

FHU ADAPT

ADdiction And Psychiatry TRANSFORMATION

thanks to Precision Medicine

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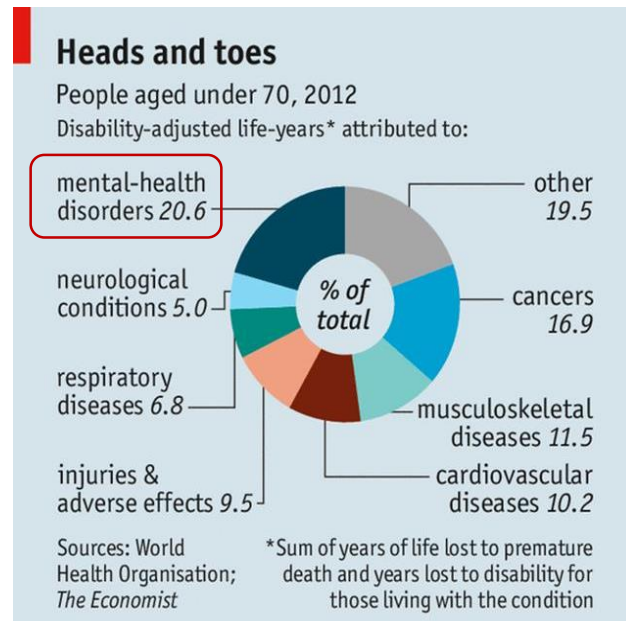
Jean-François Mangin

Information Processing Unit, Neurospin, **CEA**, Saclay

MENTAL DISORDERS: a major public health issue in great need of innovation to improve prognosis and to reduce costs

Worldwide

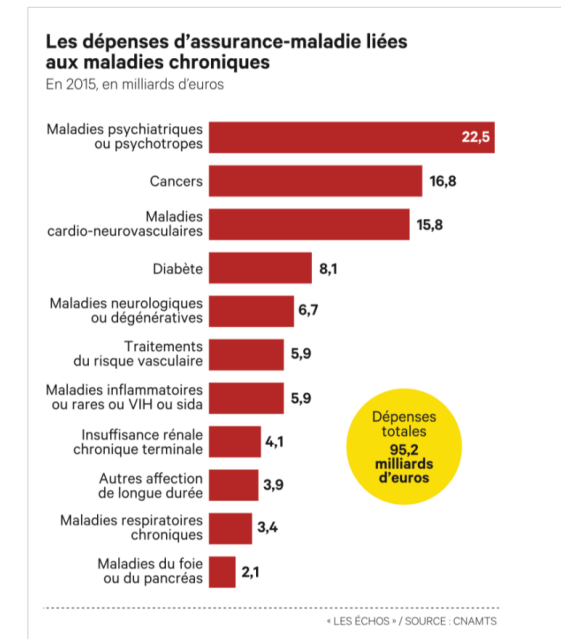
- The world's leading cause of handicap by 2020 according to the WHO¹
- 38% of 18-65 year old Europeans are affected by a mental disorder
- First cause of DALYS (Disability adjusted Life): 20.6%



¹ Murray and Lopez, Science, 1996;
WHO, European status on alcohol and health, 2001

In France

- 12 millions of French citizens affected by a mental disorder
- Total direct and indirect cost²: €109Bn per year
- First cause of health Insurance expenditures due to chronic disorders: €22.5Bn



² Chevreur et al., European J Neuropsychopharmacol, 2012

THE CHALLENGE: To break up heterogeneity of major psychiatric disorders

Heterogeneity is hindering research: non-replication of results

Heterogeneity is hindering treatment : small effect size

ONE SIZE DOES'NT FIT
ALL



OUR VISION: Precision Medicine will transform diagnosis, treatment and prognosis of patients with mental disorders

Heterogeneous
Mental disorders

Deep
phenotyping

Basic research

Stratification
Subgroups

Precise
Therapeutic
strategies



*Bipolar disorders,
Depression,
Schizophrenia,
Autism Spectrum
Disorders
OCD
Addiction
...*

Heterogeneous
Overlapping
Progressive/stages

Clinical data

Psychiatric
Somatic
Cognitive

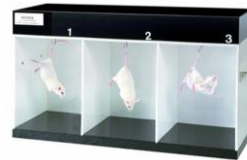
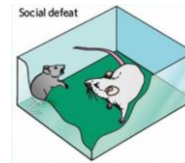
Biomarkers

- Omics (Genomics, Pharmacogenomics, Transcriptomics)
- Immunology
- Exposome
- EEG, Brain imaging

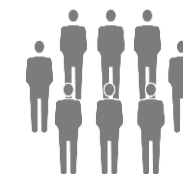
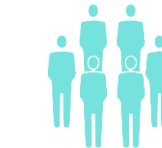
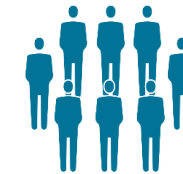
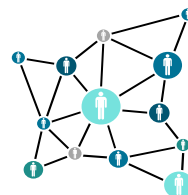
Digital phenotyping



Pre-clinical studies

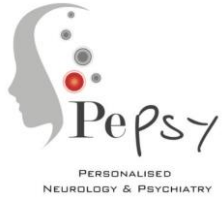


Artificial Intelligence



- Target-based treatment
 - Immuno-modulation
 - Neuro-modulation
- Psycho-social treatments (Ecological Momentary Interventions, EMI)
 - Psycho-education
 - Cognitive therapy
 - Cognitive remediation
- Life style
 - Physical health
 - Diet
 - Physical activity

A PROJECT BUILT ON TRACK RECORDS obtained within previous projects (AP-HP, PIA2)



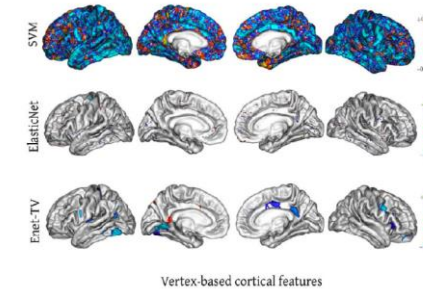
FHU ADAPT is built on track records of results obtained within

- **DHU Pe-PSY (AP-HP PI M Leboyer)**
- **Psy-COHort (PI M Leboyer)** and **LABEX Bio-Psy (PI JA Girault and M Leboyer)**, Programme Investissement d'Avenir

Preliminary results to develop Precision Medicine

- **Brain and peripheral biomarkers:** Genetic and Environment risk factors, Immunology, Metagenomic, Brain imaging ...
- **Apps, Platforms:** Digital phenotyping to enable continuous real life, objective, quantitative phenotype
- **Big data/machine learning:** Algorithms to diagnose and predict prognosis
- **Neuromodulation:** Invasive/non invasive brain stimulation

Machine Learning applied to MRI in Schizophrenia
De Pierrefeu et al. 2018



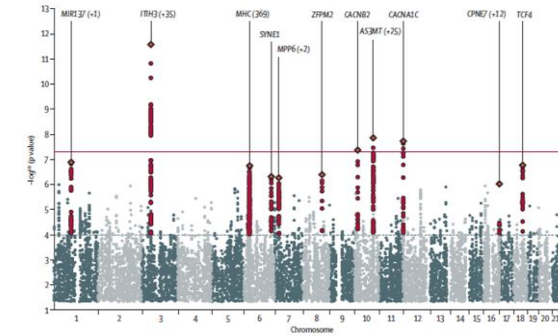
Auto-immune psychosis
Pollack et al, Lancet Psy, 2019

Autoimmune psychosis: an international consensus on an approach to the diagnosis and management of psychosis of suspected autoimmune origin

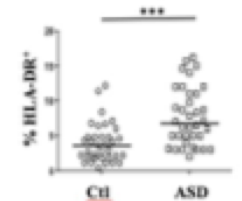
Environmental risk factors in psychosis
Pignon et al, Science Rep, 2017



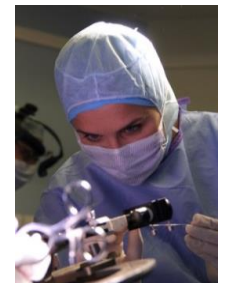
GWAS meta-analysis in Bipolar Disorder, Schizophrenia, Autism Spectrum disorder
PGC, Lancet 2013



NK Cells activation in Autism
Bennabi et al, 2019, Mol Autism



Deep Brain Stimulation in OCD
Mallet et al, NEJM, 2008 & 2019



FHU ADAPT, linking psychiatry/addictology departments (DMU IMPACT, AP-HP) with public and private research within the Grand-Paris Sud region

Neurospin Institute



Neuroimaging facility
3; 7; 11.7 Tesla
(pre-clinical 17 Tesla)

IRS Center for Data Science



Data Management,
Statistics, Machine Learning,
Design of e-health services

Population
size:
5 M

Number of
researchers:
245

NeuroPsi Institute



17 research teams dedicated to
preclinical research on CNS
functions in a new building of
12000 m², Opening: 2020
with 340 staff

PLATFORMS

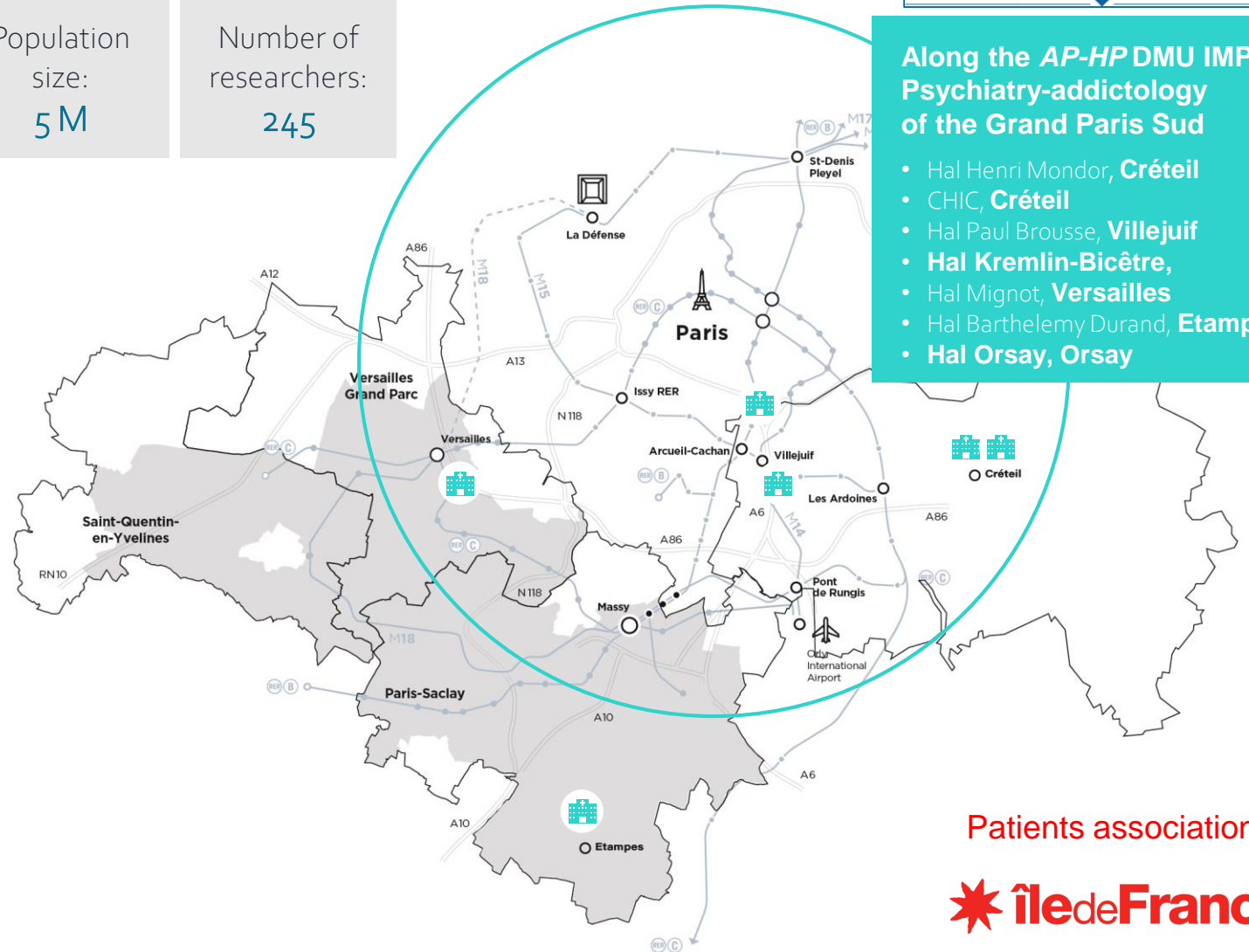
CEA, Neurospin
CEA, Genomic National Center
CEA, Metabohub
Inserm, Pollurisk (IMRB)

INSTITUTE

INRIA, Data Science
INRA, Metagenopolis
CEA, Neuro-Psi
Inserm, Institut du Fer à Moulin

Industry, SME and start-up

Biomarkers, digital phenotyping, Algorithms
Therapeutic strategies



Along the AP-HP DMU IMPACT Psychiatry-addictology of the Grand Paris Sud

- Hal Henri Mondor, **Créteil**
- CHIC, **Créteil**
- Hal Paul Brousse, **Villejuif**
- **Hal Kremlin-Bicêtre**,
- Hal Mignot, **Versailles**
- Hal Barthelemy Durand, **Etampes**
- **Hal Orsay**, Orsay

Patients associations

 **île de France**

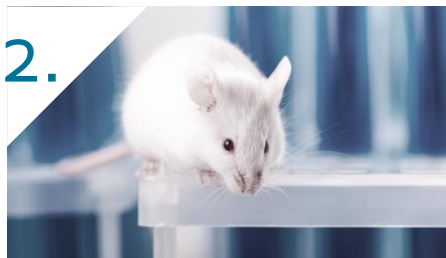
 **fondation
fondamentale**
RÉSEAU DE COOPÉRATION SCIENTIFIQUE EN SANTÉ MENTALE

FHU ADAPT, one step further towards Precision Medicine in Psychiatry



Building multimodal databases to identify homogenous clusters of patients with algorithms for patient stratification

TASK 1: Building multimodal databases (Clinical, genomics, metabolomics, immune, brain imaging, Ecological Momentary Assessment...) towards biomarkers/algorithms for patient stratification (JF MANGIN, CEA & B THIRION, INRIA)



Physiopathology underlying homogeneous subgroups of psychiatric/addiction disorders

TASK 2: Developing pre-clinical studies towards mechanisms discovery (J-A GIRAULT, Institut du Fer à Moulin, INSERM, & S GRANON, NEURO-PSI, CEA)



New diagnostic tools and therapeutic strategies towards precision medicine

TASK 3: Supporting clinical trials towards diagnostic tools and treatments discovery
P LECORVOISIER & J HOUENOU (**AP-HP** & UPEC)

- E-health (A Pelissolo)
- Neurocognitive remediation (P Roux)
- Immuno-modulation (R Tamouza)
- Non invasive brain stimulation (C Laidi)
- Invasive brain stimulation (L Mallet)
- Biotherapies (S Palfi)



Development of a new French biomedical mental health sector, Incl. digital, biotech, medtech, pharma, medical devices etc.

TASK 4: Creating tools to develop a new biomedical sector
(M LEBOYER AP-HP, UPEC, A REGNAULT, Université Paris Saclay)

- Plug in labs
- Tech meetings
- Patient registry
- Project support



Education, Implementation, attractiveness

TASK 5: Education and implementation (P VERNIER, CEA, A FAURE, Université Paris-Saclay)

- MD-PhD program
- Master classes
- Schools for residents
- University diploma in pharmacopsychiatry
- Neuromodulation academy

1. Building multimodal database to identify homogeneous clusters of patients

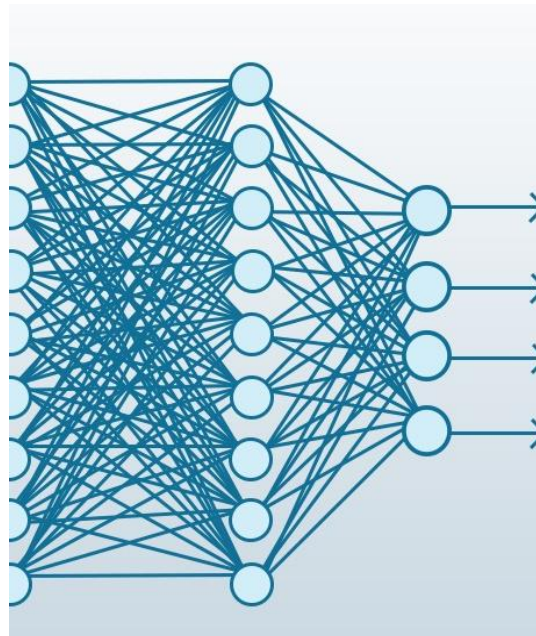
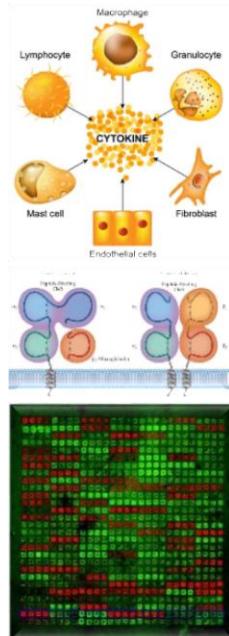
EXAMPLE of PROJECT: Stratification of psychotic patients based on blood-based inflammatory markers thanks to access to biological platforms which will then be validated by brain imaging (Pet Scan)

AP-HP, MONDOR hospital (Créteil), CEA (Saclay), INRIA (Saclay) , Inserm (Créteil), UPEC & Paris-Saclay University

1. Collecting biological markers of inflammation in existing cohorts

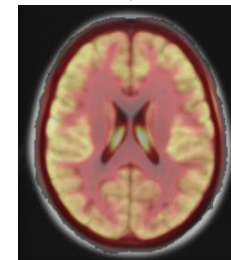
2. Stratifying inflammatory status using Machine Learning

3. Quantifying neuro-inflammation in high- and low-inflammatory subgroups by PET/MRI



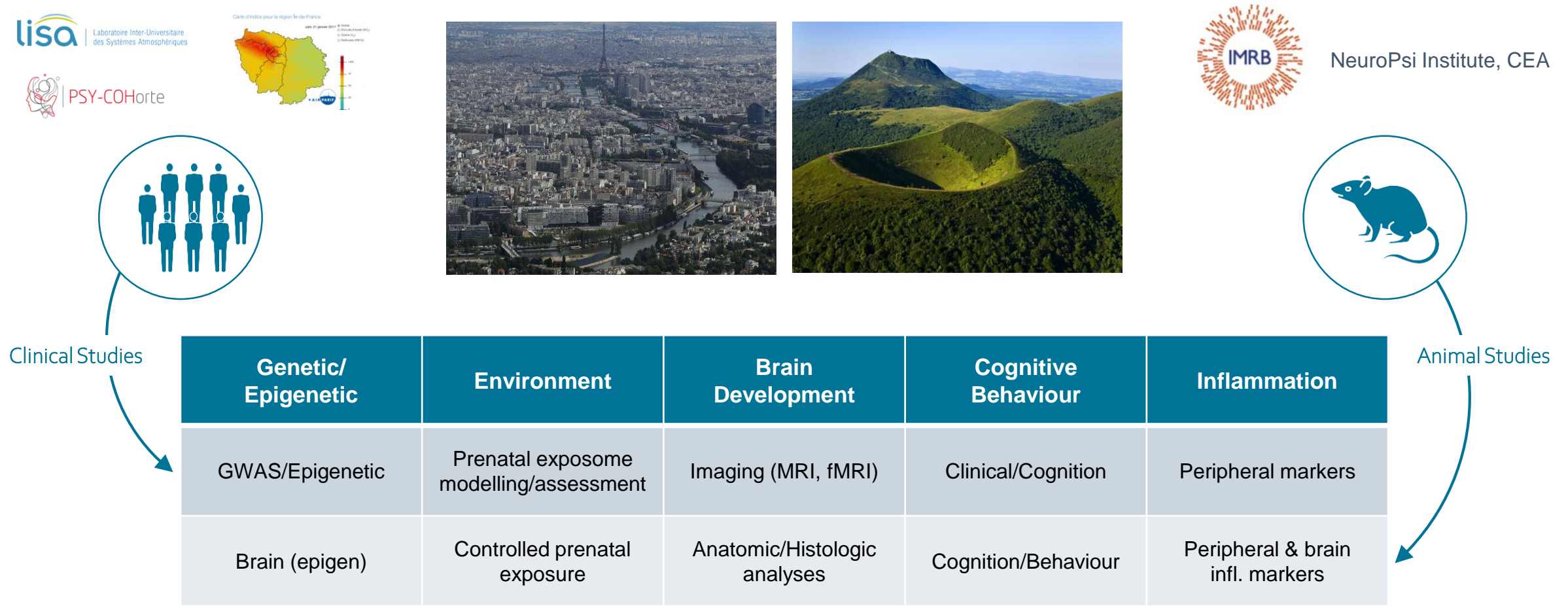
High inflammatory subgroup

Low inflammatory subgroup



2. Physiopathology underlying homogeneous subgroups of psychiatric/addiction disorders

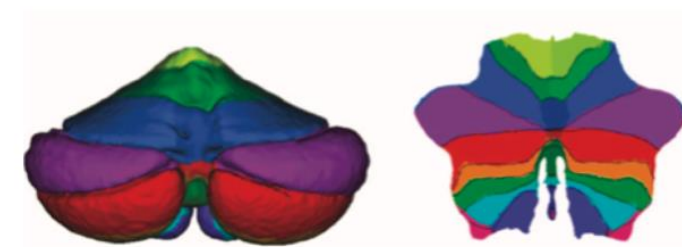
EXAMPLE of PROJECT: Impact of perinatal exposure to air pollutants on neurodevelopmental psychiatric disorders (Schizophrenia and Autism)
AP-HP, MONDOR hospital (Créteil), University Paris-Est-Créteil (Créteil), Inserm (Créteil), NeuroPsi Institute (Saclay)



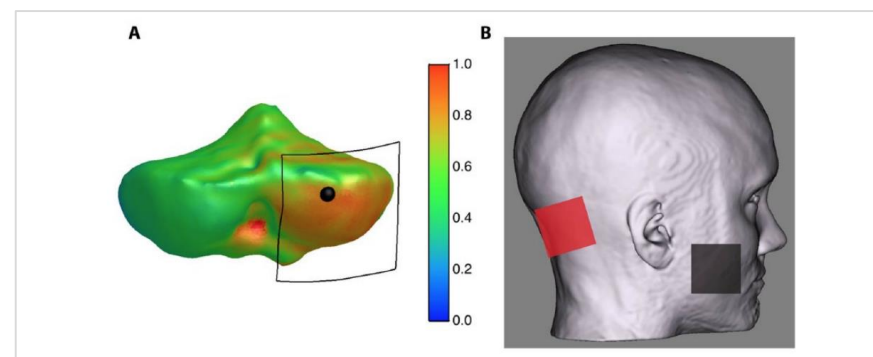
3. New diagnostic tools and therapeutic strategies towards Precision Medicine

EXAMPLE of PROJECT: Non invasive brain stimulation in patients (autism and schizophrenia) selected with brain imaging
AP-HP, MONDOR hospital, Inserm, Neurospin (CEA, Saclay), University Paris-Est-Créteil

- The cerebellum is altered in schizophrenia and autism
(Laidi et al. 2015, 2017, 2019, in prep. ; Moberget et al. 2017)
- **Step 1:** Brain imaging study
Identification of biomarkers of social withdrawal in a large database
(ex: Healthy Brain Network – Child Mind Institute, NYC, n = 10 000)
- **Step 2:** Identification of patients included in the FondaMental database with altered cerebellar anatomy
- **Step 3:** Clinical trial on selected patients with autism and schizophrenia using cerebellar transcranial direct current stimulation (tDCS) targeting social withdrawal in autism and schizophrenia



Diedrichsen et al. 2015



Ferruci et al. 2015

4. Development of a new French biomedical mental health sector, Incl. digital, biotech, medtech, pharma, medical devices etc.

EXAMPLE of tools to enhance private/public partnerships

Paris-Est-Créteil University & Paris-Saclay University and Région Ile de France



To detect opportunities for collaboration using a dedicated website describing each of the public/private FHU ADAPT laboratories' skills, expertise and technology

TECH MEETINGS #1
by Université Paris-Saclay #TMUPSaclay



To organise meetings with short presentations, one-to-one exchanges between SME, clinicians and researchers to boost collaboration

FHU ADAPT institutional partner: with the support of the Regional Council of Paris Ile-de-France



The Regional Council of Paris Ile-de-France is the local authority of the Paris Region, where all the partners of the FHU ADAPT are established. The regional authority identified:

- **Psychiatry** as a regional public health priority and as a major field for the social cohesion of the region and its economical development
- **Saclay** as one of its key economic and research areas

A strategic partnership between FHU ADAPT, FondaMental foundation and the regional council is being built in order to achieve its social and economic targets

The strategic partnership : a 3-year long program with identified operational actions

Psychiatry is an economic opportunity:
building public-private partnerships

Economic forum on mental health in early 2020

Start-up challenge on mental health in 2020,
with start-up cluster Medicen

Psychiatry is an economic opportunity:
building public-private partnerships

Regional communication plan on mental health

Financing research in psychiatry

5. Training the new generation of physicians and researchers in Psychiatry

MAIN OBJECTIVES:

- To disseminate innovation
- To increase national and international attractiveness

Paris-Est-Créteil University (UPEC) & Graduate School Life Science and Health of Paris-Saclay University

EXAMPLES OF ACTIONS:

- Action 1: To increase training in research in Psychiatry for residents and MD-PhD
- Action 2: To develop Interdisciplinary symposium in psychiatry
- Action 3: To create a Neuromodulation Institute (*Medtronic and Boston Scientific*)
 - To teach the theory, techniques, and risks attached with neuromodulation
- Action 4: French School of Innovation in psychiatry
 - Regulatory and ethical aspects, Project management methods and funding research



Key success factors of the FHU ADAPT to be followed

INDICATORS OF SUCCESS

1. To GALVANISE research in addictology and psychiatry

International

- ENIGMA, PGC, International cohorts....
- IMI
- Era-net-neuron, H2020

National

- PHRC
- ANR

Private-Public Partnership

2. To TRAIN a new generation of psychiatrists

Number of MD-PhD

3. To IMPLEMENT results of research in everyday practice

Meetings

MISSIONS

Project manager

- Identification of calls
- Project Support

- Plug in labs
- Tech meetings
- Patient registry

- Mentoring
- MD-PhD school


- Education

Chef de Clinique (assistant professor)

- Project support (patients inclusion, Information on new projects, papers writing)

- Residents meetings

- Share results of research



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CEA, Saclay*

Jean-François Mangin

Information Processing Unit, Neurospin, CEA, Saclay