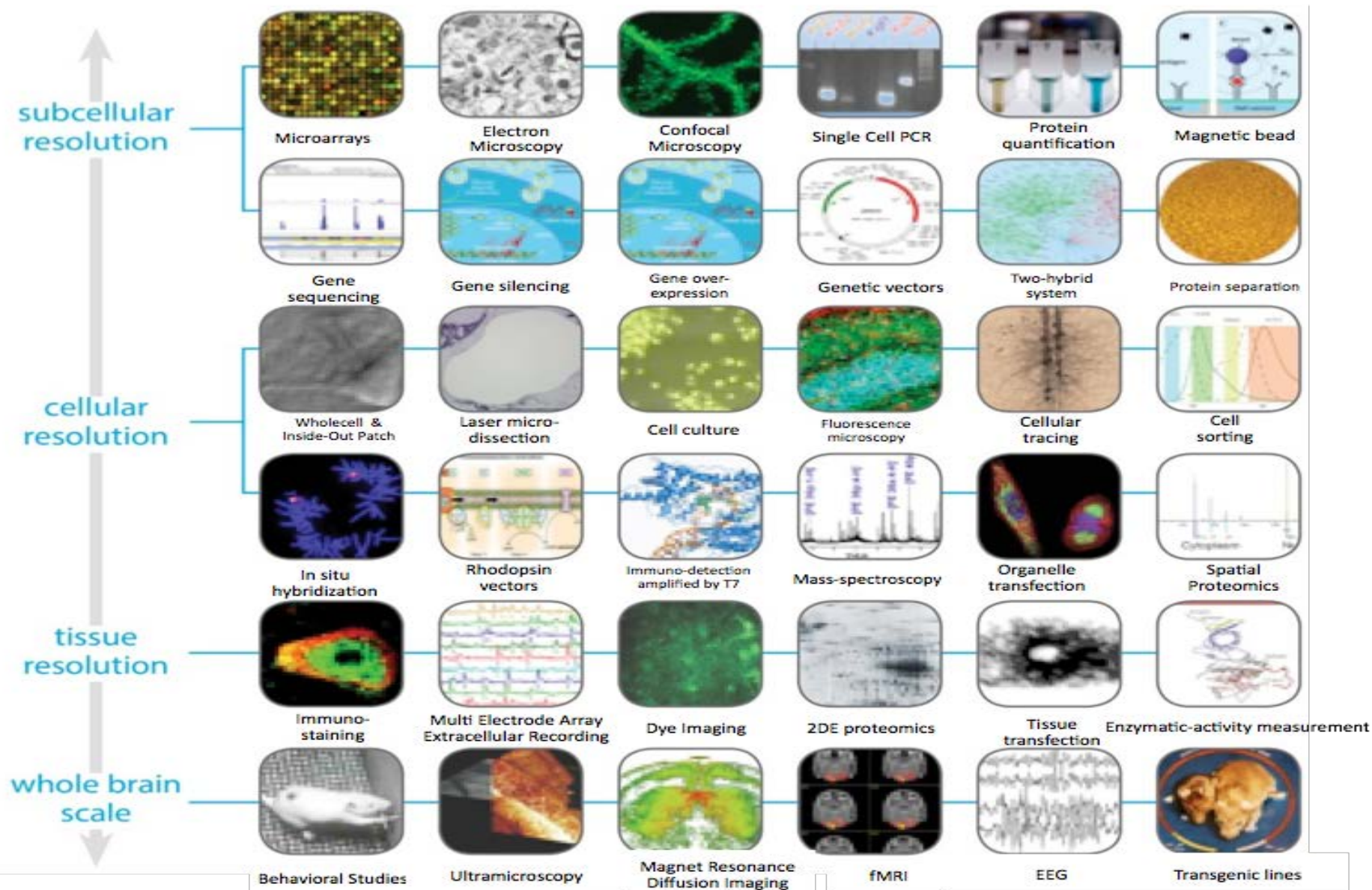
Biologically plausible
Explores multiple (all) models
Multi-scale & dimensional patterns
Additive over time
Built in reproducibility

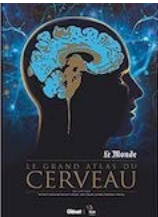


PREDICTIVE & CAUSAL



NEUROSCIENCE DATA ACROSS SCALES

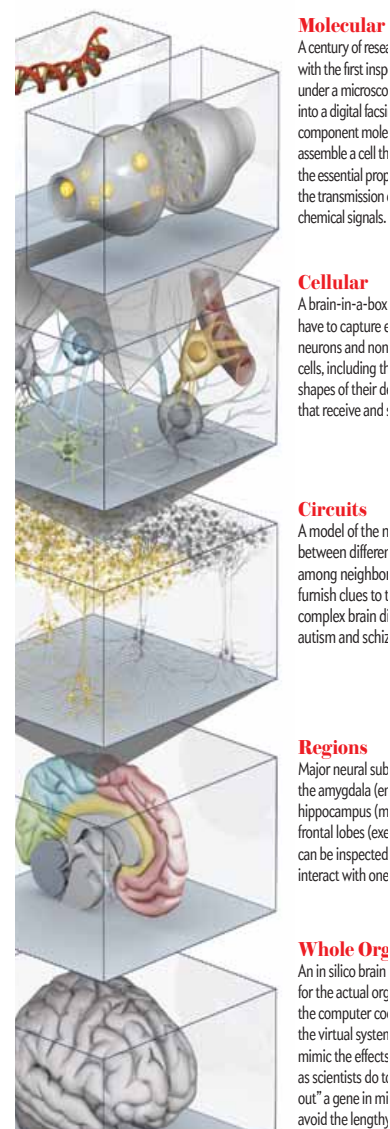




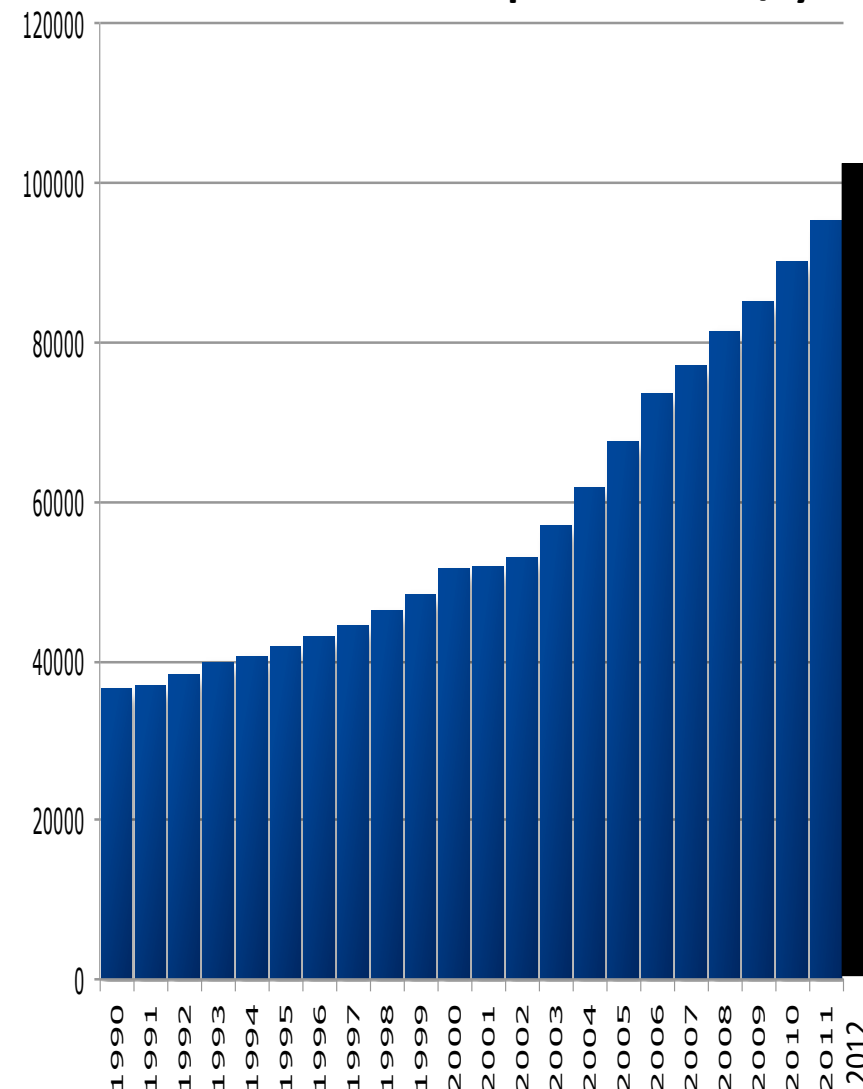
INTEGRATING DATA

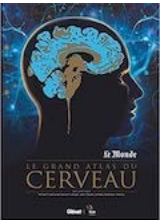
- Exponential growth
- Fragmented knowledge
- Societal benefits
- Economic health burden

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



Peer reviewed brain publications / yr





CONFRONTING or COMPLEMENTING 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)

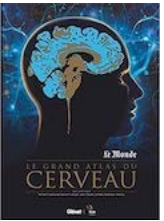
Multimodal and multivariate data

Exhaustive mining to demonstrate coherent models

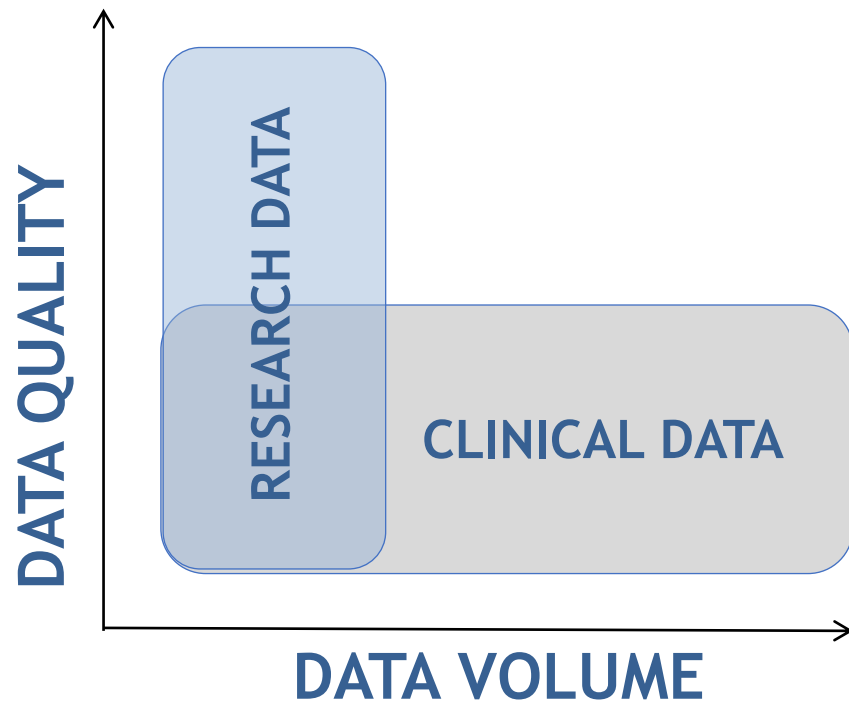
Exploration of these mathematical models as generated hypotheses

Investigation of hypotheses – clinical, mechanistic, prognostic, therapeutic

Knowledge (& causes)



DATA SOURCES AND CHALLENGES



HOSPITAL DATABASES

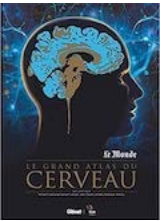
- NOT COMPLETE
- NOT STRUCTURED
- NOT STANDARDISED
- NOT CLEAN
- PROTECTED FOR PRIVACY
- PROTECTED AGAINST CORRUPTION

RESEARCH DATABASES

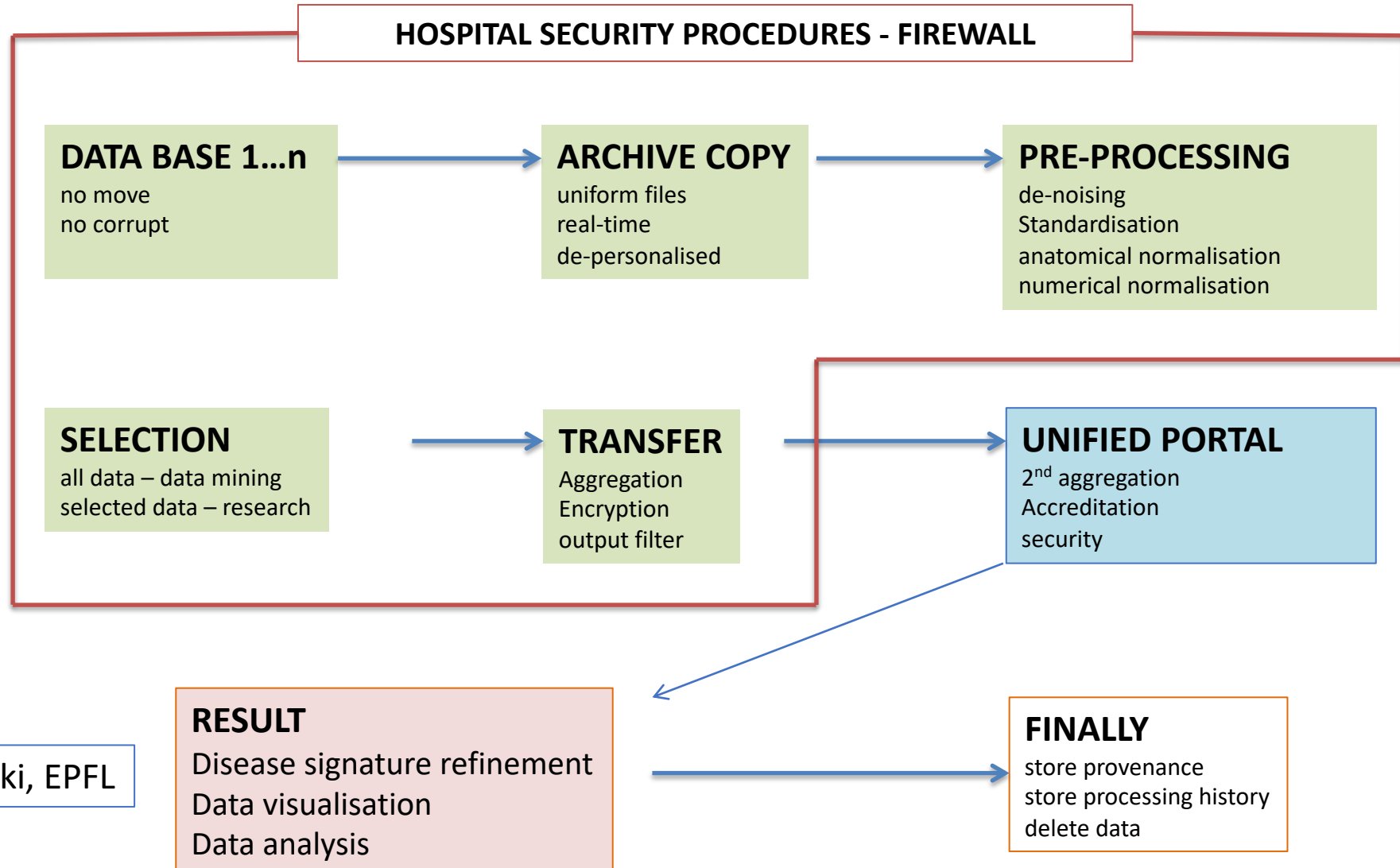
- PROTECTED CULTURALLY

PHARMACEUTICAL DATABASES

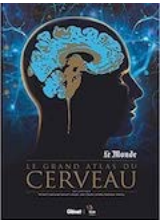
- PROTECTED COMMERCIALY



MEDICAL INFORMATICS PLATFORM - FEDERATING DATA



RAW – A Ailamaki, EPFL



ETHICAL CHALLENGES

PRIVACY

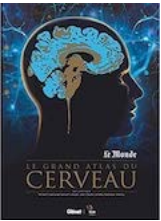
- DE-PERSONALISATION
- ANONYMISATION

CONSENT

- BROAD CONSENT
- RETROSPECTIVE - PROSPECTIVE

MANAGEMENT OF ETHICS

- LOCAL ETHICS COMMITTEES
- VALUE AND CREDIBILITY OF SCIENCE



REAL ETHICAL QUESTIONS

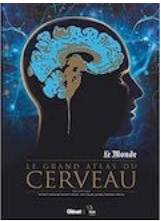
IN MEDICINE IS IT ETHICAL TO...

- ✓ 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)

??????????



BIG DATA

(not really, but getting there)

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

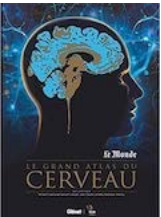
For a subsample of 2091 we knew the MMSE score

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)



FEDERATING AND INTEGRATING DATA

BRAIN IMAGING

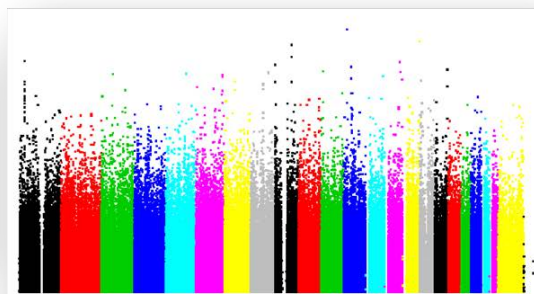


PET



MRI

CLINICAL SCALES
&
MEASUREMENTS



Organising
Tabulating

Processing...

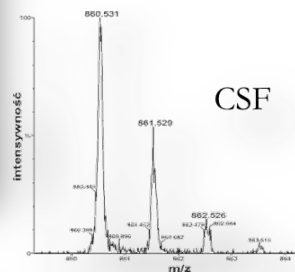
... GTGCATCTGACTCCTGAGGAGAAG ...
... CACGTAGACTGAGGACTCCTCTTC ...



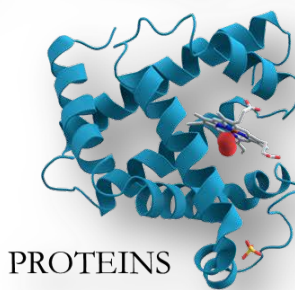
... GUGCAUCUGACUCCUGAGGAGAAG ...

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

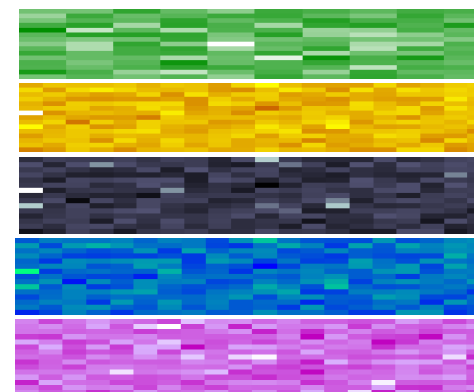
GENES



CSF



PROTEINS



MRI data

PET data

Gene data

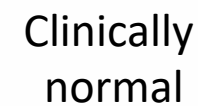
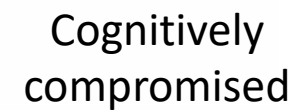
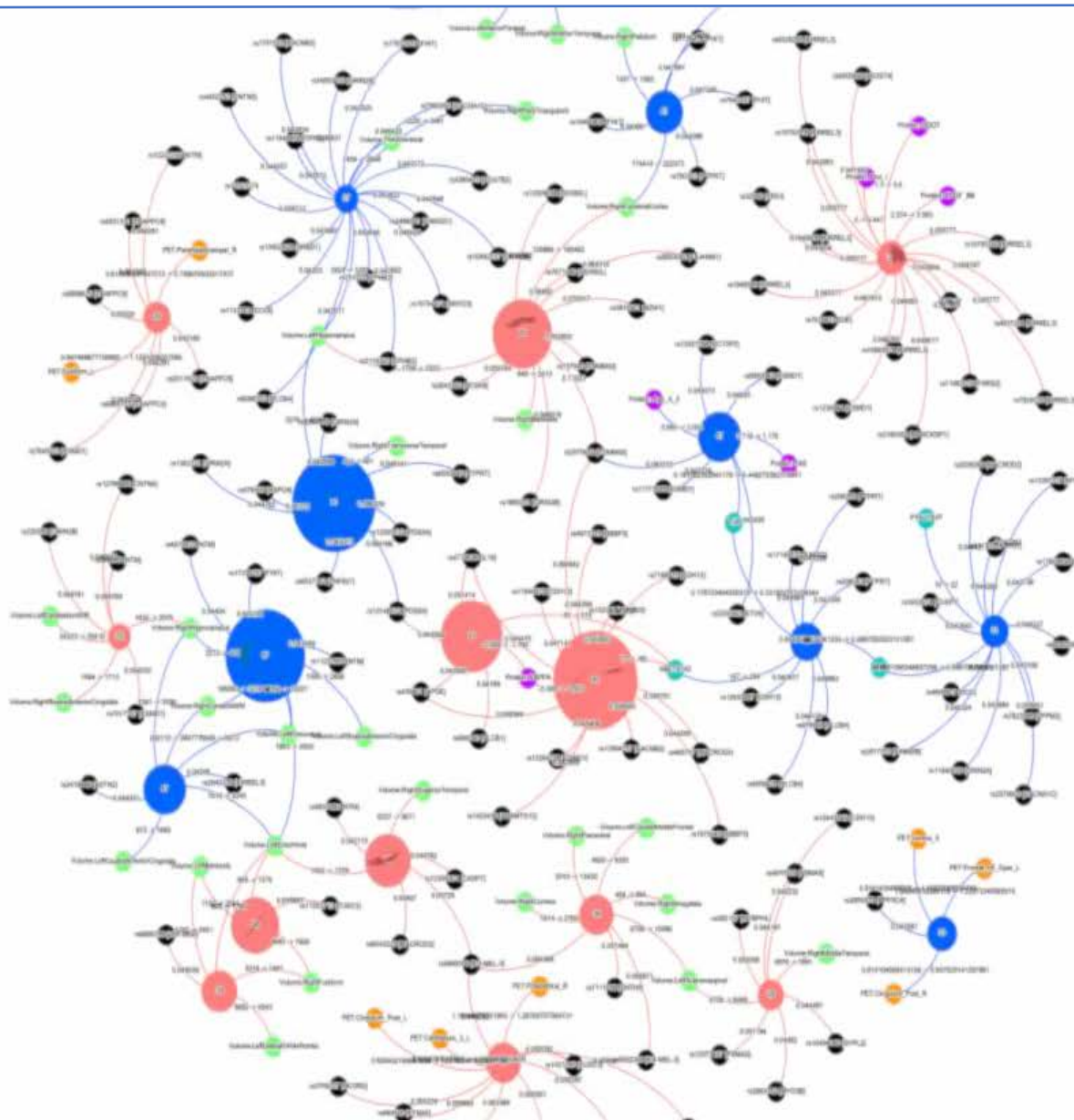
CSF data

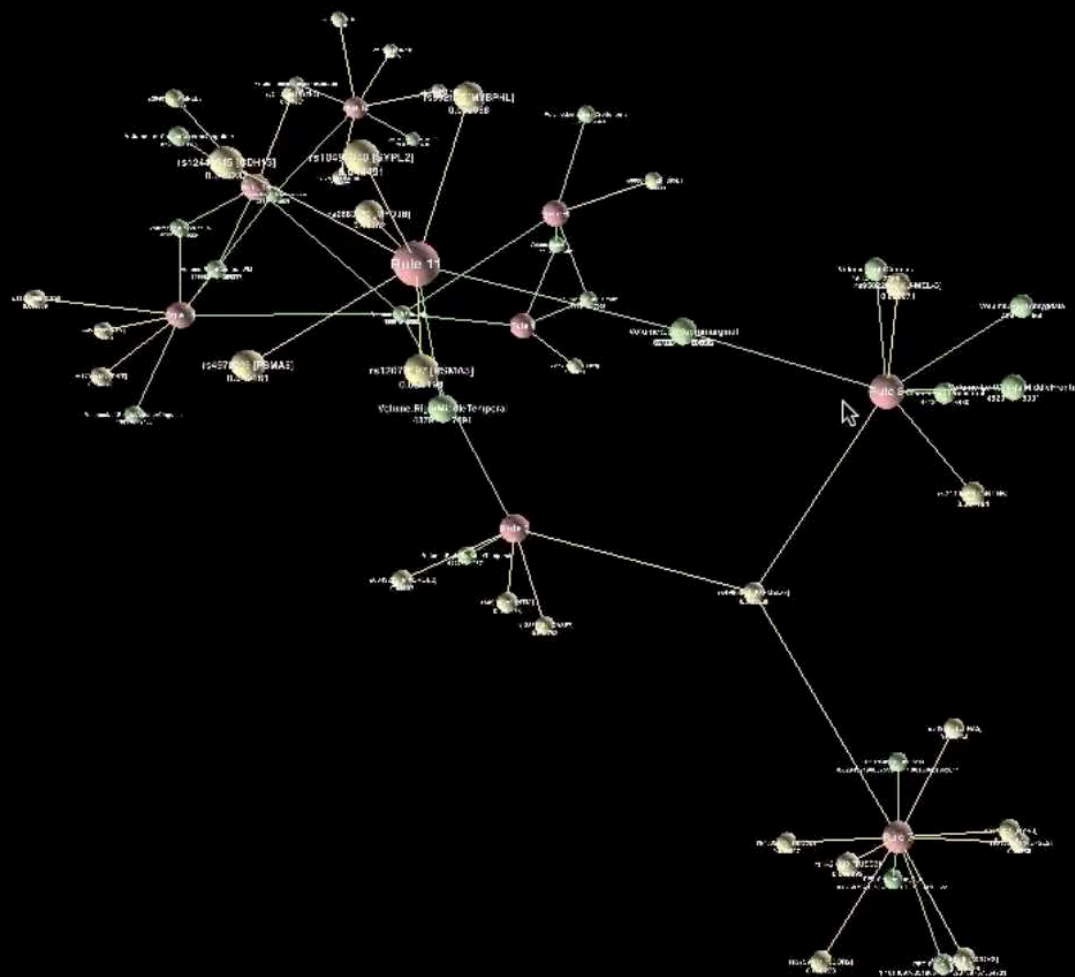
Protein data

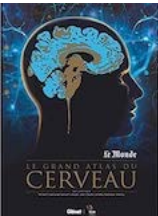
912 Alzheimer's patients
5566 Healthy controls

- Phenotype-led semi-supervised clustering
- Biologically led classification
- High dimensional feature (deep) learning



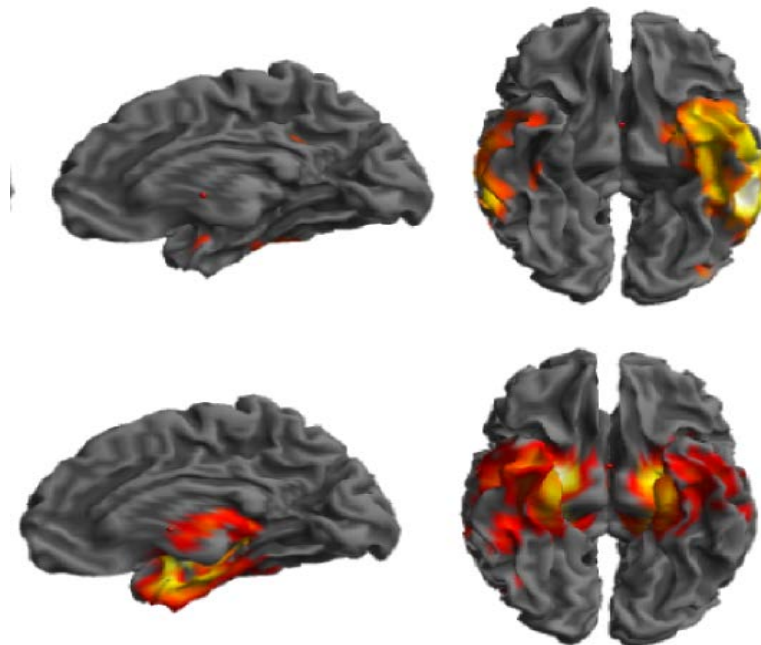
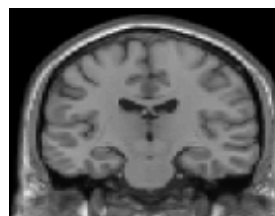
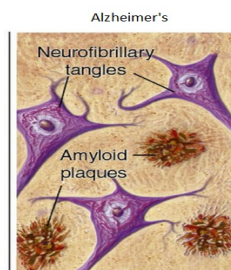
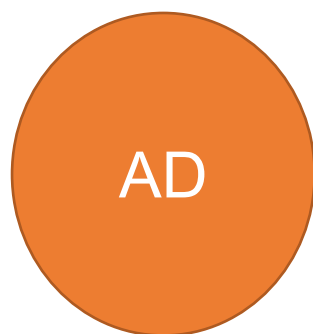






EXAMPLE OF INTEGRATION OF PHENOTYPIC AND ANATOMIC DATA

CLINICAL (SYNDROMIC) CLASSIFICATION



INTEGRATING PATHOLOGY INTO DIAGNOSIS



Symptoms +
Pathology +



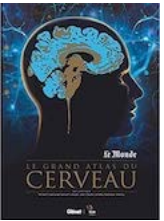
Symptoms +
Pathology -



Symptoms -
Pathology +

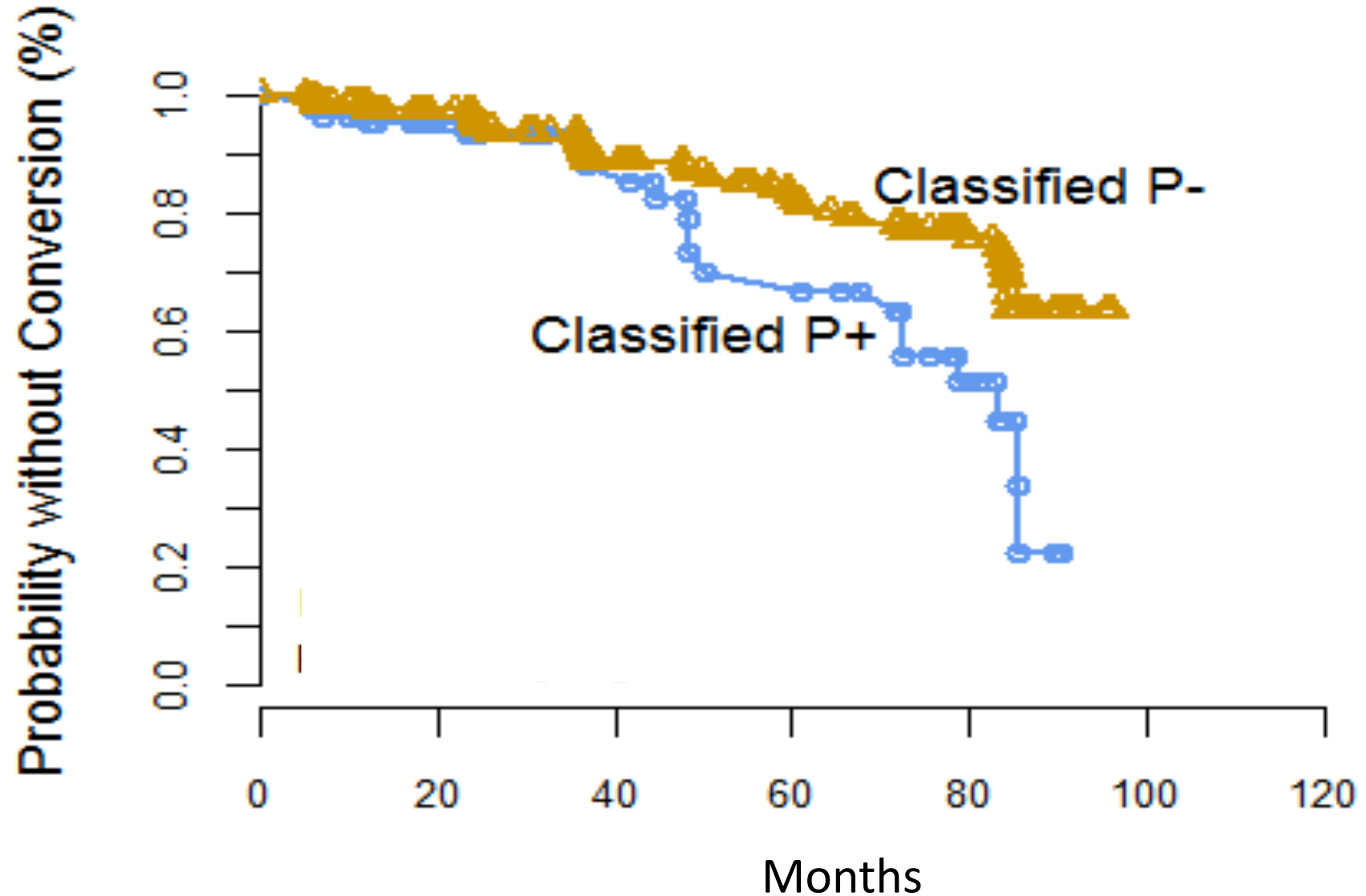


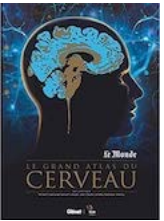
Symptoms -
Pathology -



INTEGRATED MODEL PREDICTS INDIVIDUAL PROGNOSIS

ALL SUBJECTS
COGNITIVELY
NORMAL
AT TIME = 0





FUNDAMENTAL ISSUES and CONCLUSIONS

CLINICAL AND NEUROSCIENCE DATA MUST BE INTEGRATED

SIMULATION is an analytical methodology & depends on high performance computing

SIMULATION is always bottom up – it is a reconstruction from real data

It generates complexity from simpler elements

It results in a PREDICTIVE MODEL that CONSTRAINS next level organisation

SIMULATION can start from any level but always bottom-up and data led

But data are useless unless they help reconstruction from one level to the next.

WE NEED GOOD PREDICTIVE SIMULATION MODELLING TO REDEFINE
& REFINE NEURO-DIAGNOSES IN FUTURE DIAGNOSTIC MANUALS



HBP MEDICAL INFORMATICS PLATFORM

-  Clinical neuroscientist
-  Computer scientist
-  Statistician neuroscientist
-  Ethics



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