Epigenetic biomarkers of depression and suicide

Pierre-Eric Lutz, CNRS, Strasbourg, France

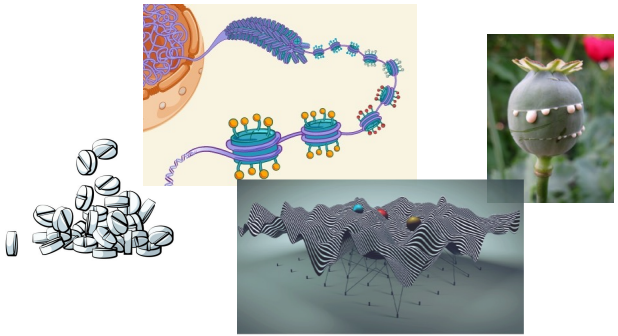
Research Connection

American Foundation for Suicide Prevention

Institute of Cellular &
Integrative Neurosciences

inci.neuro.unistra.fr/

pierre-eric.lutz@cnrs.fr



Our team:

→ Epigenomic mechanisms of psychiatric disorders

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Plan of the presentation

1. Intro : epigenetics & mental health

2. Epigenetic biomarkers of depression

Mokhtari et al, eBioMedicine 2025

3. Sensitivity to social stress and suicidal behaviors

In progress

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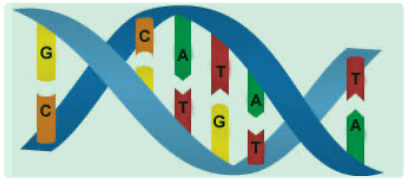
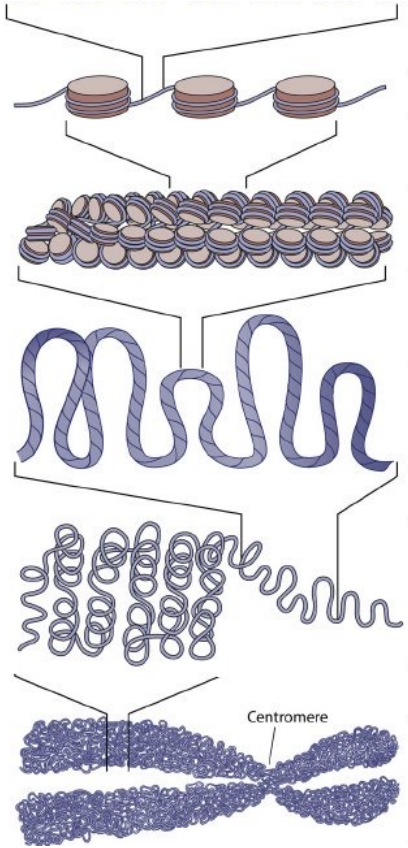
Defining epigenetics



Human genome

- ***Double helix*** structure
- Composed of 4 « letters » that represent the genetic information : A, C, G, T
- Length ≈ 3.2 billion letters ≈ 2 meters of ADN, to be compacted within a few micrometer nucleus
- Epigenetics = molecular mechanisms for the compaction of DNA (chromatin) and regulation of gene expression
  - ✓ DNA methylation
  - ✓ Micro-RNA
  - ✓ Histone modifications



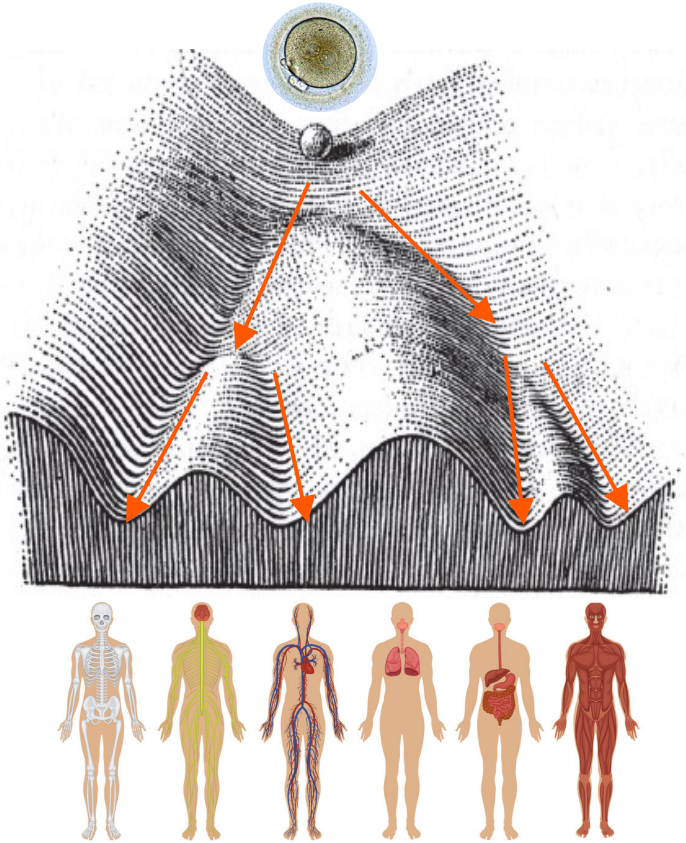
Chromatin

Defining epigenetics

Zygote
1 genetic code

Conrad Waddington, 1942

Differentiated cell types (mature organism)
Multiple epigenomes/ cell types



Historical model

- *deterministic*
- *unidirectional*
- *bounded (start & end)*

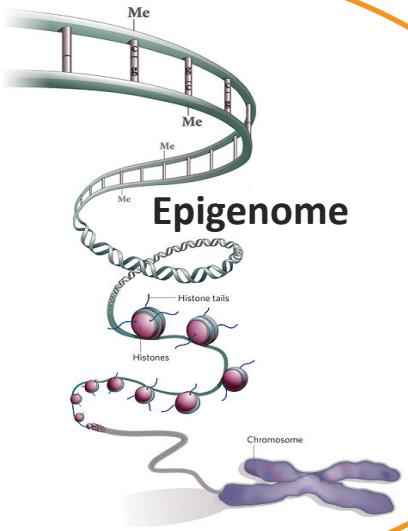
Two modern questions:

- *Which epigenetic plasticity in the brain?*
- *What role in psychopathology?*

The behavioral epigenetics paradigm

Life experiences





Epigenome

Psychopathology

Depression

Addiction

Suicidal behaviors


/


→ Translational research

♀ / ♂

→ Sex differences


/


→ Brain & peripheral tissues

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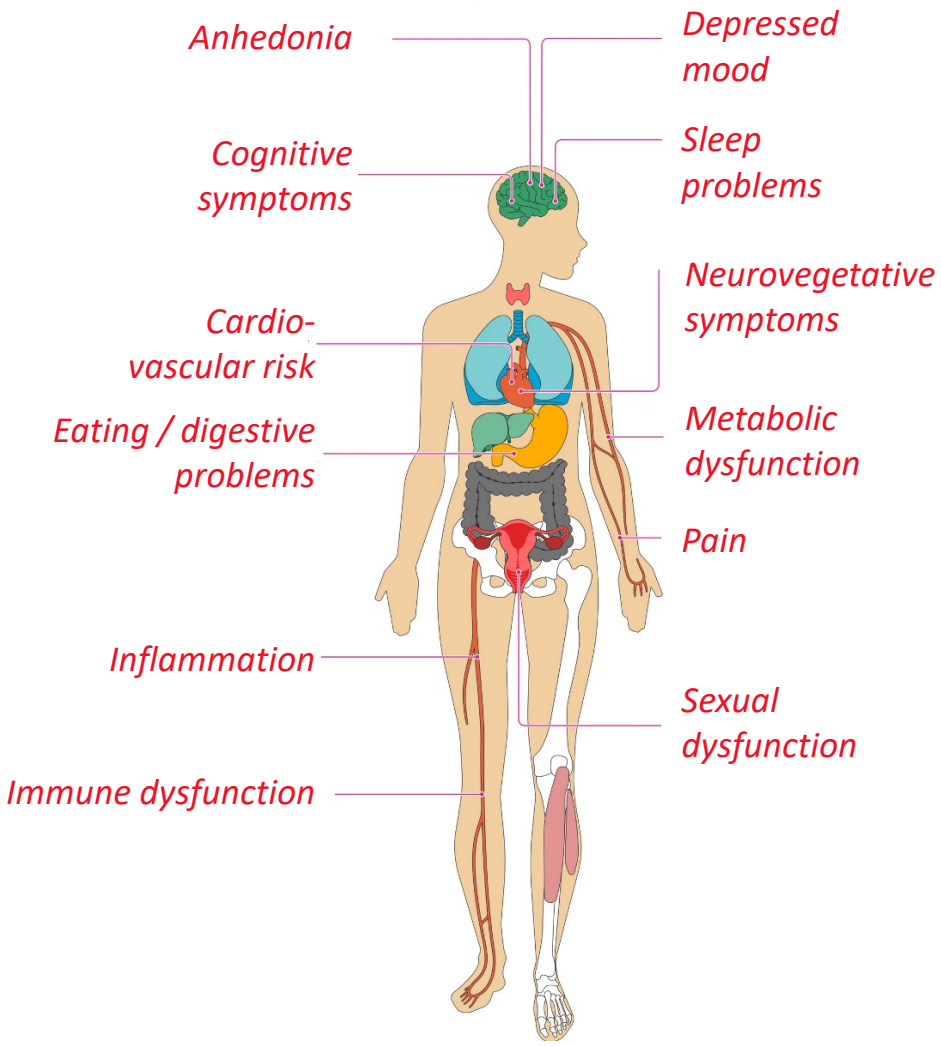
Major depressive disorder

- A systemic affection with multivisceral consequences
- Involves inter-tissular communication (hormones, exosomes)
- Molecular correlates detectable in peripheral tissues?
  - **Blood**
  - Saliva
  - CSF
  - Urine
  - Etc…



LeukoLOCK filters

RNAseq
≈ 30 millions de lectures/éch.
50bp single-end

mRNA
expression

IGBMC, Strasbourg

LeukoLOCK filters

Small RNAseq
≈ 8 millions de lectures/éch.
50bp single-end

micro-RNA
expression

Marseille

Whole blood DNA

EPIC array
1 puce/éch.

DNA methylation
levels

Vienna, Austria

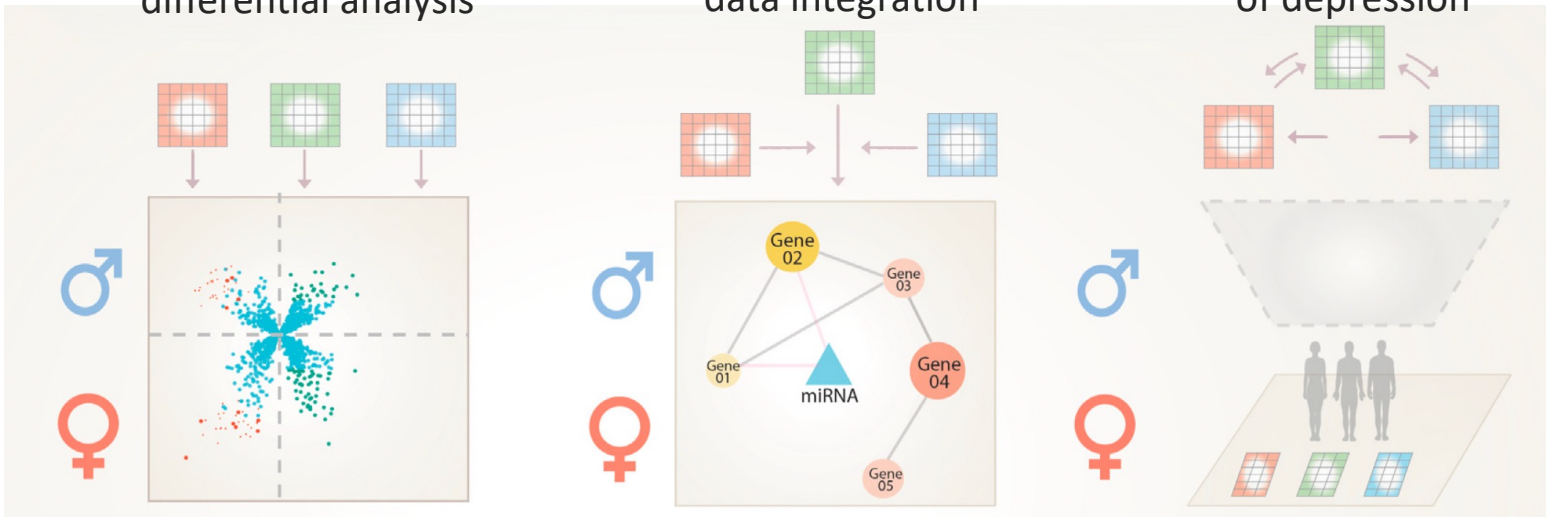
Human cohort & analytical strategy

Sex	n .max	Group	Age	BMI	HDRS
Female	55	Control	45 [32, 58]	24 [20, 28]	1.4 [0.0, 3.2]
	50	MDD	42 [29, 56]	24 [19, 29]	23.2 [19.8, 26.6]
Male	34	Control	45 [30, 60]	24 [20, 28]	1.2 [0.0, 2.4]
	30	MDD	43 [26, 60]	25 [20, 30]	23.5 [20.4, 26.5]
Total	**169**				

1. Single omic differential analysis

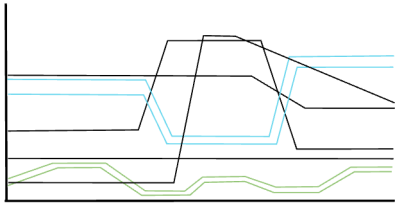
2. Network multiomic data integration

3. Multiomic prediction of depression



2. Network multiomic integration

1- Gene expression levels

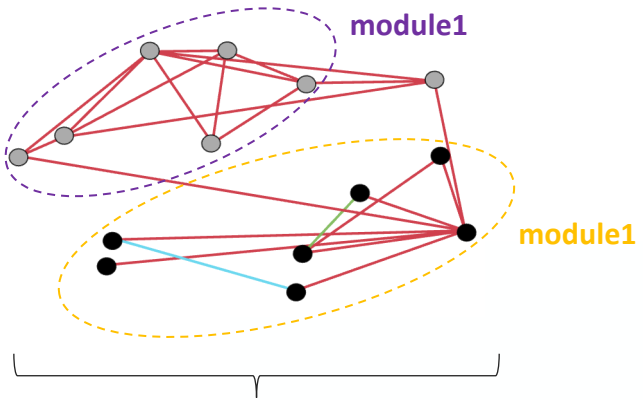


Samples

2- Expression correlation (all gene pairs)

	G1	G2	G3	G4	G5	G6	G7
G1	1	0.9	0.9	0.9	0.9	0.9	0.9
G2	0.9	1	0.9	0.3	0.3	0.7	0.0
G3	0.9	0.9	1	0.9	0.0	0.2	0.5
G4	0.9	0.3	0.9	1	0.5	0.3	0.6
G5	0.9	0.3	0.0	0.5	1	0.1	0.6
G6	0.9	0.7	0.2	0.3	0.1	1	0.9
G7	0.9	0.0	0.0	0.0	0.6	0.9	1
G8	0.1	0.5	0.7	0.3	0.1	0.2	0.3
G9	0.9	0.3	0.6	0.0	0.3	0.1	0.1
G10	0.1	0.1	0.5	0.5	0.3	0.1	0.5
G11	0.1	0.1	0.2	0.1	0.3	0.5	0.1
G12	0.8	0.2	0.6	0.2	0.5	0.3	0.3
G13	0.2	0.4	0.1	0.2	0.2	0.1	0.5
G14	0.2	0.3	0.0	0.6	0.5	0.1	0.2

3- Coexpression network



Functional annotations, enrichment for MDD-related changes, etc

2. Network multiomic integration

Networks composed of:

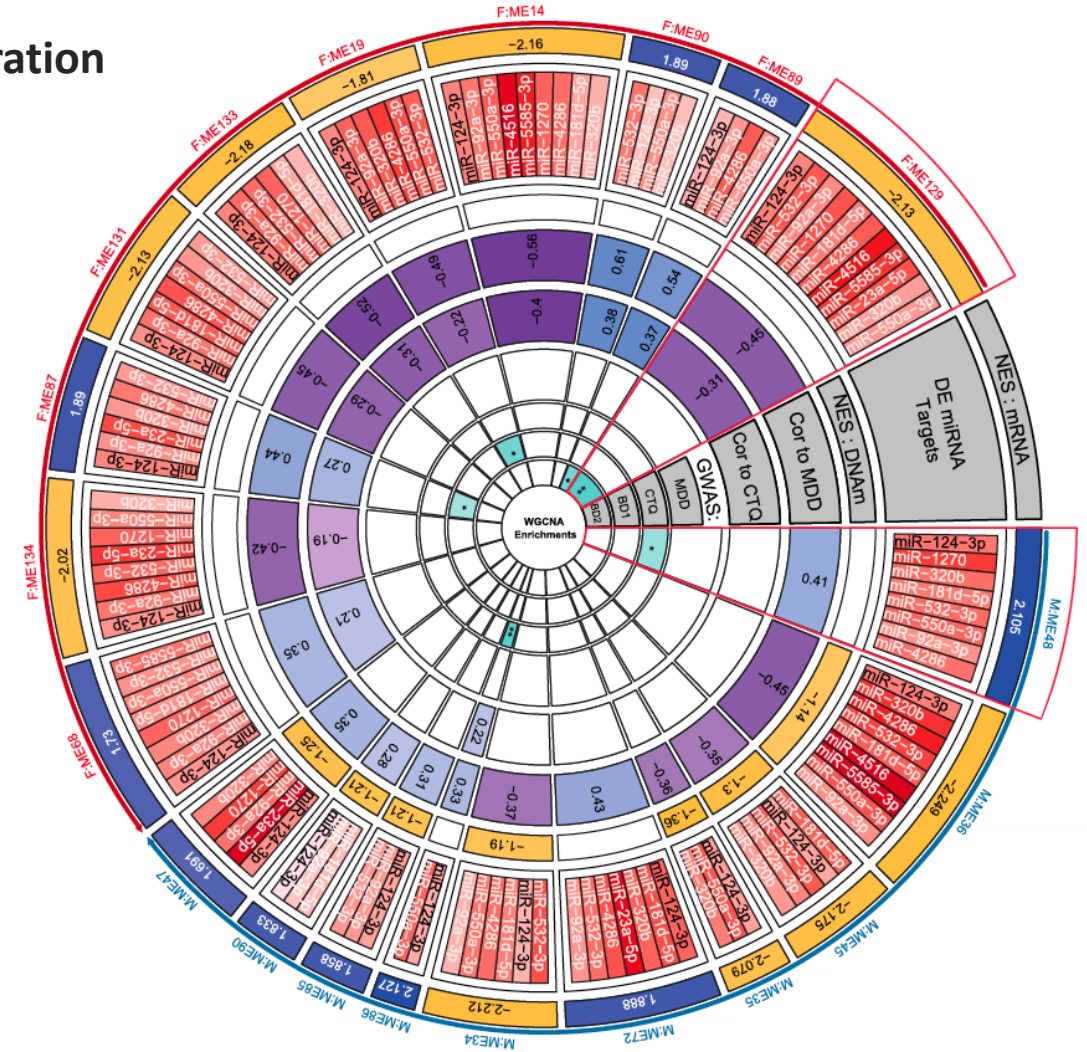
- 135 modules in females
- 111 modules in males

Gene composition of modules:

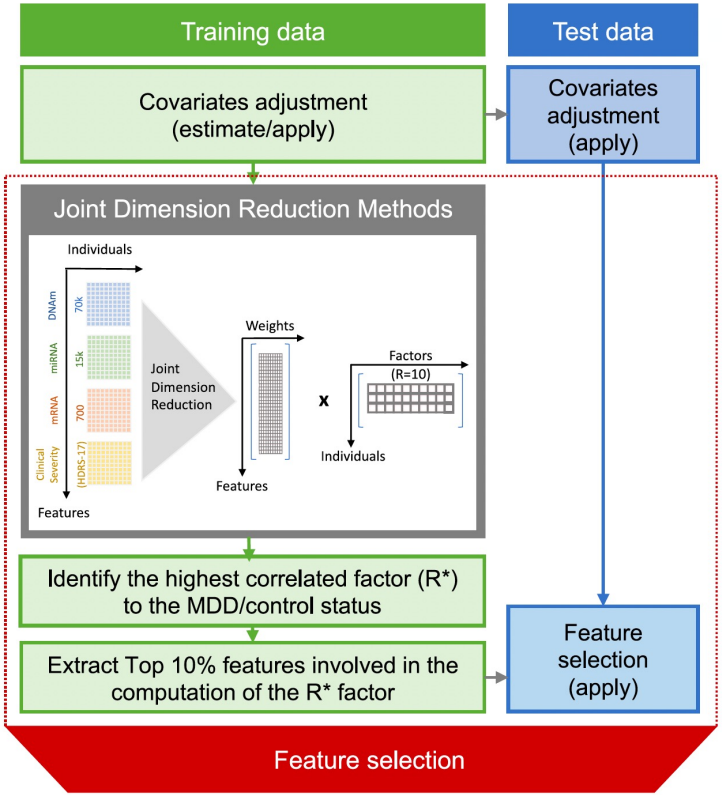
- Validated with external datasets (preservation)
- Strongly differed across women & men

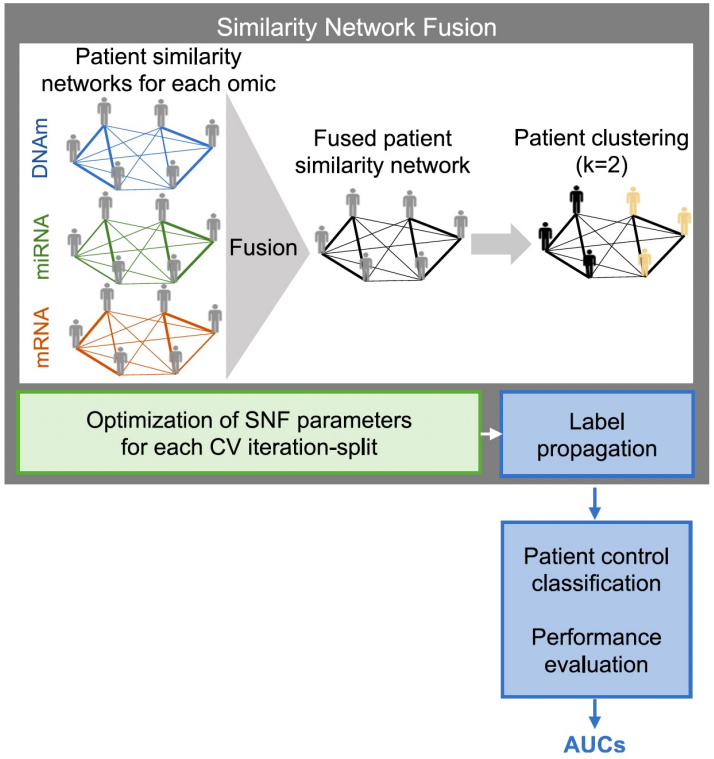
Module prioritization:

- Using enrichment for MDD-related changes for the 3 omic layers, and external GWAS data
- Female module 129 : cellular response to stress
- Male module 48 : immune response



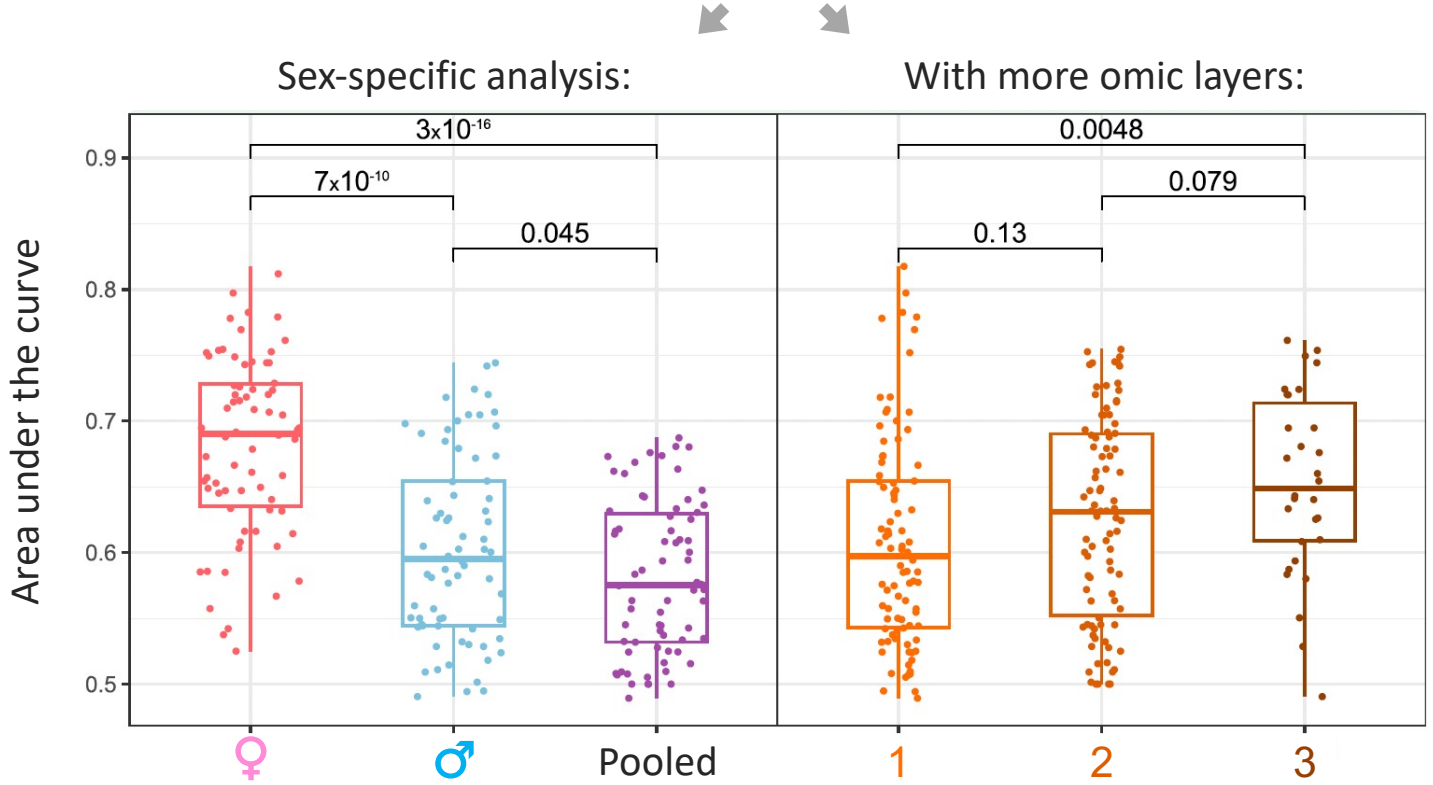
3. Multiomic prediction of depression





3. Multiomic prediction of depression

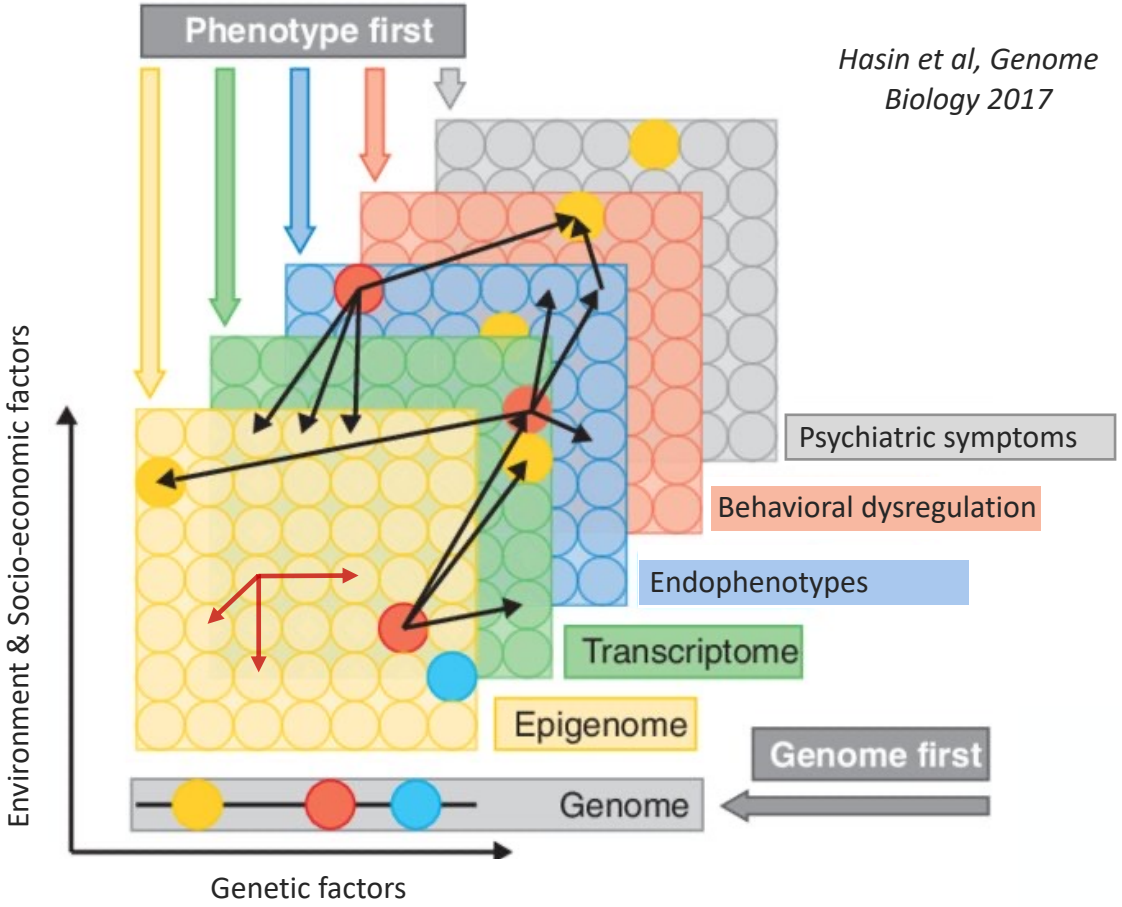
A better prediction of depression is achieved when conducting…



Towards multimodal biomarkers

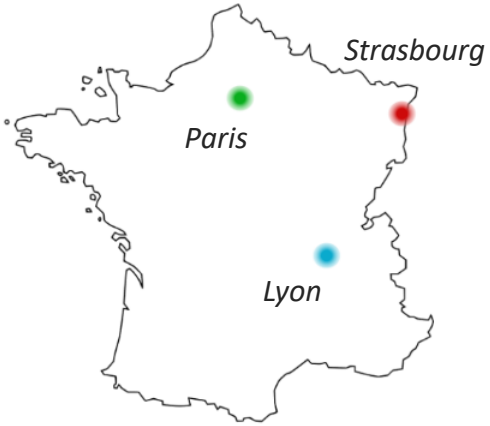
- Psychopathology stems from interacting factors:
  - ✓ Genetic
  - ✓ Environmental
  - ✓ Socio-economic
  - ✓ Etc

- Approaches spanning multiple modalities may lead to a better understanding of the "flow of information", from the causes of the disease to its clinical expression



Hasin et al, Genome Biology 2017

A multimodal study of opioid use disorder



ITHAQUE

Gaïa Paris

Multicentric cohort

Safe injection sites to recruit active abusers
n=300 (>270 already recruited)

Bio-psycho-social model of addiction

1. Multiomic measures in peripheral blood
→ DNA methylation, gene expression

2. Sociological evaluation
→ Access to care, prison, early-life adversity, work, housing

3. Psychiatric evaluation
→ Suicidal behaviors, comorbidities, other addictions

→ With a 2-year, longitudinal assessment of all modalities

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Mokhtari et al, eBioMedicine 2025

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Sensitivity to social stress and suicidal behaviors

Our hypothesis: social stress contributes to suicidal behaviors (SB)

The Trier Social Stress Test is a well-established form of social stress

Cohort of **44 women**:

	MDD-	MDD+
SB– (n=18)	7	11
SB+ (n=26)	5	21

Frisch et al,
Front Psychol 2015

Philippe Courtet
Emilie Olié

T0

Blood

mRNA expression
DNA methylation

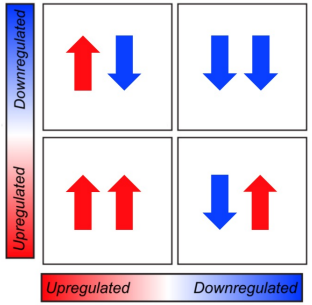
T120

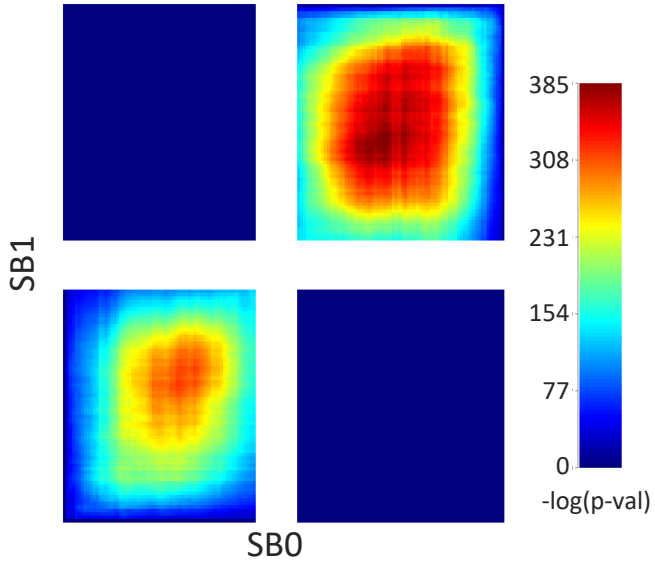
Blood

mRNA expression
DNA methylation

Sensitivity to social stress and suicidal behaviors

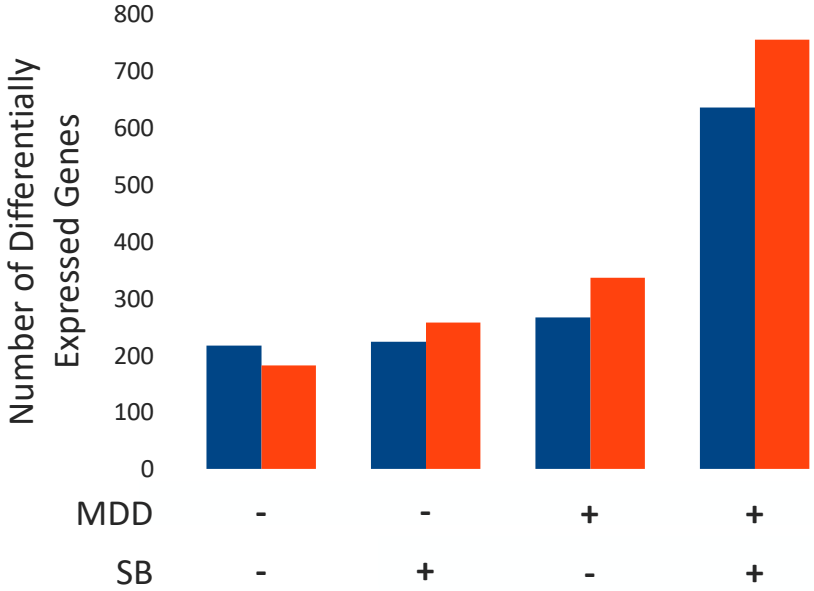
***RRHO2**: rank-rank hypergeometric overlay*





The TSST triggered gene expression changes that were:

- Similar across our 3 groups of women with or without a history of SB
- Stronger in depressed women with a history of SB



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- El Cherif Ibrahim
- **Raoul Belzeaux**
- **Andre Delahaye-Duriez**



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- **Bénédicte Nobile**
- Simon Léopold
- **Emilie Olié**
- **Philippe Courtet**




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