



Center for
Precision Psychiatry
MGH Department of Psychiatry



FRENCH PROGRAM IN PRECISION PSYCHIATRY (PEPR PROPSY)

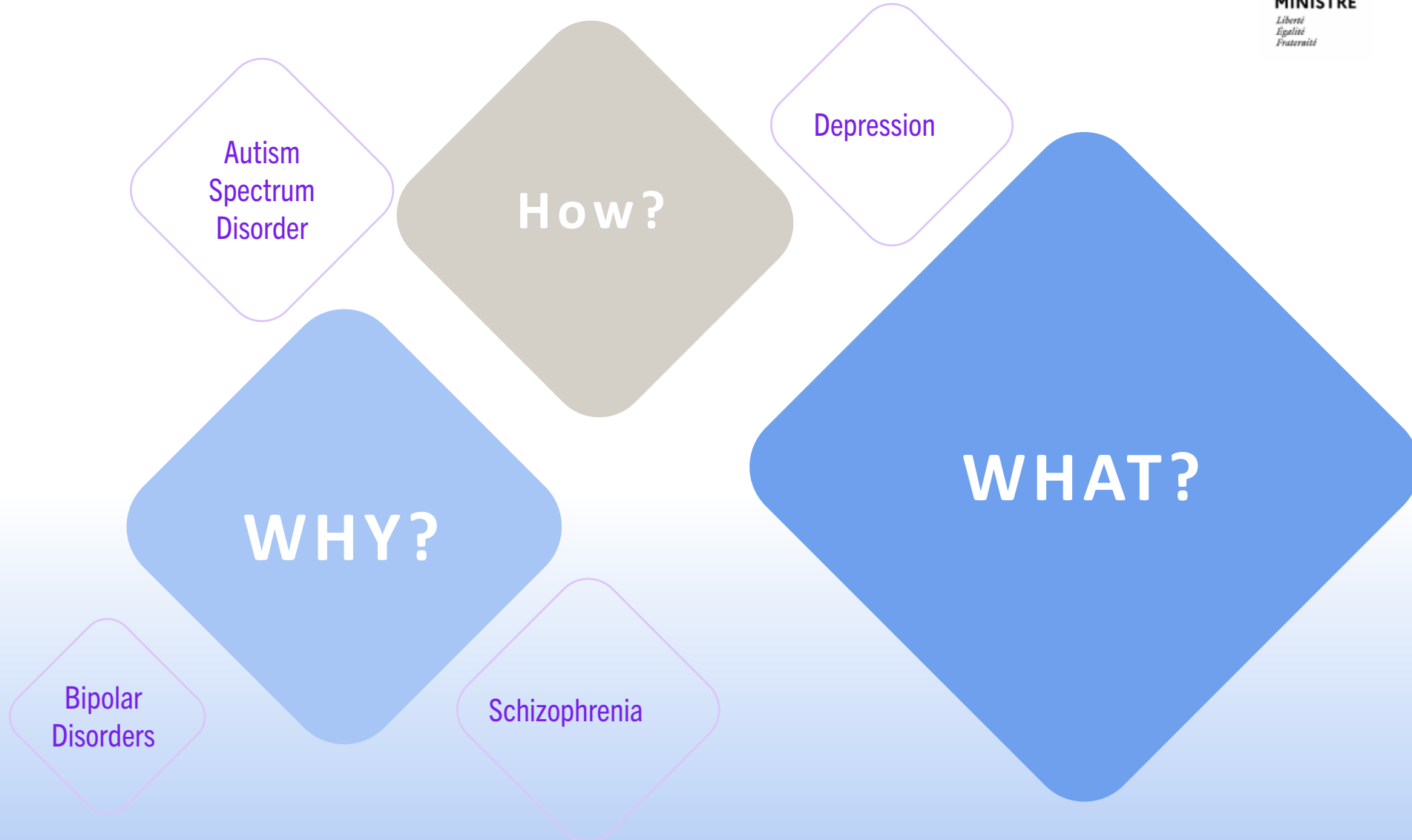
Marion Leboyer (M.D., Ph.D)

Paris-Est University, France
marion.leboyer@inserm.fr

- Department of Psychiatry, Mondor Hospital (AP-HP)
- Translational Neuro-Psychiatry laboratory (Inserm)
- CEO, Fondation FondaMental
- Scientific Director, Program Project in Precision Psychiatry (PEPR PROPSY)



FRENCH PROGRAM IN PRECISION PSYCHIATRY (PEPR PROPSY)



WHY DO WE NEED PRECISION PSYCHIATRY?

One of the greatest challenge of the 21st century

A MAJOR PUBLIC HEALTH ISSUE

- **Top 10 leading** causes of **burden** worldwide
- Affect an estimated **800 million** people worldwide, **10.7%** of the Planet's population (OECD, 2022)
- An enormous economic burden: **4%** of a nation's GDP
- First cause **of handicap** (WHO, 2020)

BUT STILL A HIGH UNMET NEED

- Delayed and unprecise diagnosis
- Partial treatment and often with side effects
- Too few innovations

WE NEED
TO DO BETTER...!

WHY DO WE NEED PRECISION PSYCHIATRY?

Very Few Significant Treatment Breakthroughs In the last 50 years

3 REASONS TO EXPLAIN FAILURES OF CLINICAL TRIALS

- **CURRENT CATEGORICAL DIAGNOSIS**
 - good inter-rater reliability but no biological validity
 - heterogeneous and overlapping
- **ENDPOINTS USED IN CLINICAL TRIALS**
 - Not objectively measurable
 - Not specific to the treatment tested
- **TREATMENTS TESTED**
 - Not mechanisms-based
 - Most psychotropic drugs have been discovered by serendipity

3 RULES OF PRECISION PSYCHIATRY

- **PRECISE STRATIFICATION BIOMARKERS**
to select homogeneous subgroups of patients
- **OBJECTIVE BIOMARKERS OF EFFICACY**
to assess efficacy in clinical trials
- **MECHANISMS-BASED TREATMENTS**
to target a specific etiological mechanism



WE NEED THE RIGHT TREATMENT FOR
THE RIGHT PATIENT, AT THE RIGHT TIME!

WHY DO WE NEED PRECISION PSYCHIATRY?

To improve measurement and stratification of heterogeneous categorical entities towards mechanisms-based treatments



MOVING away from

“ONE SIZE FIT ALL”



TO GO to

HAUTE COUTURE “



HOW CAN WE MOVE TO PRECISION PSYCHIATRY?

What is needed to bring change to practice,

HOW?



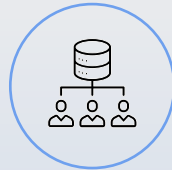
TO ORGANIZE DEEP PHENOTYPING

Ex: French Networks of Expert Centers



TO YIELD and GATHER MULTI-MODAL DATA into Data Warehouse

Ex : Suicidal behavior



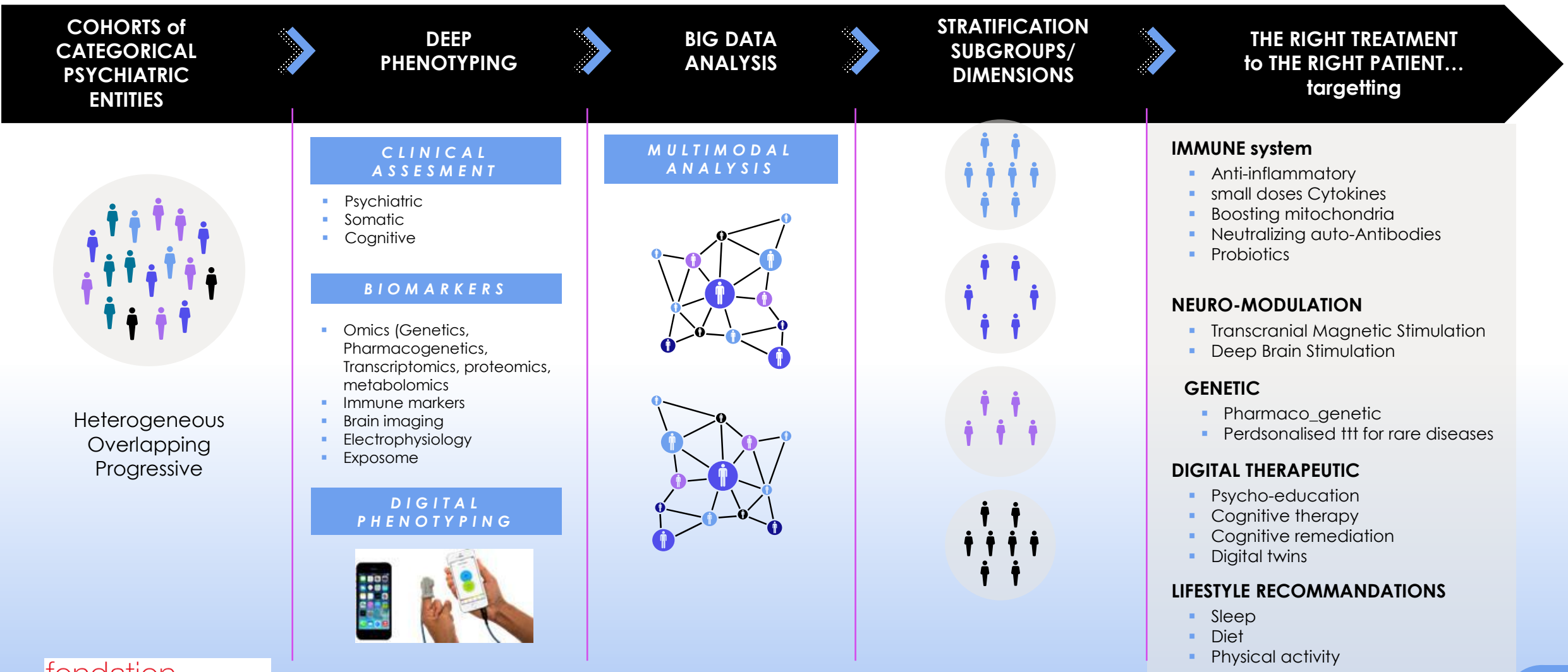
TO SHARE EXISTING DATA

Ex: Cohort Club



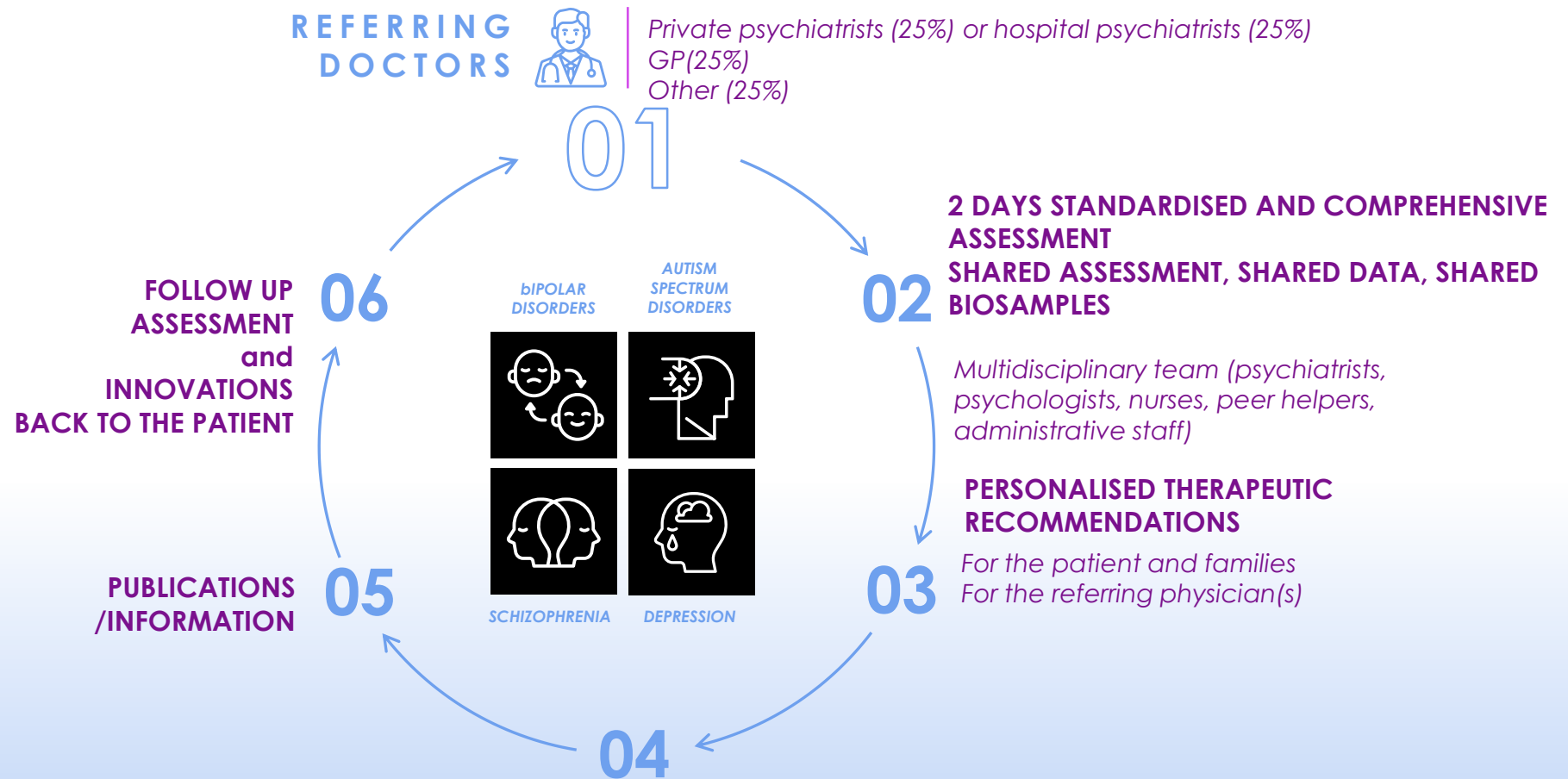
HOW TO ORGANIZE PRECISION PSYCHIATRY?

Large cohorts of deeply-phenotyped patients



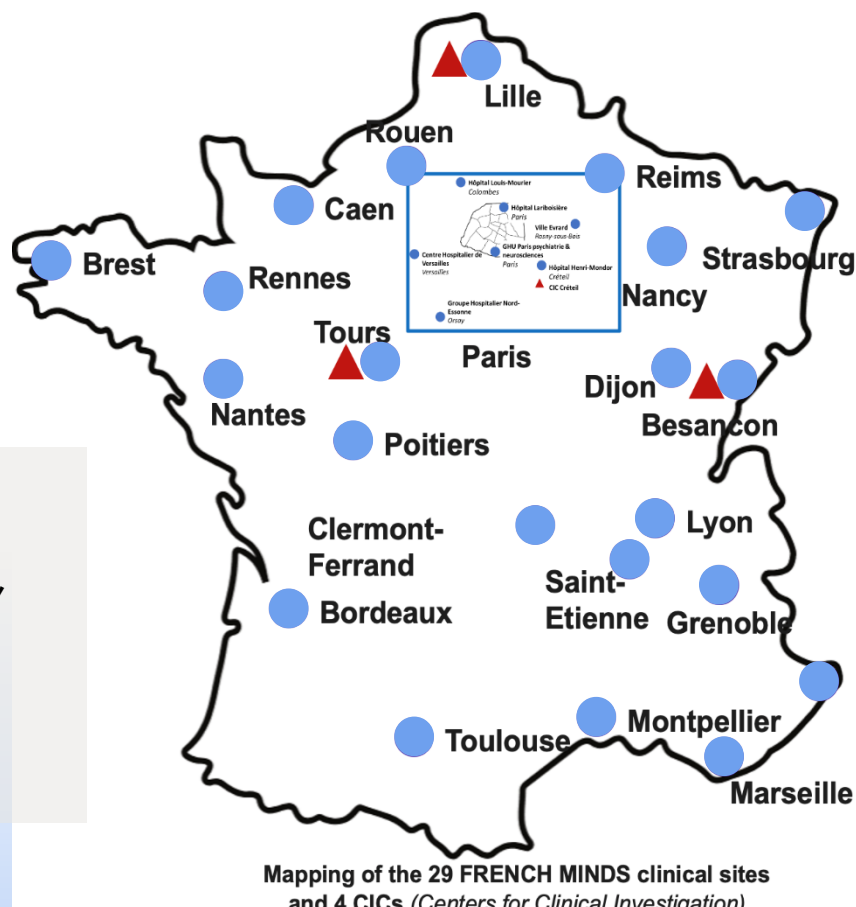
IN FRANCE, SINCE 2010, 4 NETWORKS OF 55 EXPERT CENTERS FOR PSYCHIATRIC DISORDERS COORDINATED BY FOUNDATION FONDAMENTAL

**FRENCH EXPERT
CENTERS:
PLATFORMS
FOR DIAGNOSIS
AND RESEARCH**



NETWORKS OF EXPERT CENTERS IN FRANCE

sharing data and biobanks to create multimodal databases open for collaboration



National networks of expert centers for mental disorders, SHARING e-CRF, data, databases and biobanks



4 networks for bipolar disorder, schizophrenia, resistant depression, autism



55 Expert Centers



4 shared data base « FACE »
(FondaMental Advanced Center of Expertise)



1 shared biobank
(DNA, RNA, PBMC, serum, plasma)



9000 patients included in the FACE Data base



300 publications



1 CENTRALIZED DATA WAREHOUSE OPEN FOR COLLABORATIONS

www.fondation-fondamental.org

MEASURING THE IMPACT AFTER AN ASSESSMENT IN AN EXPERT CENTER : IMPROVEMENT OF PROGNOSIS

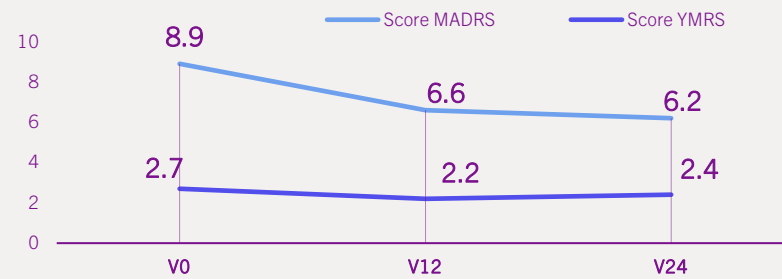
Example of bipolar disorder

N=987 individuals with bipolar disorder followed for 2 years

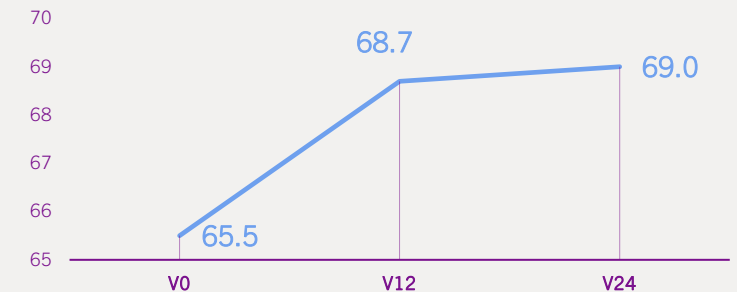
EXPERT CENTRES contribute to:

- **Clinical improvement** of symptoms, general functioning, and adherence to treatment
- **Screening** for psychiatric and somatic comorbidities

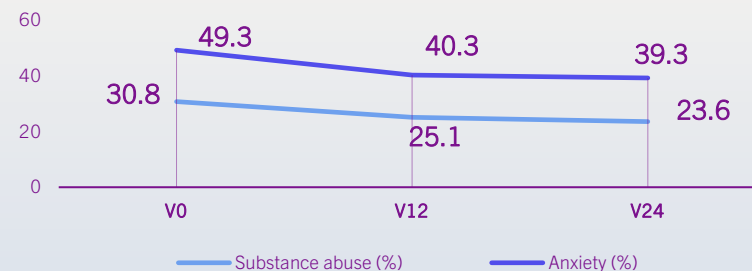
Depressive and manic symptoms



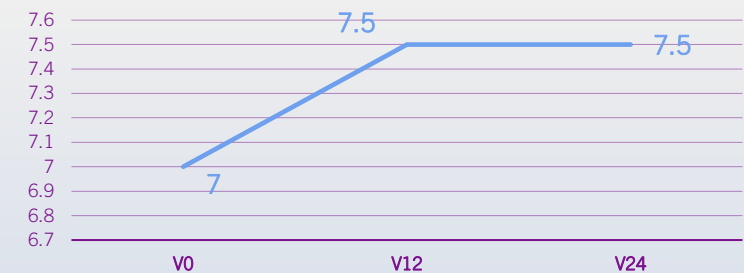
General functioning



Psychiatric and somatic comorbidities



Adherence to treatment (MARS)



Belzeaux et al, *J Aff Disorders*, 2013

Godin et al, *J Clinical Psy*, 2014

Henry et al, *Bipolar Disord* 2017

Laidi et al, *J Aff Disorders*, 2022

MEASURING THE IMPACT AFTER AN ASSESSMENT IN AN EXPERT CENTER : COST REDUCTION

Example of bipolar disorder



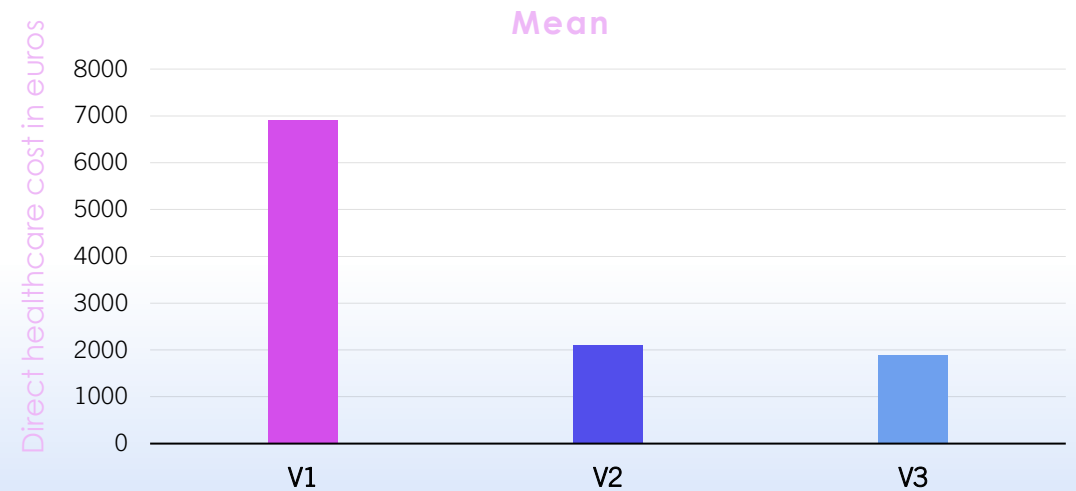
NUMBER OF DAYS

RE-HOSPITALIZATIONS



DIRECT COST

(HOSPITALIZATIONS, CONSULTATIONS, MEDICATIONS)



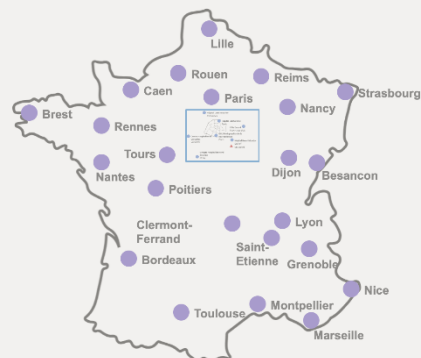
REDUCTION of **50%*** | the number of days re-hospitalization



REDUCTION of **50%*** | the direct cost of bipolar disorder

EXTENSIVE DATA COLLECTION TOWARDS

Creating a multimodal, interoperable, open data warehouse: “FRENCH MINDS”



e-CRF



Digital data



**Genomics
Metagenomic**



**Immunology
Metabolomic
Proteomic**



**Brain imaging
Electrophysiology**



Pseudonymisation, quality control, harmonisation, data ingestion, multi modal integration, inter operability



Data Management



**Data analysis
platform**



**Data Replication (“Cohort-
club”)**



Pre-existing French cohorts
N=7000



Interoperability

French Minds
Multimodal data sets



Interoperability

International databases
Catalogue of meta data

**Catalogue
of meta data**

Data access

Personal & Secure Access
Secure insulated bubble
Choice of computing power: CPU, RAM, GPU

Analysis

Environment of choice

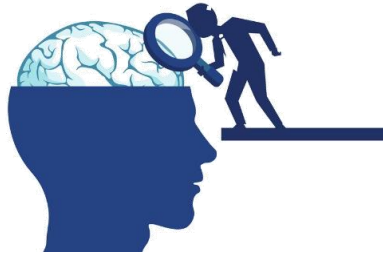


DZHK
DEUTSCHES ZENTRUM FÜR
HERZ-KREISLAUF-FORSCHUNG E.V.



HOW TO SHARE DATA: THE COHORT CLUB

Towards precision psychiatry



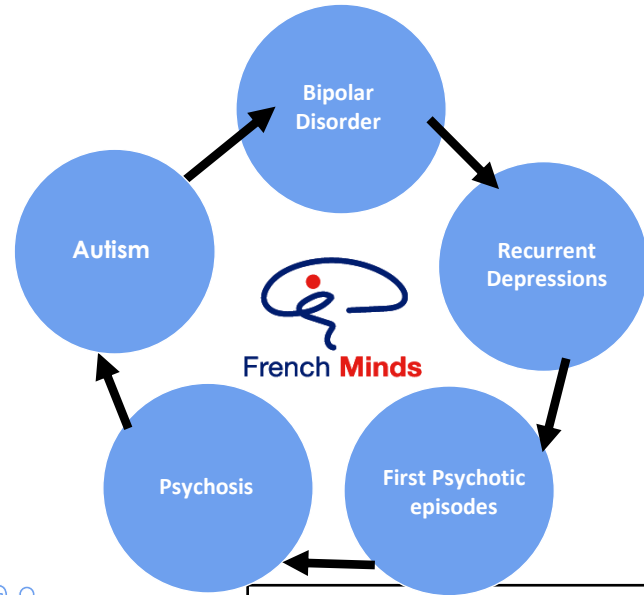
Objectives – To create an online platform offering a map of existing European as well as Australian or North & South American cohorts for psychiatric conditions fostering collaborations on existing datasets.

»» 22
P.I.'s COHORTS
enrolled in this initiative

NAME OF ACCEPTED PARTICIPANT	COUNTRY	NAME OF COHORT
Europe		
Marion LEBOYER	FR	FACE BP/SZ/DR/ Autism & French Mind
Thomas SCHULZE	DE	PsyCourse
Andreas MEYER-LINDERBERG	DE	
Ole KÖHLER-FORSBERG	DK	Danish Cohort
Ole ANDREASEN	NO	Nodic Cohort
Per QVIST	DK	Cohorts of normal subjects
Brenda PENNINX	NL	NESDA Cohort
Peter FALKAI	DE	Centers of excellence
Nikos KOUTSOULERIS	DE	CDP cohort
Florian RAABE	DE	PRONIA cohort
Livia DE PICKER	BE	Utrecht
Paolo BRAMBILLA	IT	Italy
Celso ARANGO	SP	CIBERSAM first episode cohort
United Kingdom		
Neil HARRISON	Cardiff	
Carmine PARIANTE	London	
Rahcel UPTHERGROVE	Oxford	
Australia		
Michael BERK	AU	
Canada		
Ana ANDREAZZA	CA	
Brazil		
FLAVIO KAPCZINSKI	BR	USP cohort in Bipolar Disorder
USA		
Hilary BLUMBERG	US	Yale cohort
Mark FRYE	US	Mayo Clinic
LEANNE WILLIAMS	US	Stanford

FRENCH PROGRAM IN PRECISION PSYCHIATRY

The creation of the French "French Mind" cohort (10,000 patients and controls)



9000 patients included
in the FACE Data base

FRENCH MINDS COHORT



2500 Patients
500 controls



CLINICAL
PHENOTYPES

Behavioural
Somatic
Cognitive

DIGITAL

Conversational Agent
Self rating questionnaires

Ecological Momentary assessment
Sleep, physical activity
Social activities



DEEP
PHENOTYPING

OMICS

Genomics
Metabolomics
Proteomics
Epigenetics
Immunological

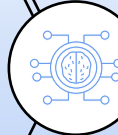


EXPOSOME

Pollution
Stress
Infections...

BRAIN
IMAGING

MRI 3T, 7T
fMRI
Diffusion MRI
Spectroscopy
Electrophysiology



WP2: EXPLORING
MECHANISMS



WP3: VALIDATING BIOMARKERS
CLINICAL TRIALS WITH MECHANISMS
BASED TREATMENTS
IN SPECIFIC SUBGROUPS



WP4: PUBLIC-PRIVATE
PARTNERSHIPS



WP5: Inform & educate
Patients and Relatives
Healthcare professionals
Researchers, decision-makers...

OBJECTIVES OF THE FRENCH MINDS COHORT

Identify trans or a-nosographic dimensions / homogeneous clinical forms

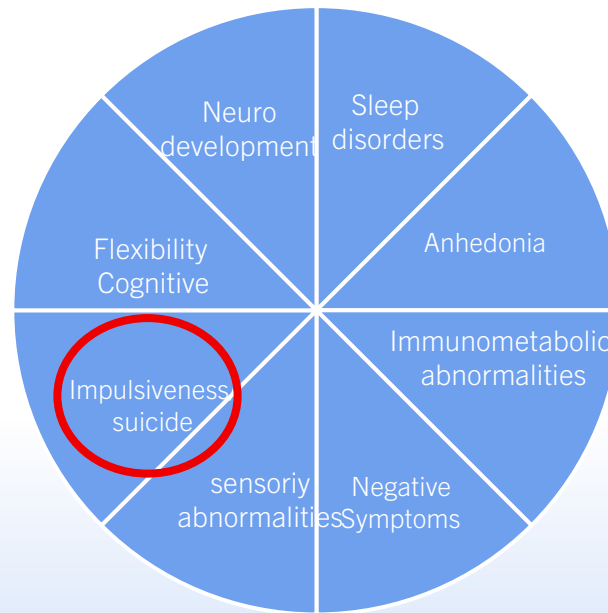
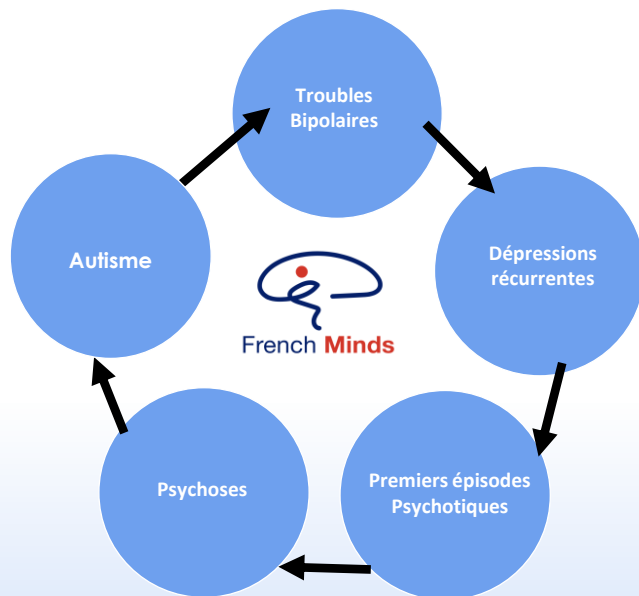
DIAGNOSTIC CATEGORIES



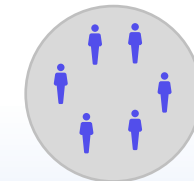
QUANTITATIVE TRANSNOSOGRAPHIC DIMENSIONS

&

HOMOGENEOUS SUBGROUPS



HOMOGENEOUS SUBGROUPS:
CLINICAL-BIOLOGICAL SIGNATURE
EX : AUTO IMMUNE PSYCHOSIS



To integrate clinical, cognitive, digital and biological data to search for uni/bi/multimodal signatures of transnosographic dimensions which may be the target of specific therapeutic strategies



ON THE ROAD TO PRECISION MEDICINE IN PSYCHIATRY...

Examples from French projects in precision psychiatry



WHAT?



IMMUNO-METABOLISM: can we stratify patients with immuno-metabolic activated pathways towards precise treatments?



GENOMICS: can we stratify patients with genomic association or mutations towards precise treatments?



BRAIN IMAGING : can we stratify patients with brain imaging abnormalities towards precise treatment strategies?



CLINICAL TRIALS OF ANTI-INFLAMMATORY DRUGS IN DEPRESSION HAVE FAILED

Why?



INCLUSION CRITERIA



Problem

Studies have included **heterogenous depressed populations** despite the fact that inflammation is only found in subgroups of depressed patients

We need to stratify and enrich



DRUGS



Problem

Most anti-inflammatory drugs tested have multiple target effects, and there have been few studies examining a specific immune dysfunction

We need to identify etiological mechanisms and to target them



OUTCOME



Problem

Primary outcomes are behavioral **measures** not specifically associated to inflammation

We need to use objective biomarkers as outcomes

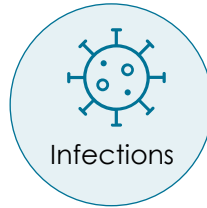


Jha, Leboyer, Pariante, Miller, **JAMA PSY**, April 2025, *Should inflammation be a specifier for depression in the DSM-6*

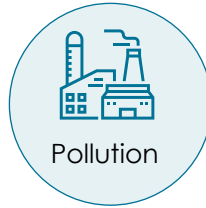


IMMUNO-PSYCHIATRY: WHAT HAVE WE LEARNT?

ENVIRONMENTAL Risk Factors



Infections



Pollution



Stress/
Trauma



Lifestyle

INTERACTIONS WITH THE IMMUNO-GENETIC BACKGROUND

Innate Immunity genes
TLR, NOD...

Maintaining inflammation
Mitochondria genes

Adaptive Immunity
HLA

CHRONIC INFLAMMATION and ABNORMAL METABOLITES in 40% of PATIENTS with MENTAL ILLNESS



- Inflammation
- Neurotransmitter & Connectivity abnormalities



- Inflammation
- Immune cells



- cellular energy



- Digestive inflammation
- Changes in gut flora

Auto-immune
Psychosis

Retro-virus
Human Endogenous

Abnormal Metabolism/
mitochondria

Accelerated Aging

Intestinal
dysbiosis

Immuno Modulation trial
TIM Depist In progress

SOMATIC AND PSYCHIATRIC COMORBIDITIES
Schizophrenia, bipolar disorder, depression, autism...

Polymicrobiotherapy trial
« Swing » *In progress*

Therapeutic trial with
small doses of
Interleukin 2
Leboyer et al,
**Brain, Behav and
Immunity** 2024



IMMUNO-PSYCHIATRY ON THE ROAD TO PRECISION PSYCHIATRY:

The example of « Auto-Immune Psychosis »: anti NMDA-R, anti alpha7 nicotinic R...

CLINICAL PRESENTATION

Rapid onset of of Psychiatric symptoms:
Catatonia

Neurological soft signs
(e.g. Headache
paresthesia...)

**Intolerance
/resistance to**
antipsychotics

BLOOD BIOMARKERS

**Circulating
Autoantibodies**
against
neurotransmitter
receptors

**Other immune
markers:**
CD-14/various
autoantibodies

AUTO-IMMUNE PSYCHOSIS

**Family/personal
history of**
autoimmune
disorders

Past history
of infection

MEDICAL HISTORY

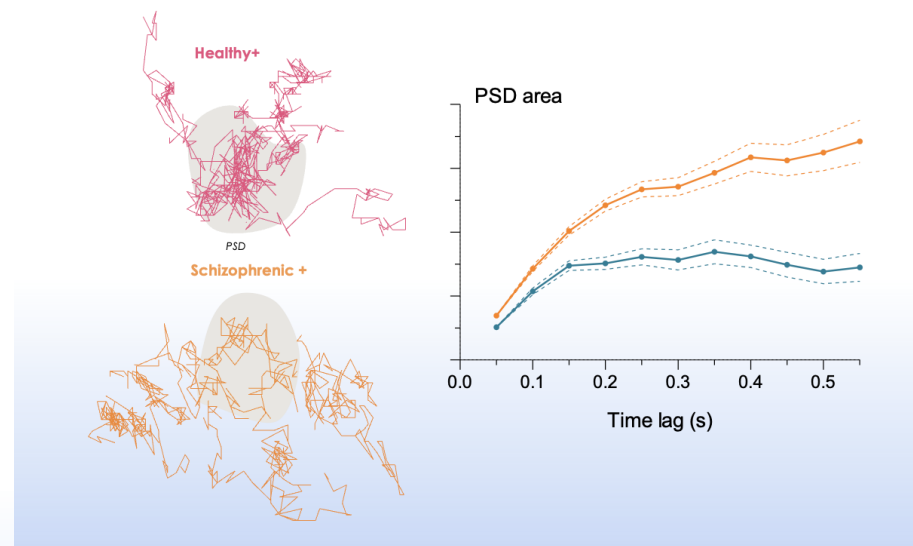
Ellul...Leboyer, **Frontiers in Psychiatry**, 2017
Jezequel et al, **Biological Psychiatry**, 2017 Nov 15;82(10):766-772.
Polack et al, **Lancet Psychiatry**, 2020 Jan;7(1):93-108.
Darrau...Leboyer, Maskos, **Translational Psy**, Fev 2024

fondation
fondamental

French Program in Precision psychiatry : auto-AB, exploration
of mechanisms of action, therapeutic trials, training

UNDERSTANDING MECHANISMS

USING SINGLE NANO PARTICLE TRACKING IN SYNAPTIC AREAS



Jezequel...Leboyer, Groc **Nature Comm** Nov 27, 8 (1) : 1791

TIMDEPIST PROTOCOL (2023-26)



2 perfusions
at 15 days
RITUXIMAB

**ONLY IN PATIENTS WITH BLOOD AUTO ANTIBODIES
AGAINST Brain Receptor (NMDA..)**



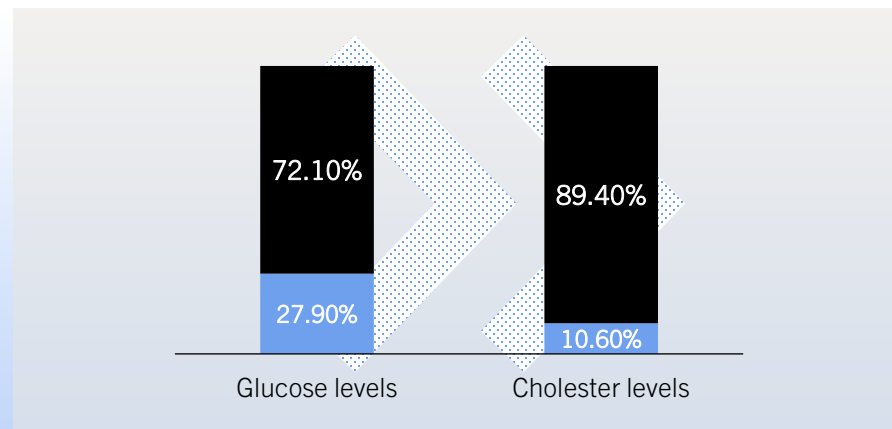
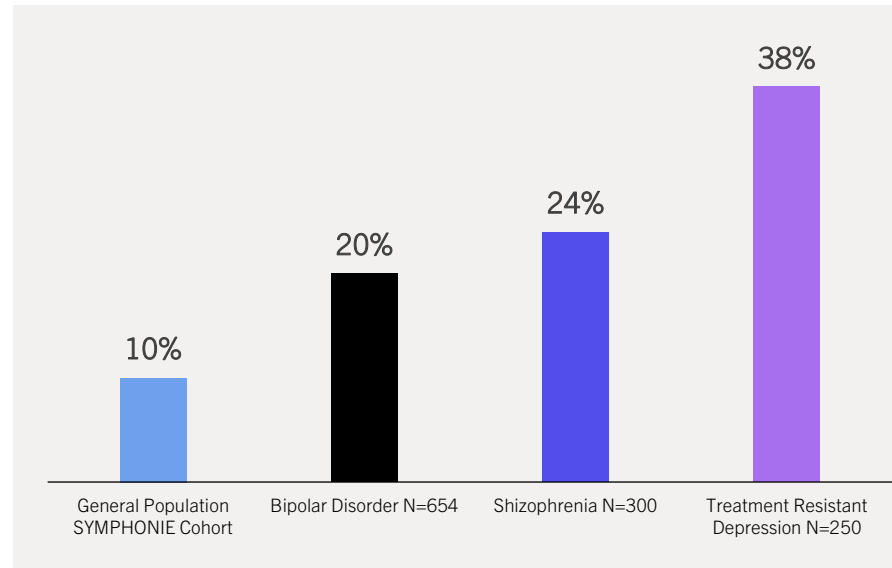
IMMUNO-METABOLIC PSYCHIATRY ON THE ROAD TO PRECISION PSYCHIATRY

The example of metabolic syndrome in the FACE data bases (FondaMental Advanced Centers of Expertise)



Metabolic syndrome definition

- Waist circumference ≥ 94 cm for men and ≥ 80 cm for women
- Hypertriglyceridemia
- Low HDL cholesterol level ≤ 1.03 mmol/L for men and ≤ 1.29 mmol/L for women
- High Blood pressure $\geq 130/85$ mm Hg or taking antihypertensive medication
- High Blood glucose ≥ 5.6 mmol/L or use of hypoglycaemic drugs



Review

Can bipolar disorder be viewed as a multi-system inflammatory disease?

Marion Leboyer^{a,b,*}, Isabella Soreca^b, Jan Scott^{a,c}, Mark Frye^d, Chantal Henry^{a,b}, Ryad Tamouza^c, David J. Kupfer^b



Metabolic syndrome, abdominal obesity and hyperuricemia in schizophrenia: Results from the FACE-SZ cohort

O. Godin^{a,b,c}, M. Leboyer^{a,d}, A. Gaman^a, B. Aouizerate^{a,n,o,p}, F. Berna^{a,d,e}, L. Brunet^{a,d,f}, D. Capdevielle^{a,h}, I. Chereau^{a,i}, J.M. Dorey^{a,j}, C. Dubertret^{a,k}, J. Dubreucq^{a,l}, C. Faget^{a,m}, F. Gabayet^{a,j}, Y. Le Strat^{a,h}, P.M. Llorca^{a,j}, D. Misdrach^{a,k,l}, R. Rey^{a,j}, R. Richieri^{a,m}, C. Passerieux^{a,n}, A. Schandrin^{a,h}, F. Schürhoff^{a,d}, M. Urbach^{a,n}, P. Vidalhet^e, N. Girerd^o, G. Fond^{a,d,s}, the FACE-SZ group

* Fondation FondaMental, Océfil, France



Review article

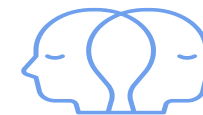
Prevalence of type 2 diabetes mellitus, impaired fasting glucose, general obesity, and abdominal obesity in patients with bipolar disorder: A systematic review and meta-analysis

Yuhan Karida Liu^{a,b}, Susan Ling^{a,b}, Leanna M.W. Lui^a, Felicia Ceban^a, Maj Vinberg^{c,d}, Lars Vedel Kessing^{e,f}, Roger C. Ho^{g,h}, Taeho Greg Rhee^{i,j}, Hartej Gill^k, Bing Cao^l, Rodrigo B. Mansur^{a,c}, Yena Lee^h, Joshua Rosenblatt^{m,n}, Kayla M. Teopiz^a, Roger S. McIntyre^{a,b,c}



IMMUNO-PSYCHIATRY ON THE ROAD TO PRECISION PSYCHIATRY

The example of metabolic syndrome and abnormal mitochondria in Bipolar Disorder

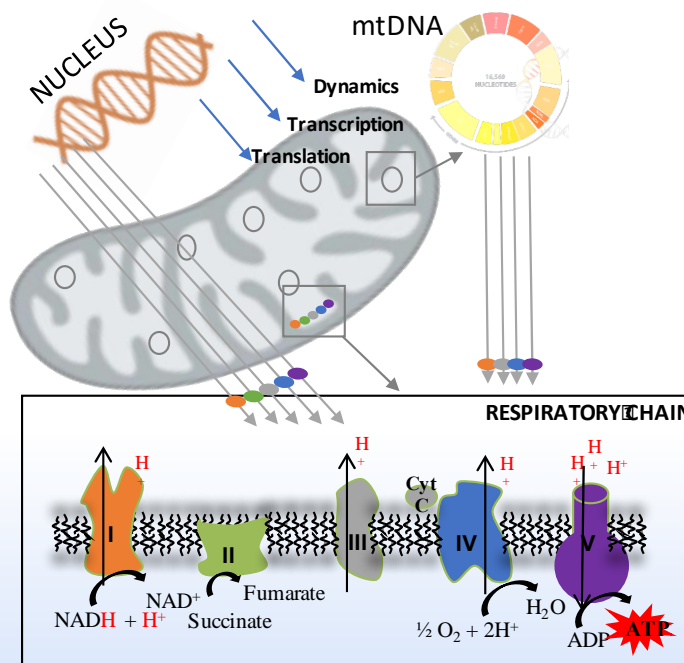


FUNCTIONAL MITOCHONDRIA

- Cells of brain require energy (20% of our total energy)
- High mitochondrial density support energy demands, establish membrane excitability and execute complex processes of neurotransmission and plasticity

DYSFUNCTIONAL MITOCHONDRIA

- Alter neurotransmitter release and firing rates
- Patients with classical mitochondrial disease present neurological manifestations including seizures, stroke-like episodes, developmental delays, neurological decline,
- And often psychiatric symptoms



Mitochondrial dysfunction in Bipolar Disorder is supported by

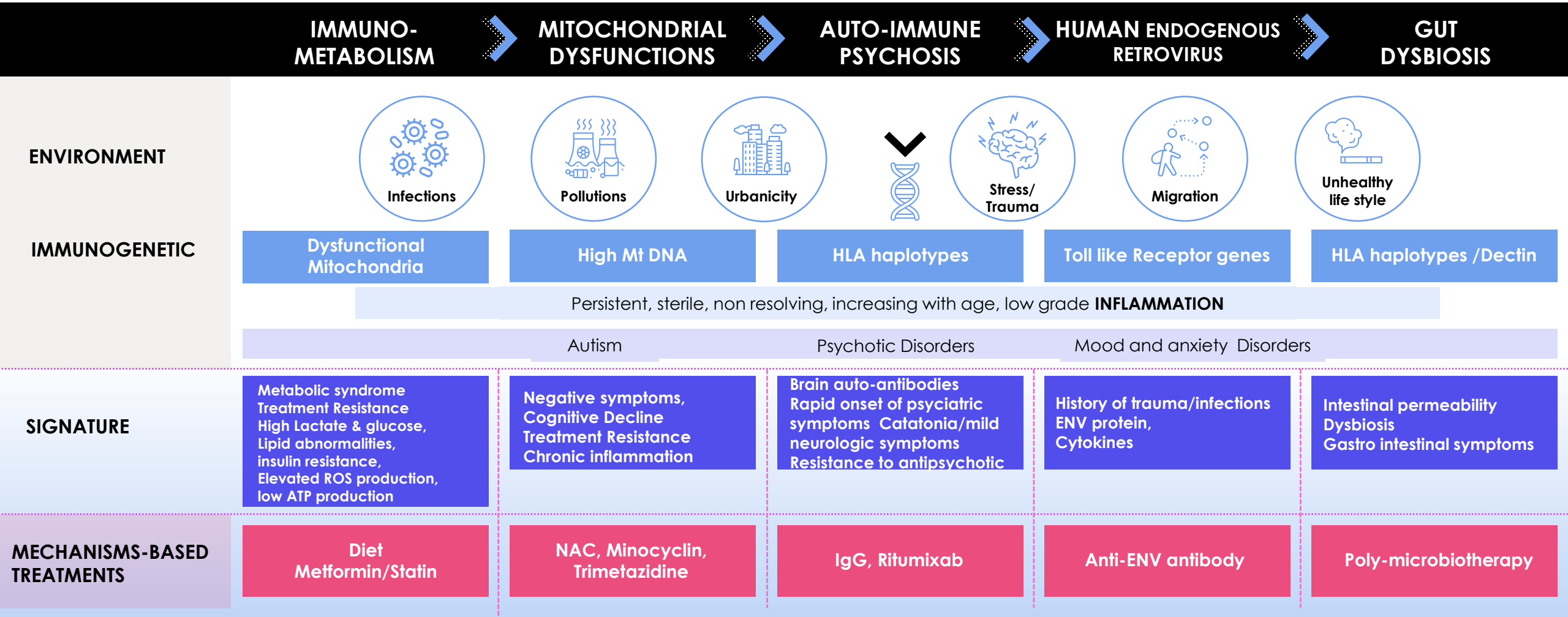
- Decreased mtDNA content (-36%)
- Higher frequency of mitochondrial DNA mutations
- Decreased mitochondrial complex I activity
- High levels of mitochondrial metabolite lactate levels
- Increased Reactive Oxygen species (ROS) production and increased oxidative stress in Dopamine prefrontal cortical regions

French Program in Precision psychiatry (PEPR PROPSY)

Identifying which patients are affected by mitochondrial dysfunction to select patients for future clinical trials targeting mitochondria.



HOW TO STRATIFY PATIENTS WITH IMMUNO-METABOLIC ABNORMALITIES TOWARDS MECHANISMS BASED TREATMENTS?





USING GENOMICS TO DEVELOP DIAGNOSTIC TOOLS AND TREATMENTS IN PSYCHIATRY HAVE FAILED:

Genes don't read DSM...



DIAGNOSTIC

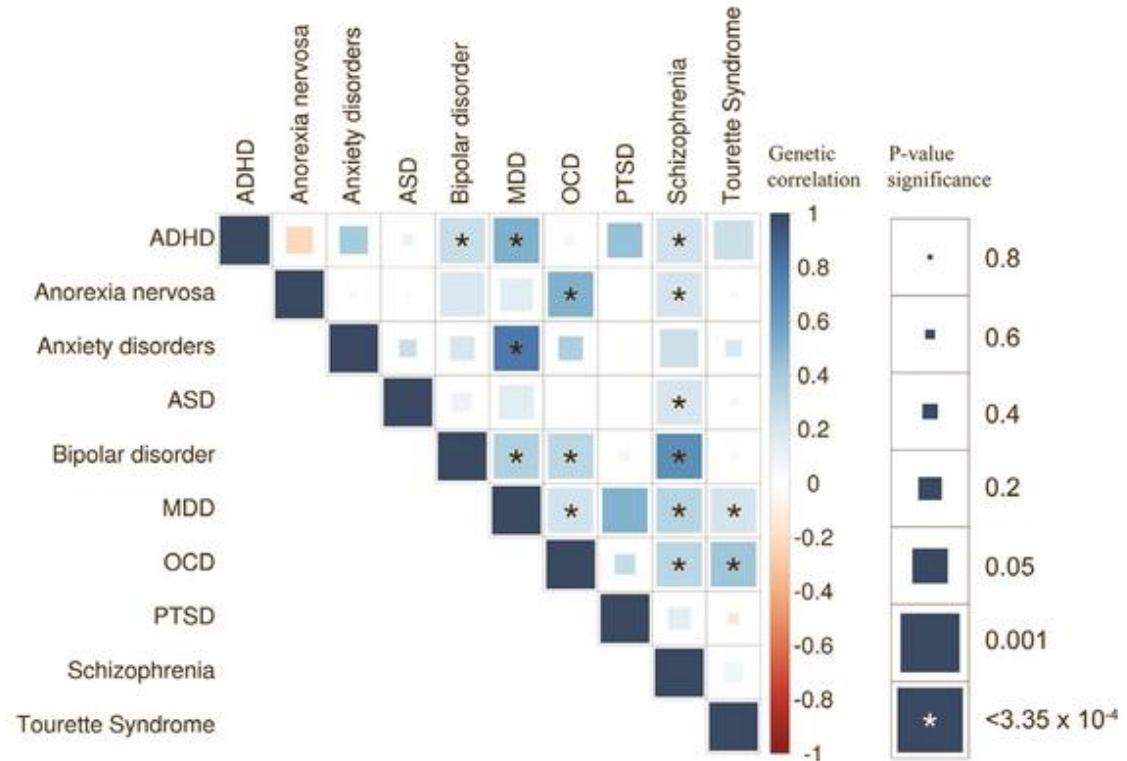


Problem

Genes don't read DSM...

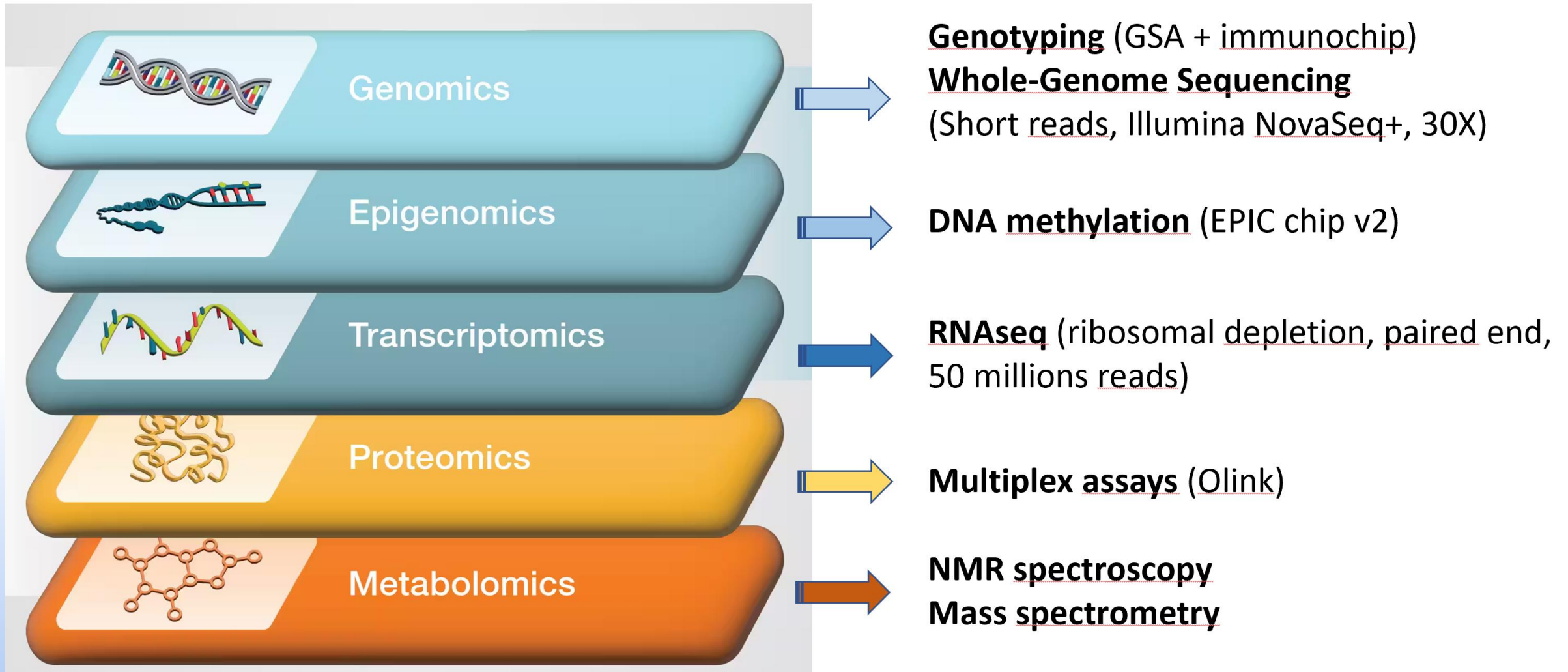
We need to use molecular biology

- To identify rare disorders
- To personalize treatments
- To stratify patients
- To integrate environmental risk factors



Brainstorm Consortium - **Science** 2018, 22;360(6395)

FRENCH MIND COHORT: OMICS ANALYSIS



CRITERIA FOR ELIGIBILITY TO WHOLE GENOME SEQUENCING

PFMG2025–integrating genomic medicine into the national healthcare system in France

THE LANCET *Regional Health*
Europe

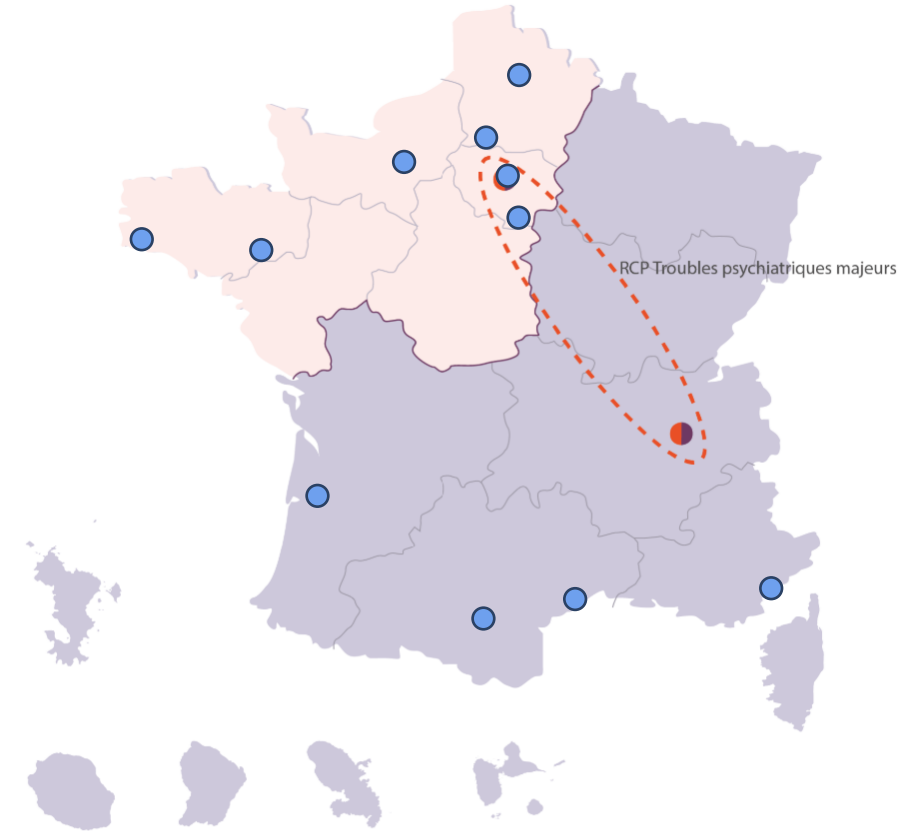
PFMG2025 contributors^a

SCHIZOPHRENIA OR BIPOLAR DISORDER WITH AT LEAST ONE OF THE FOLLOWING RED FLAGS

- Early age of onset
- Resistance to treatment
- Early and significant adverse effects of treatment
- Associated neurodevelopmental disorder (e.g. autism spectrum disorder, intellectual development disorder, learning disability, special schooling, etc.)
- Cognitive or motor disorders suggesting a neurodegenerative origin (e.g., decline in executive or memory functions at an early age)
- Dysmorphia or organic disease suggesting a genetic origin (e.g. poorly stabilized epilepsy, associated heart disease, etc.)
- Family history of psychiatric disorders or sporadic case
- Atypical presentation of the disorder (e.g. visual hallucinations, confusion, catatonia, etc.)



Genomic data collected during clinical care are uploaded to the CAD (Data Collector and Analyzer) for research purposes.



The number of centers able to prescribe whole genome sequencing has raised since 2023 from 2 to 13.



HOW TO USE GENETICS TO PERSONALISE AND IMPROVE THERAPEUTIC STRATEGIES?

	Autism	Psychotic Disorders	Mood and anxiety Disorders	
CATEGORY	RARE DISEASES	PHARMACO-GENOMICS	GWAS and POLYGENIIC RISK SCORE	EPIGENOME
CLINICAL RED FLAGS	Age at onset, neuro-developmental features...	Resistance to treatment Severe side effects	Somatic comorbidities...	Exposure to environmental risk factors
BIOMARKER	Whole Genome Sequencing Intellectual disability (ID): ~50% ASD with ID: ~30% ASD without ID*: ~10-15% Schizophrenia: ~5% Schizophrenia & neurodev features*: ~25% *french unpublished data	Genotyping Determining the genotype of genes involved in absorption, distribution, metabolism, and excretion HLA genotype helps to predict tolerance and response	Individual risk profiles -PRS related to certain pathways (ex: MitogeneRisk) -Testing the correlation between traits (ex: metabolic disorders) and diseases	Testing the impact of environmental risk factors Developing a DNA methylation score of the disorders or of exposure to certain environmental factors or episignature
STRATEGY	<ul style="list-style-type: none">- Integrating genomic medicine into the national health care system- Developing etiological treatments	Developing a pharmacogenomic passport to help choose the drug & the doses	Stratification based on PRS risk profiles, for ex <ul style="list-style-type: none">- Cardiovascular risk could be better estimated- Treatment boosting mitochondria in the subgroup with high mitoRisk score	To obtain an objective marker of environmental exposure

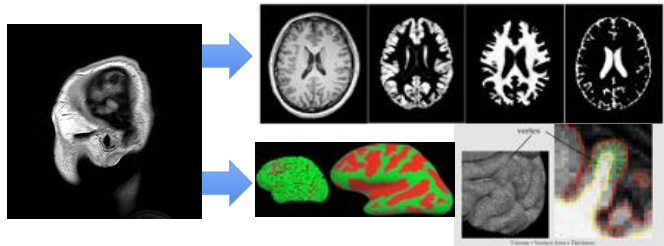
As of August 2025, France has authorized the clinical sequencing of over 300 individuals diagnosed with specific forms of schizophrenia or bipolar disorder.



HOW CAN WE USE NEUROIMAGING IN PRECISION PSYCHIATRY



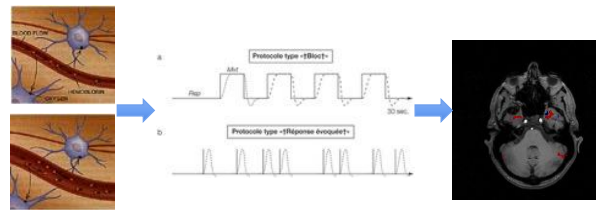
Transdiagnostic atypicalities in schizophrenia, bipolar disorder and autism



Anatomical MRI

Decreased cortical thickness

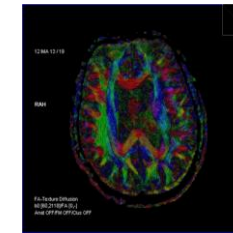
Laidi, Leboyer, Houenou et al.
Biological Psychiatry 2022 PMID: 36137706



Functional MRI

Altered functional connectivity

Krystal, Houenou Favre et al.
Molecular Psychiatry 2023 PMID: 38724567



Diffusion MRI

Decreased anatomical connectivity

d'Albis, Leboyer, Mangin, Houenou
Brain 2018 PMID: 30423029

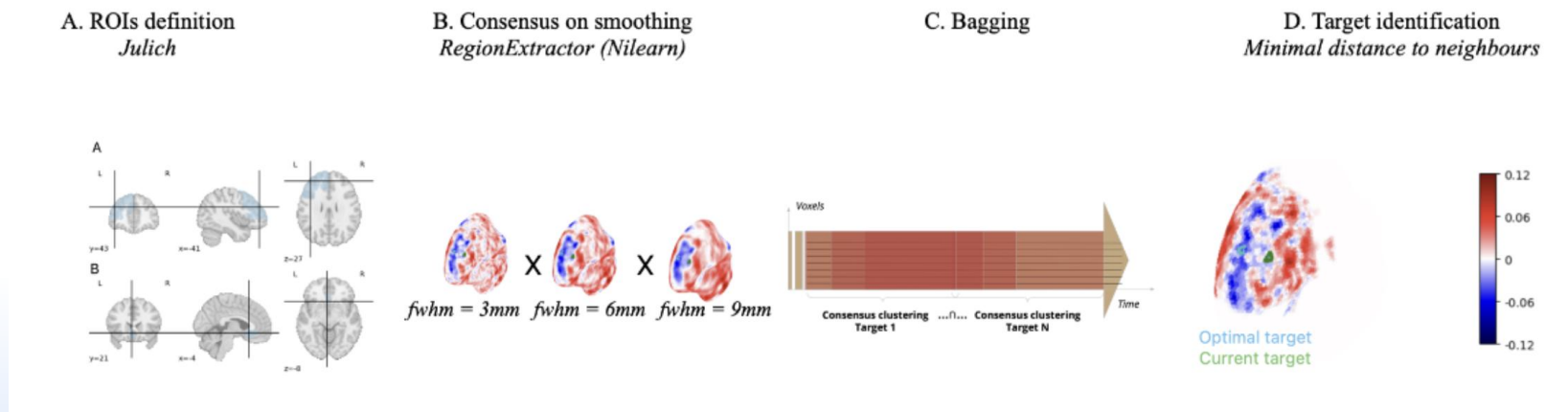
No MRI modality / brain region is involved in a specific psychiatric disorder

Neuroimaging can guide targeted interventions in psychiatry



FROM NEUROIMAGING TO TREATMENT PERSONALIZATION

Individualized target for Transcranial Magnetic Stimulation in depression



Mondor-stim: an open-source pipeline to optimize the targets for Transcranial Magnetic stimulation, based on fMRI Functional Connectivity

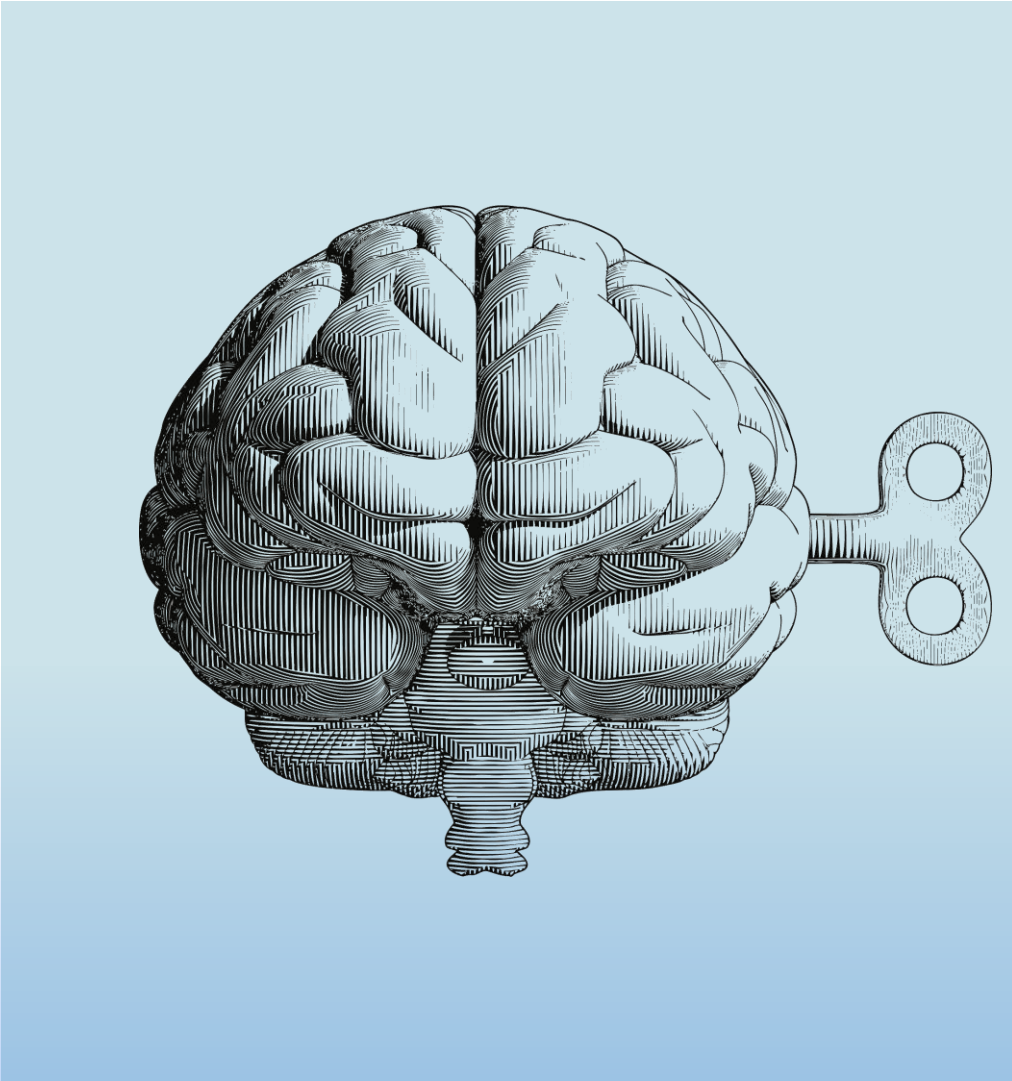
Talou, Bouaziz, Bertrand, Laidi et al. 2024

Zenodo archive <https://doi.org/10.5281/zenodo.13323615>

BRAIN IMAGING PAVING THE WAY TO PRECISION PSYCHIATRY:

Hypothetical subgroups identification and mechanisms-based treatments

	DECREASED CORTICAL THICKNESS	ATYPICAL FUNCTIONAL CONNECTIVITY	CEREBELLAR ALTERATIONS
CLINICAL SIGNATURE	<p>Autism</p> <p>Early age at onset Negative symptoms Cognitive impairment Chronicity</p>	<p>Psychotic Disorders</p> <p>Anhedonia Apathy Blunted affects</p>	<p>Mood and anxiety Disorders</p> <p>Negative symptoms Cognitive Decline Treatment Resistance</p>
BLOOD BASED SIGNATURE	<p>Complement activation HLA / C4 Gene</p>	<p>Chronic inflammation ?</p>	<p>Maternal immune activation ?</p>
MECHANISMS-BASED TREATMENTS	<p>Immuno-modulation?</p>	<p>Immuno-modulation?</p>	<p>Non-invasive brain stimulation</p>



It is time for **PRECISION PSYCHIATRY...**

marion.leboyer@inserm.fr

www.foundation-fondamental.org

<https://pepr-propsy.fr>