

# HUMAN BRAIN PROJECT





# THE MEDICAL COMPONENT OF THE HBP

# **.**

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

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**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**.



# HAVE WE REACHED A DEAD END CLINICALLY?





# **HYPOTHESIS 1**

Phenomenology alone

is insufficiently discriminative

for diagnosis and prognosis

**Genotyping does not** 

replace descriptive medicine





# **HYPOTHESIS 2**

### **PATTERNS** OF PIXEL ABNORMALITIES

### ARE OF DIAGNOSTIC

and/or

**PROGNOSTIC SIGNIFICANCE** 



# **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 <b>PATHOLOGY</b>	96%	100%	93%
		d e e	
BINARY CLASSIF	ICATION BY R MACHINE		boundary
		group B	



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

**SVM ANALYSIS** 



# QUANTITATIVE MULTI-PARAMETER MAPPING BASED ON BIOPHYSICAL MODELS

Lorio et al., 2016 *HBMapp* Lutti et al., 2012 *PLOS One* Draganski et al., 2011 *NeuroImage* 





# **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



# **FUNCTIONAL CONNECTIONS**

	$ \begin{array}{l} \text{LEFT LATERAL VIEW} \\ \leftarrow \text{Anterior}: \text{Posterior} \rightarrow \end{array} $	SUPERIOR VIEW	ANTERIOR VIEW	The posterior aspect of the STN projects to
Thalamus		P4 >=	Ser 1	structures consistent with a motor structure: Posterior putamen Posterior GPe Mid caudate nucleus
Caudate Nucleus	Carlor and			Ventro-lateral thalamic nuclei Posterior Insula Posterior hippocampus
Putamen				The anterior aspect of the STN projects structures consistent with a limbic structu
Globus Pallidus external segment		\$	¢ 🚯	Baso-lateral amygdala Posterio-medial GPi Inferio-mid putamen
Globus Pallidus internal segment		No. 🤳	16	Mid-GPe Ventral-anterior and ventral-lateral thalamus Anterior Insula Anterior hippocampus
Hippocampus	and the second s	<b>É</b> 🍃	-	The middle "associative" STN projects to
Amygdala		- e		regions encompassing both the motor and limbic projections



### PREDICTING CLINICAL SCORE COMPARING TO ASSESS RESERVE

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### **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)



# **FUNDAMENTAL ISSUE**

### 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



# **BIG DATA & INFORMATICS**



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





# DATA SOURCES AND CHALLENGES





• **PROTECTED COMMERCIALLY** 



# MEDICAL INFORMATICS PLATFORM FEDERATING DATA





# **MEDICAL INFORMATICS PLATFORM**





# **ETHICAL CHALLENGES**



- **DE-PERSONALISATION**
- ANONYMISATION

### CONSENT

- BROAD CONSENT
- **RETROSPECTIVE PROSPECTIVE**

### MANAGEMENT OF ETHICS

- LOCAL ETHICS COMMITTEES
- VALUE AND CREDIBILITY OF SCIENCE



# **SUBJECTS & METHODS**

### 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)

## **DATA EXTRACTION**

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# DATA INTEGRATION





# LINKING CLINICS TO BIOLOGY





# **USING ANATOMY TO CONSTRAIN DIAGNOSIS**



Brain atrophy pattern characteristic of pathological disease provides constraints on diagnosis



# PREDICTING OUTCOME MORE ACCURATELY

**NC** subjects with two patterns of brain atrophy



ALL COGNITIVELY NORMAL ON RECRUITMENT AT BASELINE = 0

Jing Cui 2016 - in preparation



# SUPERVISED SEARCH FOR AD SUBTYPES IN ADNI DATA

# Six subtypes identified



- 2. Atypical AD
- 3. Hippocampus spared
- 4. Amnestic MCI
- 5. Depression suspected
- 6. Cognitively Normal





# DISSECING CLINICAL GROUPS



# A UNIVERSE OF PERSONALISED DIAGNOSES





# **MULTI-SCALE DISEASE SIGNATURES**

The MIP provides methods to analyse federated data from hospitals, research centres and biobanks and aim to federate the different communities of users from these different locations.





# **REVERSE ENGINEERING – TO VALIDATE**

**Brain Atlases Biological Parameter Constraints & Biological Principles** Multi-constraint Algorithms Configurations Brain Reconstruction Workflows Data source Disease Principles Disease Vacul Principles Data Data ¢ ularizer Bouton AA AA Α Α density Synthe (mor Synthes Synapse В BB (project B BB density S nesizer 5 Syns/con sizer 4 CC С apses) nect Biological Data & principles Ρ Synthe (intrace Biochemicaliz er Connect Synaptic Functionalizer Respons e DISEASE

NORMAL

DATA INTEGRATION AND CAUSAL ANALYSIS

# **DISEASE SIGNATURES**

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



A PIXEL is an INFORMATION ANCHOR with COORDINATES in STANDARD BRAIN ANATOMICAL SPACE THAT LINKS TO INFORMATION ABOUT IT IN THE LITERATURE

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

PATTERNS ARE THOUGHT TO BE MECHANISTICALLY SPECIFIC and SO MORE RELEVANT to THERAPEUTICS – <u>TO BE PROVEN</u>

THE FUTURE IS IN DATA-LED HYPOTHESIS GENERATION FOLLOWED by CLINICAL, BIOLOGICAL AND GENETIC CHARACTERISATION – DISEASE SIGNATURES

SUCH CHARACTERISATION SHOULD GENERATE THERAPEUTIC STRATEGIES AND TARGETS IN A MORE PRINCIPLED MANNER THAN AT PRESENT – <u>TO BE PROVE</u>N

RCTs MAY HAVE MORE FOCUSED USES – BIG DATA ANALYSES TO REPLACE DOUBLE BLIND CONTROLS BY REMOVING NOISE - MASSIVE DATA SETS DO NOT NEED TO BE COMPLETE, CLEAN OR UNIFORM – <u>TO BE VALIDATED</u>



# THE ROLE OF DISRUPTIVE SCIENCE IN HBP-MIP

### 1. Move to a "no database" federated data analysis infrastructure

- ✓ Security, privacy, research, ethics considerations
- ✓ Advances in "virtualisation" "streaming" and "peer-to-peer" technologies
- ✓ Use of products of EC funded research (eg Exareme)
- $\checkmark$  Open source and cross-disciplinary specification
- ✓ Unlocking hospital databases for research

### 2. Breaking **conservative** medical IT culture

- ✓ Recruitments of university hospitals
- ✓ Recruitment of structured research databases
- ✓ Playing to "data sharing" revolution (NIH, EC, Wellcome initiatives)

### 3. Introduction of "disease signatures" concept

- ✓ Cultural change from pure symptomatic & syndromic disease definitions
- ✓ Preliminary classifications

# **HBP MEDICAL INFORMATICS PLATFORM**

Clinical neuroscientist Computer scientist Statistician neuroscientist Ethics

HP



**Bogdan Draganski Ferath Kherif Richard Frackowiak** Mira Marcus Kalish Saso Dzezowski **Boudewijn Lelieveldt** Anastasia Ailamaki Vasilis Vassalios Yannis Ioannidis Frank Schneider **Andrew Pocklington** John Ashburner **Alexis Brice Kathinka Evers** 

Jean-Francois Dartigues

Giovanni Frisoni Yoav Benjamini

Nada Lavrac Thomas Heinis

