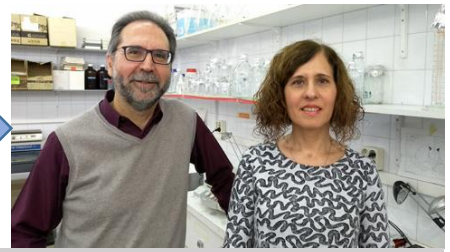
Genomic, epigenetic and proteomic biomarkers in psychosis: a translational approach including high-risk individuals, patients with schizophrenia and animal models

ERA-NET PROJECT (GEPI-BIOPSY)

Coordinator: Javier Labad

(Fundació Parc Taulí – Neuroscience Translational Unit I3PT - UAB)

ERA-NET NEURON

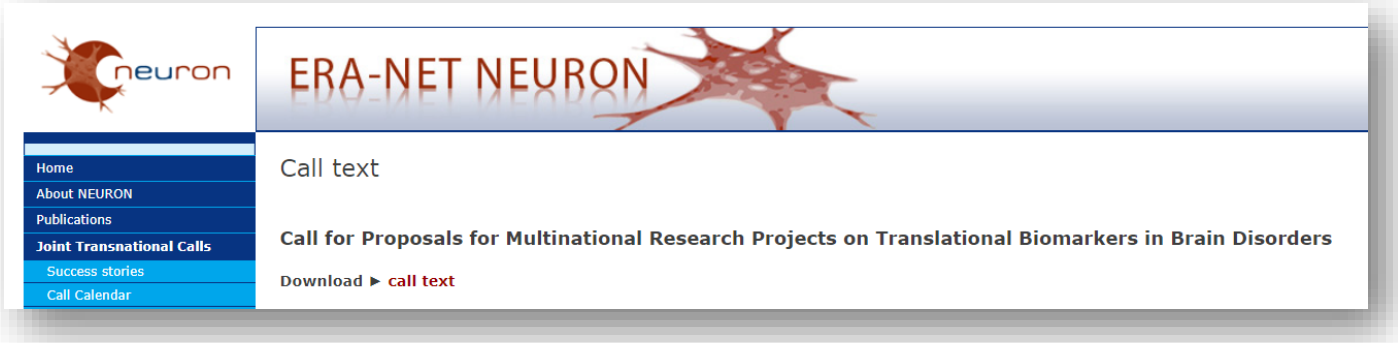


Neuroscience Translational Unit
I3PT – UAB
CIBERSAM (CB19/09/00029)

Biomarkers (genomics, epigenetics, proteomics) in psychosis with a translational approach

Institute of Psychiatry and Neuroscience (Paris)

Institute of Psychiatry Phenomics and Genomics – IIPG (Munich)



Under the umbrella of NEURON, a joint transnational call (JTC2019) is launched in the field of biomarkers in disorders of the brain. For the afflicted patients a correct diagnosis and individualized treatment without severe side effects are of crucial importance.

Aims… **multinational, collaborative research projects** that will address the unmet medical need for valid and reliable biomarkers for the diagnosis, patient stratification, prognosis, monitoring and prediction of treatment response and side effects in neurological and psychiatric diseases.

… promote **multi-disciplinary work and translational research** proposals that combine basic and clinical approaches. In the context of the present call, the **inclusion of psychiatrists and/or neurologists in the postulating consortia is highly encouraged, along with fundamental neuroscientists**. The consortia are expected to submit novel, ambitious ideas that can only be achieved by the complementary collaboration between partners.

PARTNERS ERA-NET GEPI-BIOPSY PROJECT

1

Spain: Parc Taulí Hospital Universitari – UAB (Neuroscience Translational Unit), Sabadell (Barcelona)

Javier Labad (PI), Roser Nadal, Antonio Armario, Jesús Giraldo

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France: INSERM U1266, Paris

Marie-Odile Krebs (PI), Boris Chaumette

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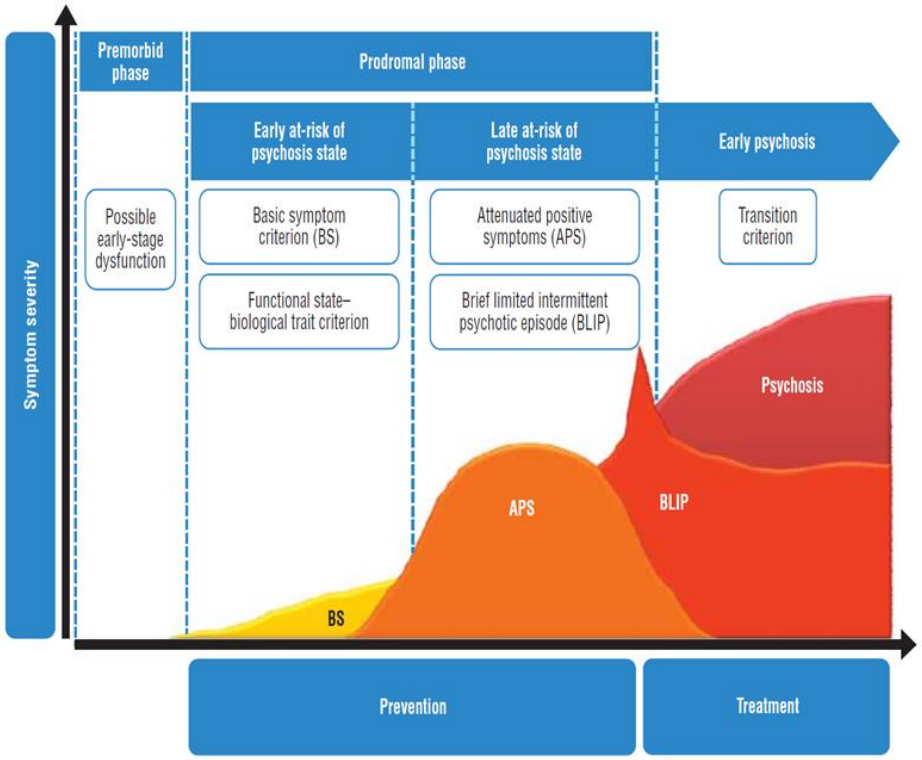
Germany: University Hospital, Ludwig Maximilian University, Munich

Thomas Schulze (PI), Mathias Mann, Sergi Papiol, Philipp Geyer, Mojtaba Oraki

INTRODUCTION

Schizophrenia and psychotic disorders are prevalent conditions and constitute a major health burden world-wide.

The research field has moved to studying people with prodromal symptoms (At Risk-Mental States or Ultra-High-Risk).



Early detection is a promising approach for reducing the duration of untreated psychosis and improving the outcome

Clinical symptoms are not very good at predicting who will develop a psychotic disorder

30-40% will develop a psychotic disorder

UHR research includes help-seeking individuals (‘stressed’ – potential bias)

INTRODUCTION (II)

Recent interest in adding ‘omics’ biomarkers to the predictive value of psychosis transition in UHR

DNA methylation: methylation of gene promoters and pathways relevant for psychosis, including oxidative stress regulation, axon guidance and inflammatory pathways in those UHR with a psychotic transition *(Kebir et al., 2017).*

Other groups have also reported the utility of DNAm patterns for psychotic experencies during adolescence (ALSPAC Cohort) *(Suderman et al., 2019).*

Validation of a set of 26 biomarkers in plasma: AUC= 0.82 for transition to schizophrenia *(Chan et al., 2015).*

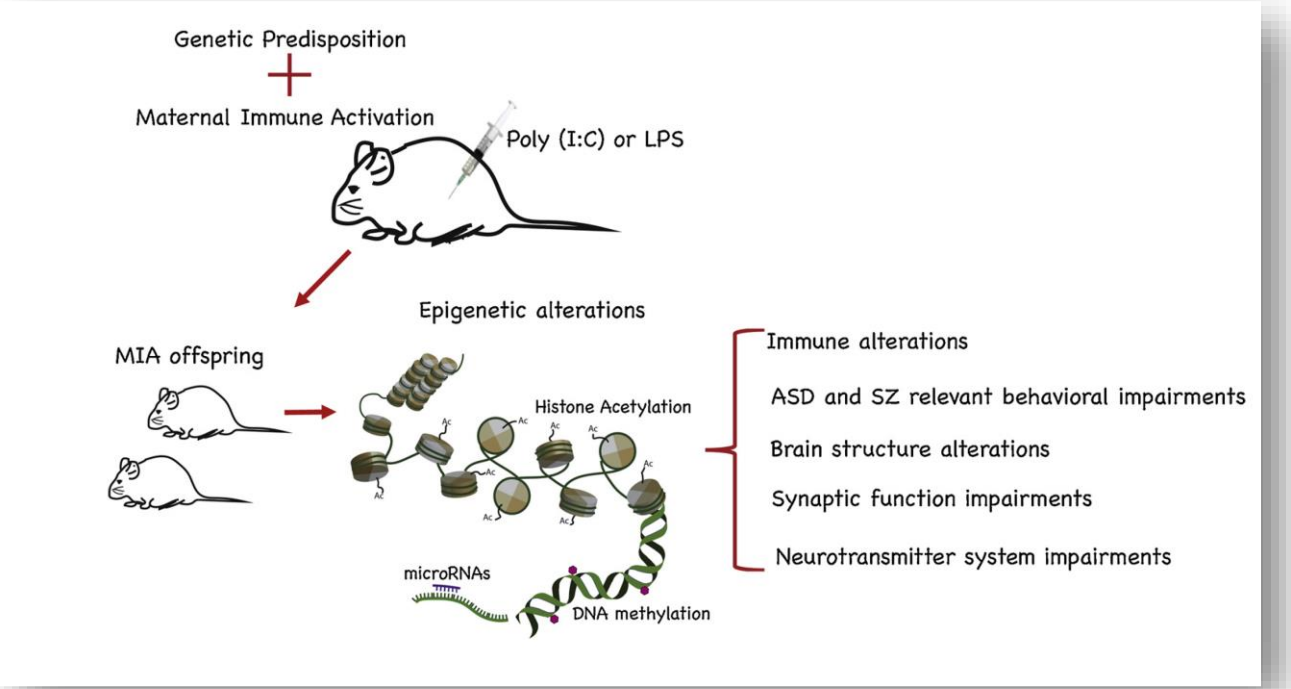
Polygenic risk scores cannot be used alone to predict psychosis transition (AUC= 0.59-0.65) *(Chaumette et al.; Perkins et al., 2020).*

Recent interest in proteomics for increasing prediction of psychosis in UHR (AUC= 0.96) *(Mongan et al., 2020)*

1. The combination of ‘omics’ and clinical data with machine learning might improve the diagnostic accuracy
2. Most longitudinal studies focused on dichotomic variables (psychotic transition) and help-seeking UHR
3. Better definition of phenotypes with a translational approach (use of animal models) might help to improve the detection of biomarkers that are important for the psychotic phenotype

INTRODUCTION (III)

THE MATERNAL IMMUNE ACTIVATION MODEL OF SCHIZOPHRENIA



BEHAVIOURAL CHANGES IN THE OFFSPRING

Similar phenotype to the observed in people with schizophrenia and ultra-high-risk populations:

Impairment of sensomorimotor gating abilities (pre-pulse inhibition)

Cognitive disturbances

Social deficits

Anhedonia

BRAIN CHANGES IN THE OFFSPRING

Structural brain changes

Structural and functional neuronal impairments

IMMUNE ALTERATIONS AND EPIGENETIC CHANGES IN THE OFFSPRING

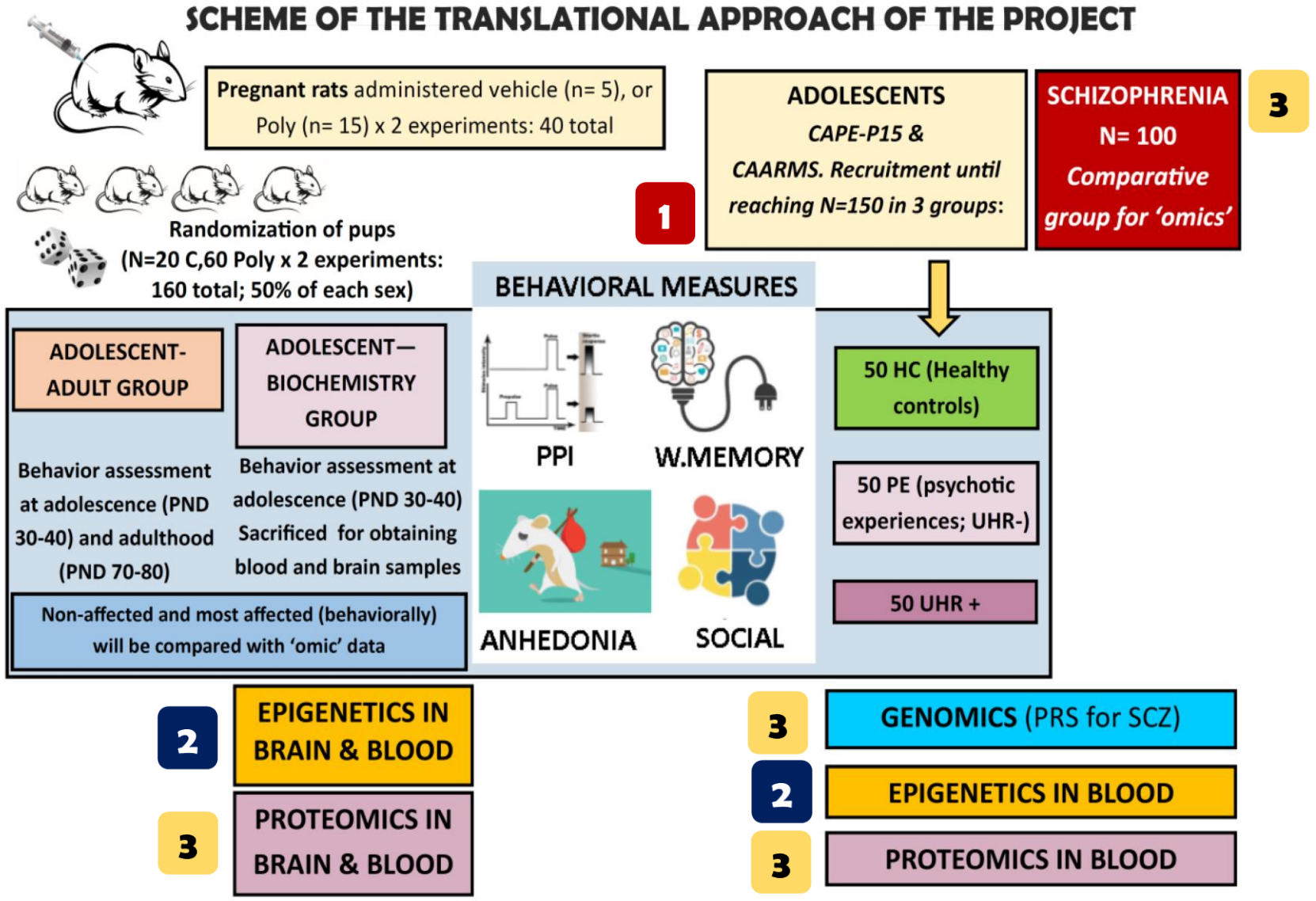
Bergdolt & Dunaevsky, 2019

IDENTIFY 'OMIC' BIOMARKERS IN PSYCHOSIS:
Genomics
Epigenetics
Protomics

Relationship with psychotic features (diagnosis) in humans

Relationship with behavioural measures in both rats and humans

To study the correlation between epigentics and proteomics in blood & brain (rats)



Abbreviations: PND= Postnatal day; PPI= Pre-pulse inhibition; HC= healthy control; PE= Psychotic experiences; UHR= Ultra-High Risk; PRS= Polygenic risk scores; SCZ= Schizophrenia.

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ADOLESCENT HIGH-RISK SAMPLE

Permissions from Education (Generalitat de Catalunya) And Local Ethics Committee

APPROVED

Written informed consent to participate – 2 parts:
Epidemiological step
Clinical study

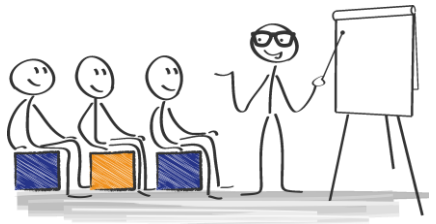
adolescents

parents (both)

ASSIGN ID FOR THE STUDY

EPIDEMIOLOGICAL STEP: RECRUITMENT AT SCHOOLS

Sabadell: 220.000 habitants
35 schools
2500 students/year



Students complete an on-line questionnaire including three psychometric scales: **CAPE-P15** (psychotic experiences), **APRI** (bullying), **CBQ** (cognitive biases)
Clinical staff from the Early Intervention Service from psychosis conduct informative workshop on psychotic experiences the same day (after online questionnaire)

CLINICAL STUDY: RECRUITMENT AT PARC TAULÍ HOSPITAL

Selection of extreme phenotypes based on CAPE-15:
Low vs High psychotic-like experiences (PLE)
CAARMS administration for 3 groups (N= 50 each):

Healthy controls	PLE without UHR	UHR
CAPE -; CAARMS -	CAPE +; CAARMS -	CAPE +; CAARMS +

3

SAMPLE OF PEOPLE WITH SCHIZOPHRENIA

PsyCourse

PsyCourse cohort of affective and non-affective psychosis patients and healthy controls.
More than 1,600 participants (>1,300 patients and >300 controls) have been enrolled at 17 sites in Germany and Austria.

Already recruited
Extensive prospective phenotyping (2500 variables)
Blood/serum/plasma available (Biobank)

N=100 will be selected for inclusion in the current ERA-NET Project

- 50 schizophrenia at early stage
- 50 schizophrenia at later stage

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Check for updates

RESEARCH ARTICLE

WILEY

A longitudinal approach to biological psychiatric research: The PsyCourse study

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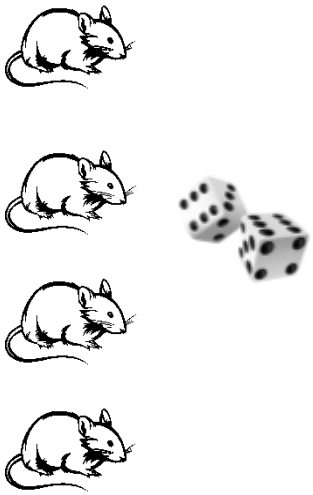
ANIMAL STUDY: MIA MODEL

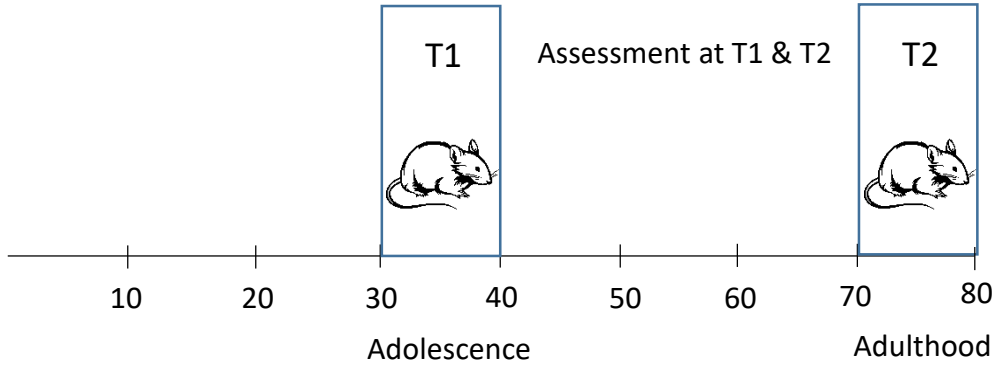
Pregnant Long-Evans rats
Vehicle (N=5) or Poly (N=15)
x 2 experiments

OFFSPRING



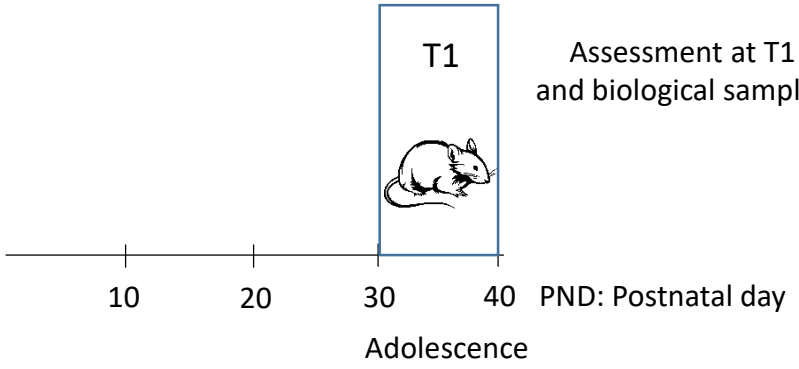
ADOLESCENT – ADULT BEHAVIOUR COHORT

(20 controls; 60 Poly: 50% each sex)



ADOLESCENT – BIOCHEMISTRY COHORT

(20 controls; 60 Poly: 50% each sex)



Blood samples: 1.5 ml
1 ml blood for epigenetics
0.5 ml plasma for proteomics

Brain samples
Prefrontal cortex
(hippocampus for future studies)

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TRANSLATIONAL PHENOTYPING

Adolescents and rats

Snaith-Hamilton Pleasure Scale (SHAPS) Self-report, 14 items of pleasant experiences	**ANHEDONIA**	**Saccharin consumption** Rats will have free access to food (3 days) and two bottles of tap water and solution with saccharin
Social Adaptation Self-Evaluation Social Scale (SASS) Self-report (20 items): social motivation & behaviour	**SOCIAL INTERACTION**	**Social interaction test** 1 session of social interaction with 2 pairs of non-siblings with same-sex rats
CANTAB Cognitive battery **Spatial Working Memory (SWM)**: visuospatial WM RTI (processing speed), PAL (visual M), OTS (Executive f.), MTT (set-shifting), RVP (attention), ERT (emotion processing), VRM (verbal M).	**WORKING MEMORY**	**T Maze** 4-5 sessions: Habituation trial (1 session) + Training (3 consecutive days) + Test trial
PPI of the acoustic startle reflex Assessment with a BIOPAC MP160 system EMG recording (orbicularis oculi muscle)	**PRE-PULSE INHIBITION (PPI)**	**PPI of the acoustic startle reflex** SDI-lab system (1 session) Two standard startle chambers (SR-LAB)

2

EPIGENETICS

Humans: Blood (Adolescents + Schizophrenia; N= 250)

Genome-wide Methylation

Infinium MethylationEPIC Bead Chip (Illumina): >850.000 CpG loci

Extraction (signal intensities) with Illumina Genome Studio + Analyses with R and Chip Analysis Methylation Pipeline

Supplementary Quality Check

Rats: Blood and brain (N= 80)

Reduced Representation Bisulfite Sequencing (RRBS)

Methylation of > 2 million CpG

Sequencing on an Illumina platform

Quality check control

3

PROTEOMICS

Humans: Plasma (Adolescents + Schizophrenia; N= 250)

Rats: Blood and brain (N=80)

Pipeline developed in the laboratory of Mathias Mann

Highly reproducible and quantitative high-throughput information of 100s to 1000s of proteins

Measurement with Liquid Chromatography-Mass Spectrometry (LC-MS)

Analyses with MaxQuant software

Peptide lists searched against Uniprot FASTA database

Cost and complexity of determination much higher in brain samples

Planning: first running pilot analyses in plasma and brain and decide analyses (global vs targetted)

If technique works fine for all samples, priorize selection of samples based on available budget and/or request additional funds if necessary in other calls

1 2 3

STATISTICS

Classical statistical approaches

Univariate and multivariate analyses (e.g. ANCOVA, regression analyses).

Study of dimensions and subtypes: Principal Component Analysis (PCA), Cluster Analysis, Correspondence Analysis, Multidimensional Scalling

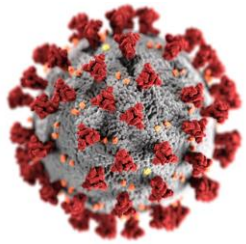
Machine Learning

Exploratory machine learning approach for the identification of psychotic-related subtypes considering behavioural data and 'omics' (genomic, epigenetic and proteomics) biomarkers

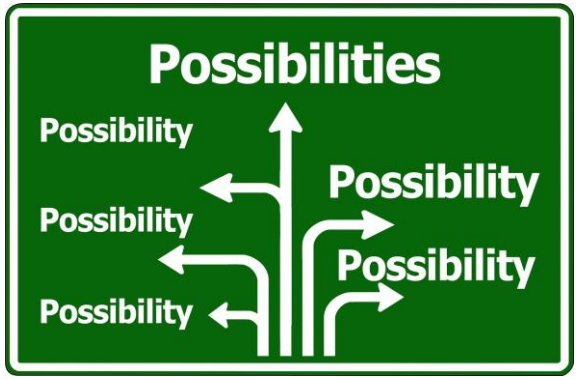
Two waves of analyses: 1) Behavioural data (second year Project); 2) 'Omics' ± behavioural (end Project)

Unsupervised and supervised machine learning techniques: Associations Rules, Decisions Trees and Random Forest, Neural Networks, Support Vector Machine, Evolutionary Computation, Emergent Self-Organizing feature Maps (ESOM)

Laboratory of Molecular Neuropharmacology and Bioinformatics (Jesús Giraldo, David Roche)



COVID-19 IMPACT ON ADOLESCENT STUDY



CONTINGENCY PLAN

Clinical part of the adolescent recruitment stopped due to the COVID-19 situation
(difficult to recruit healthy adolescents in the hospital)

Proposal to include UHR cohorts that are already recruited with biological samples:

1) Paris (Marie-Odile Krebs)
2) Other cohorts – contact with other PIs who might be interested in collaborating.

Ideal to have both plasma and DNA samples in a same cohort. However, it might be considered to include different cohorts for replicating analyses.


Thank
you !