environMENTAL - Reducing the impact of major environmental challenges on mental health
Seminar 2 – April 22, 2022

Leveraging multi-omics data towards a molecular and neurobiological understanding of mental illness

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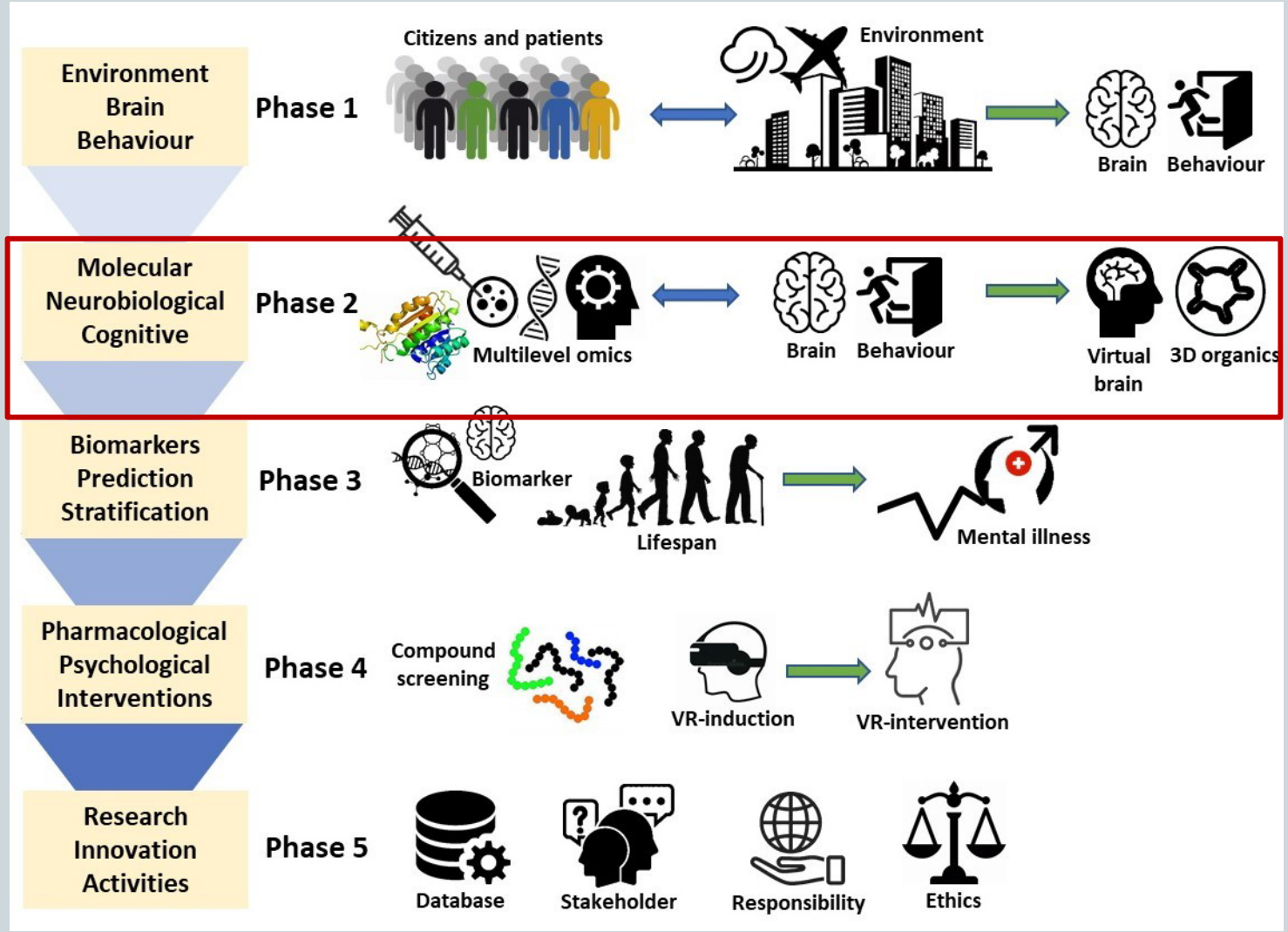
Molecular, neurobiological and systemic mechanisms underlying brain and behaviour

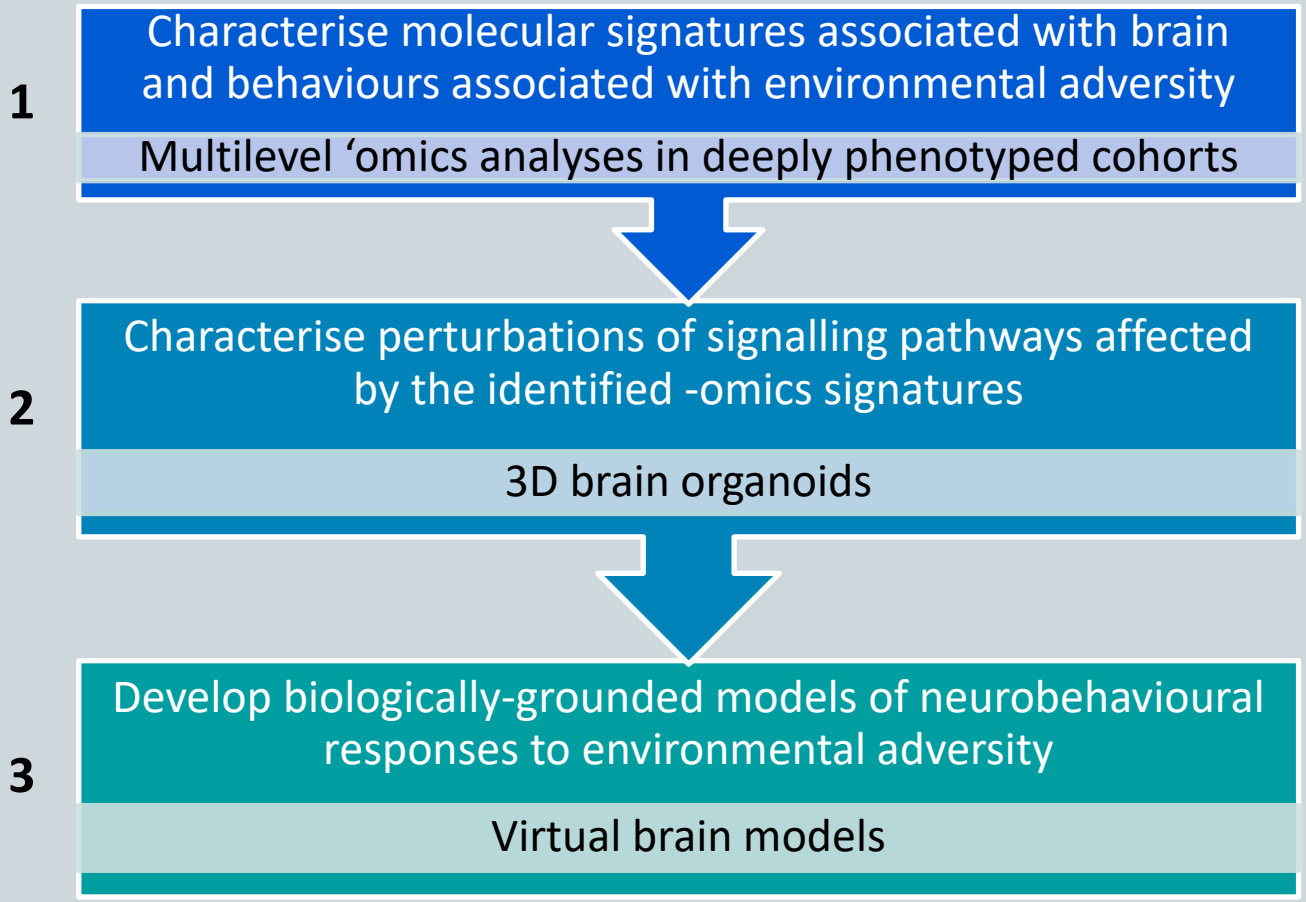
environMENTAL - Seminar 2

Reducing the impact of major environmental challenges on mental health

Seminar 2



Aims & Approaches



Seminar 2 – Agenda

Molecular analyses: multi-‘omics

- 10:05-10:30 Leveraging multi-omics data towards a molecular and neurobiological understanding of mental illness (Sylvane Desrivières)
- 10:30-11:00 Ultra-high-throughput proteomic analyses (Markus Ralser)

Virtual Brain models

- 11:00-11:30 Systemic characterisation in virtual brain models (Viktor Jirsa)
- 11:30-12:00 Simulation of Digital Twin Brains and Applications (Jianfeng Feng)

Cellular models & 3D brain organoids

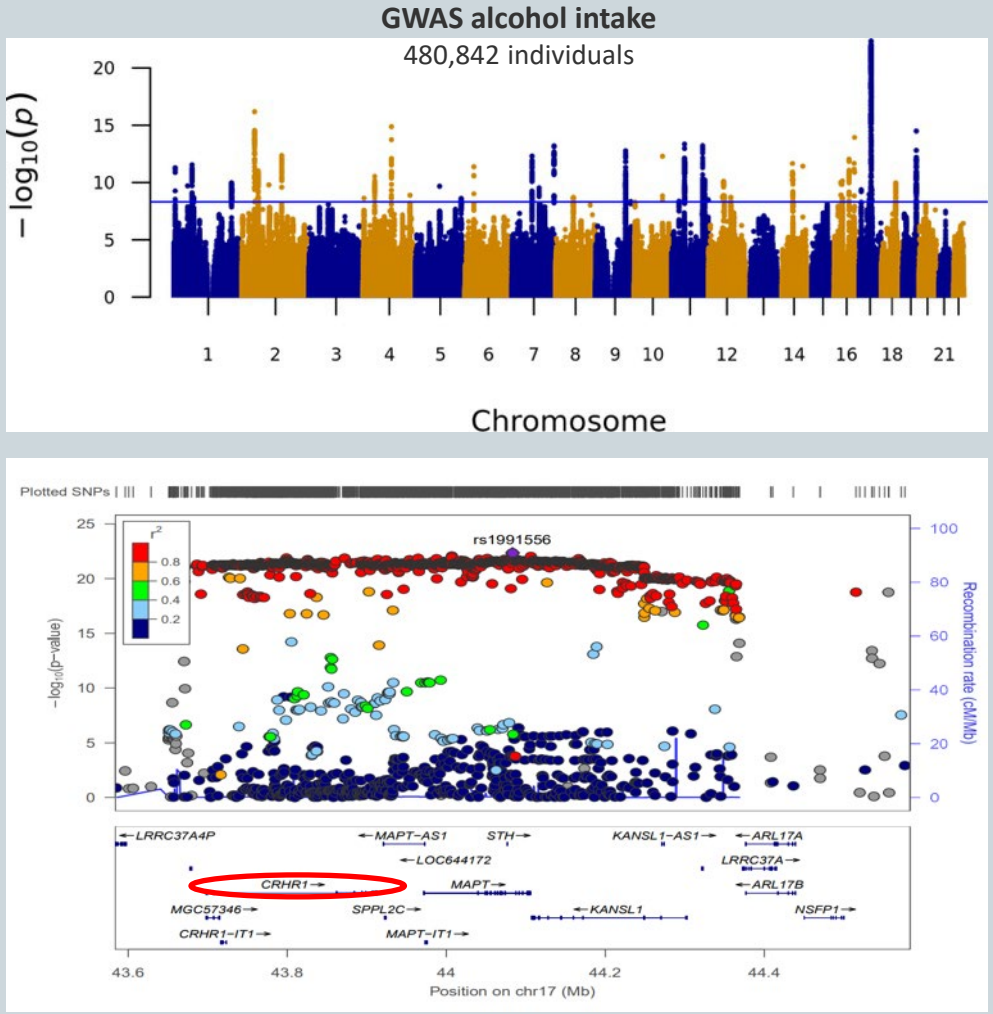
- 12:00-12:30 Pluripotent stem cell lines and 3D brain organoids (Gaia Novarino)

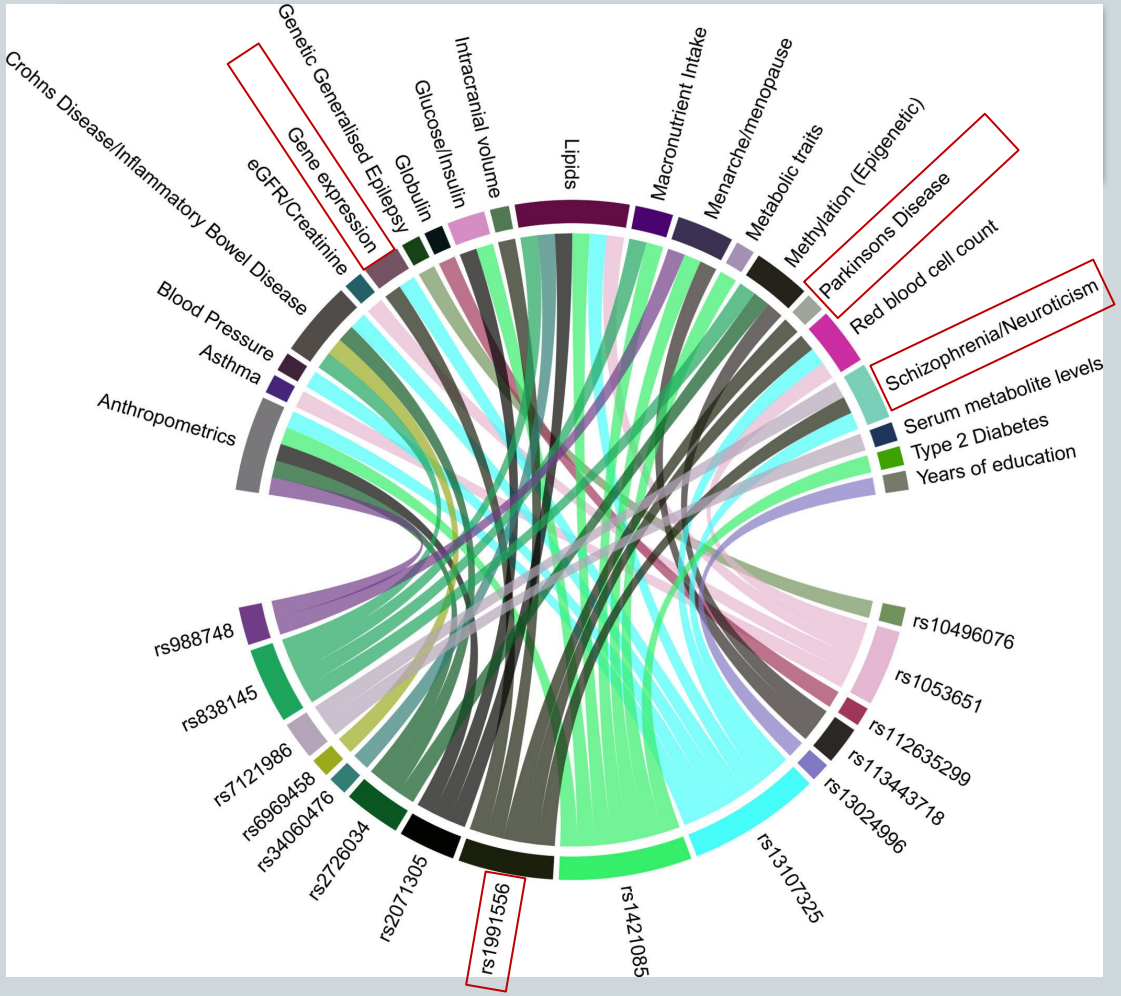
Closed meeting

- 12:30-13:00 General discussion

Leveraging multi-omics data towards a molecular and neurobiological understanding of mental illness

Multilevel ‘omics data help fine mapping of complex loci and identification of causal genes





Evangelou *et al.* *Nature Human Behaviour* volume 3, pages 950–961 (2019). New alcohol-related genes suggest shared genetic mechanisms with neuropsychiatric disorders

The Corticotropin Releasing Hormone Receptor 1 pathway and stress

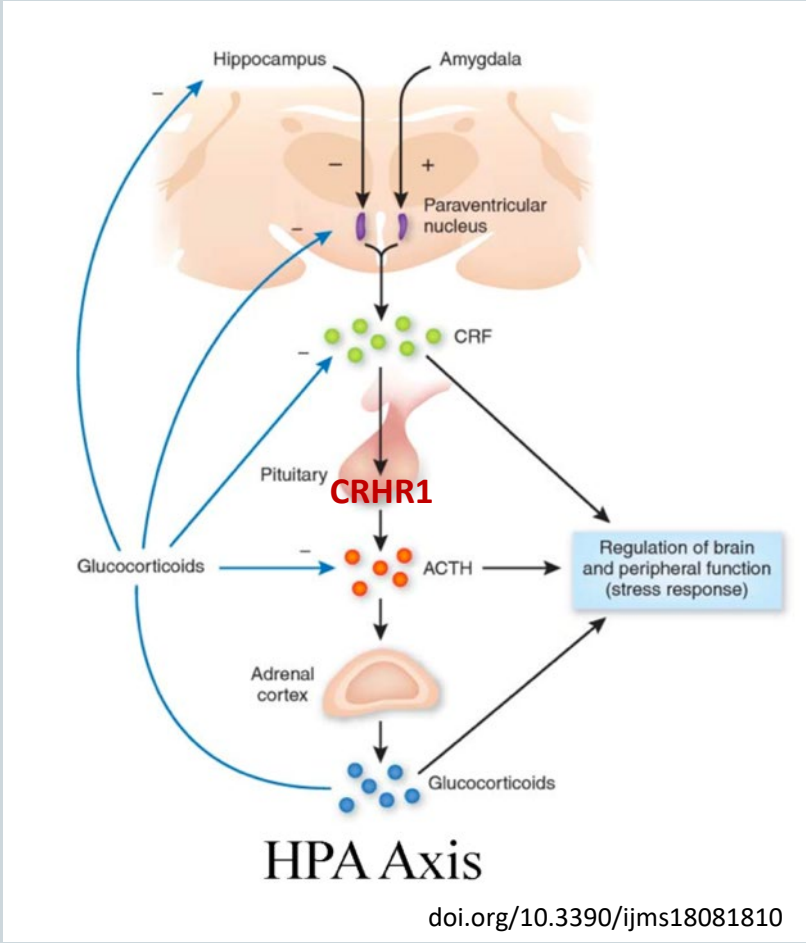
- SNPs in *CRHR1*
  - interact with stressful life events to predict heavy alcohol use.
  - Allele associated with stress-related heavy drinking is linked to increased expression of *CRHR1* (= expression quantitative trait loci; eQTL) in several tissues, including the brain that alter.

- Activation of the CRH pathway is associated with anxiety.
- Blockade of the CRH pathway reduces anxiety.

- *Crhr1* mutant mice show impaired stress response and reduced anxiety.

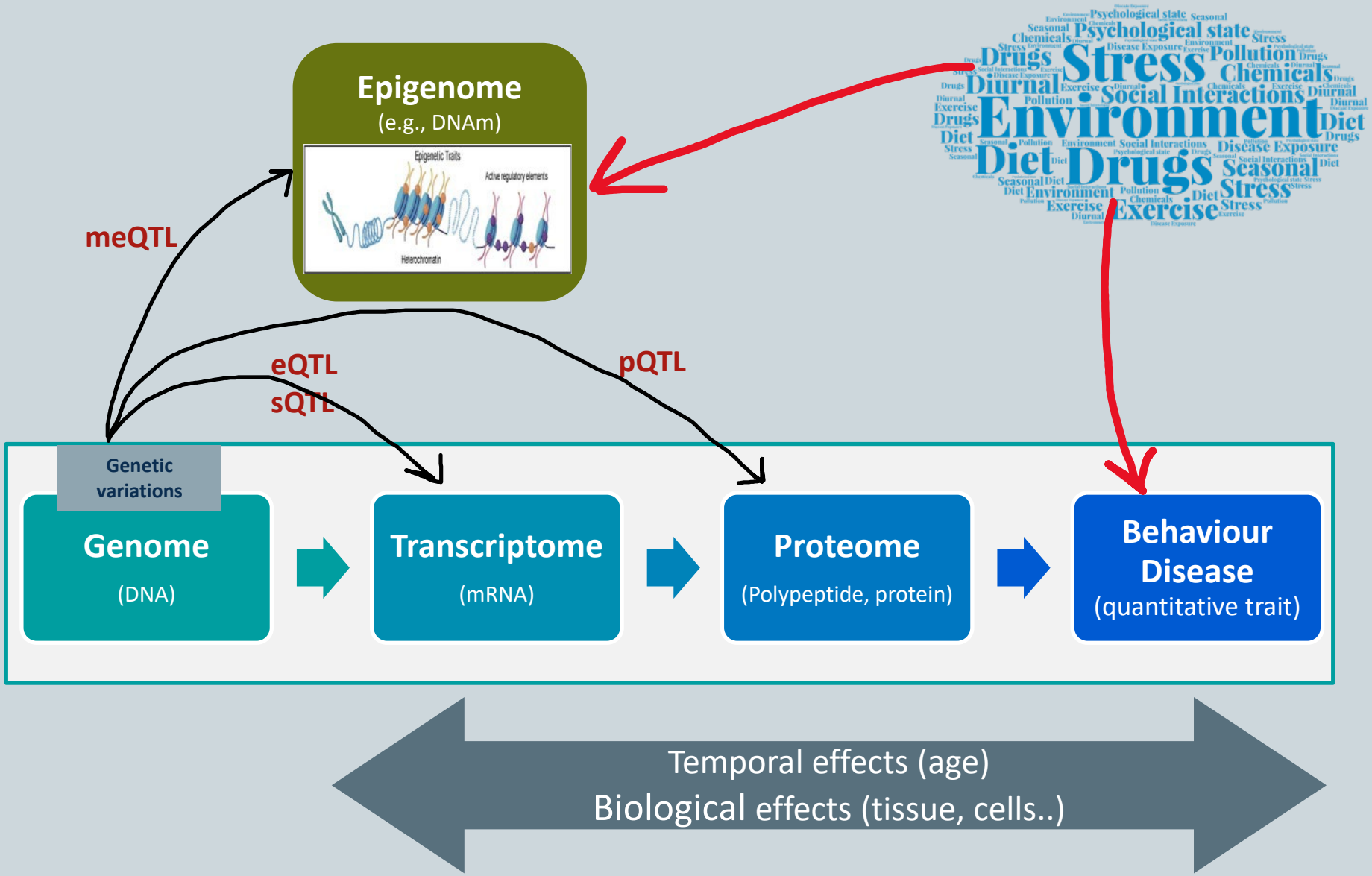
- CRHR1 = easy drug target (plasma membrane receptor)

CRHR1 is part of the stress-activated HPA axis



doi.org/10.3390/ijms18081810

Integrating measures of environmental influences into ‘omics analyses



Blood DNA methylation as biomarker for psychopathology

Epigenome-wide associations studies of externalizing behaviours (ages 14y + 19y)

IMAGEN sample; N=506

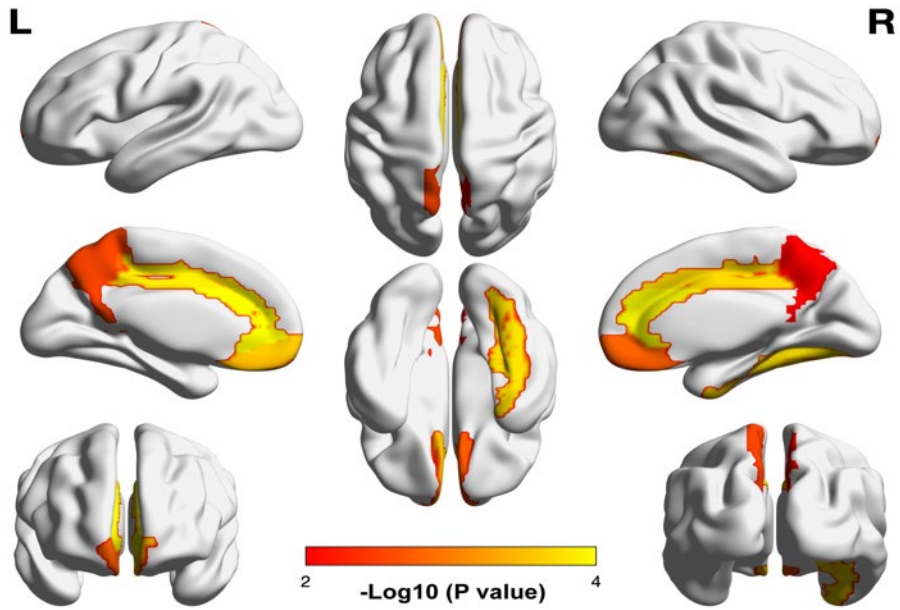
DNA methylation risk scores for externalizing behaviours (eMRS)

Associations with

Brain (grey matter volumes)

Stressful life events

eMRS associates w/ Brain structure underlying ADHD and conduct problems

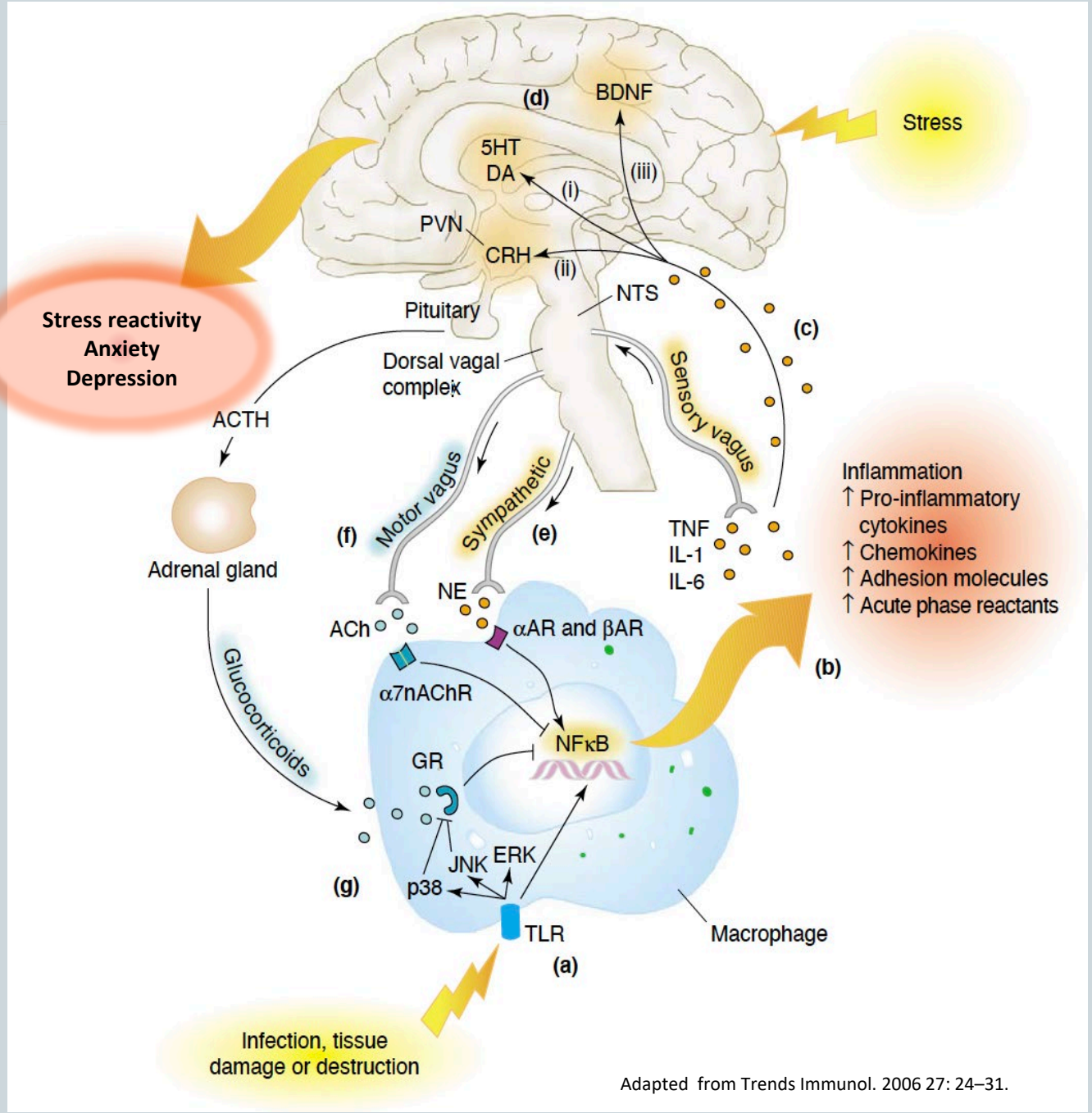


Sun Y., Jia T., *et al*. (under review)

➢ **Enrichment analyses:**

- Biological Process: regulation of tumor necrosis factor-mediated signaling pathway
- Mouse Phenotypes: small adrenal glands; abnormal substantia nigra morphology

The HPA axis, stress and the immune system

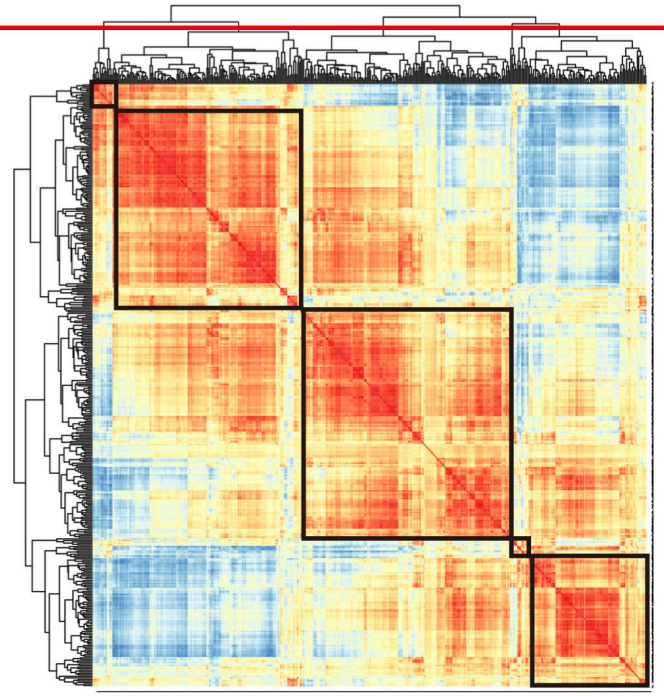


Adapted from Trends Immunol. 2006 27: 24–31.

Longitudinal study of DNA methylation

ENIGMA-Epigenetics

Clusters of conserved, co-regulated DNA_m across adolescence

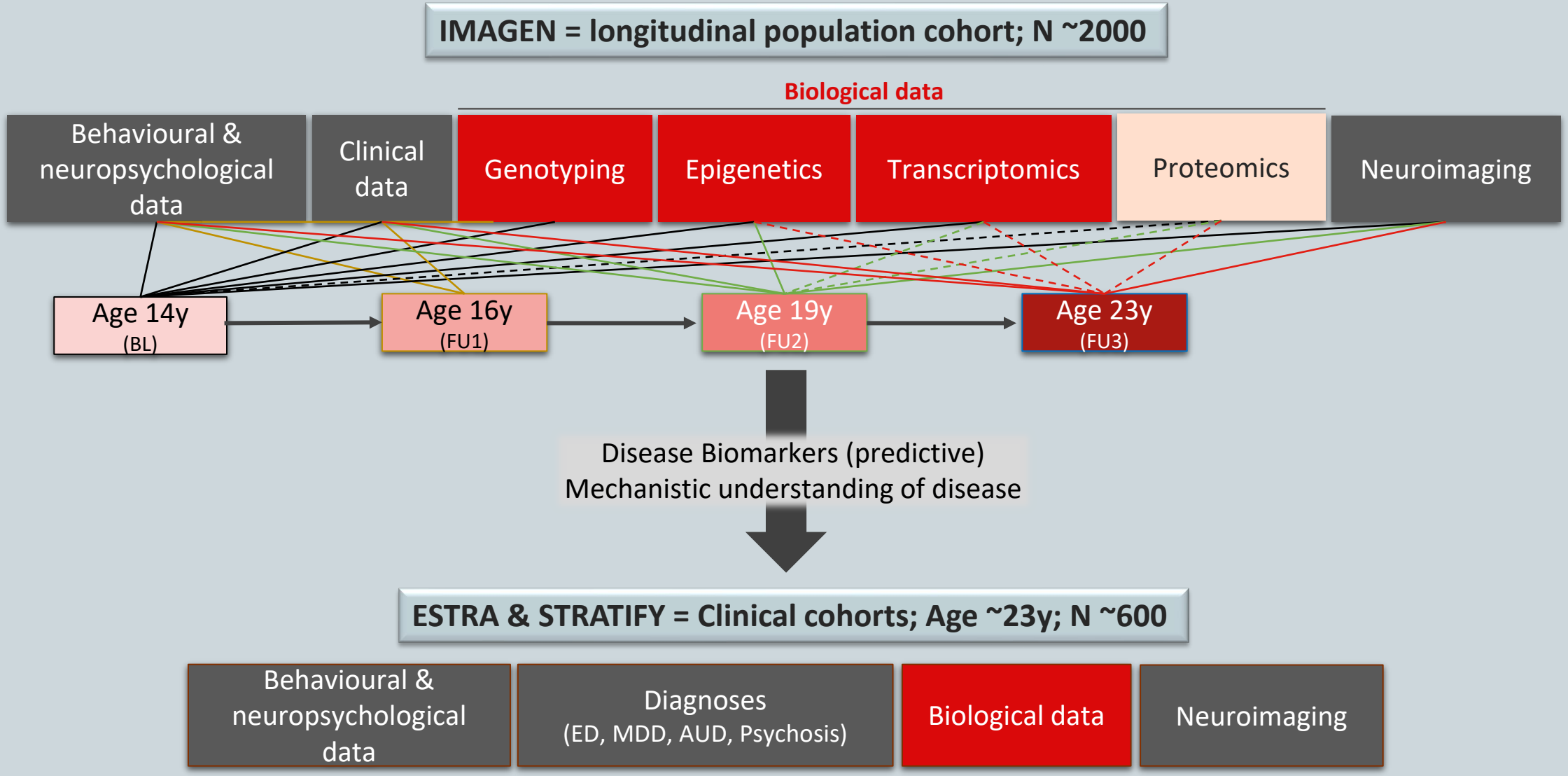


Di Chen, Tianye Jia et al., in preparation

Enrichment analyses				
	Biological process (GO)	**FDR**	**Pathway (KEGG)**	**FDR**
Cluster 1*	nervous system development	8.42E-09		
Cluster 2*	Cellular macromolecule metabolism	8.58E-71	neurodegeneration	1.69E-08
			endocytosis	6.11E-06
			spliceosome	9.22E-06
			cancer	9.22E-06
			HPV infection	9.22E-06
Cluster 3	localisation	2.58E-08	actin cyotoskeleton	5.06E-03
	neuron projection	2.58E-06	Insulin signalling	1.02E-02
	anatomical structure development	2.92E-06	Axon guidance	1.30E-02
Cluster 4	Cell fate commitment	2.25E-04	Stem cell pluripotency	4.00E-03
	Brain development	2.25E-04	Breast cancer	8.60E-03

*Large overlap with S Horvath DNAm age

IMAGEN, STRATIFY & ESTRA – Deeply phenotyped longitudinal cohorts



Enrichment of deeply phenotyped cohorts by acquisition of multi-omics data

IMAGEN, ALSPAC & ABCD

Integrative analyses with other data layers

Environmental profiles

Acquisition of longitudinal multi-'omics data

Genome (SNPs genotyping)

Transcriptome (RNA seq.)

Age 14 | Age 19 | Age 23

Epigenome (DNA_m; EPIC array)

Age 14 | Age 19 | Age 23

Proteome (Scanning SWATH)

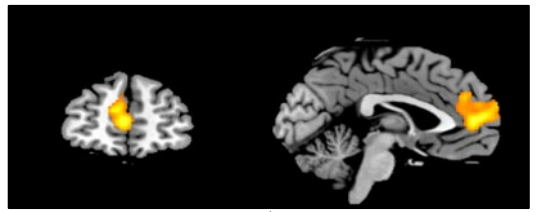
Age 14 | Age 19 | Age 23

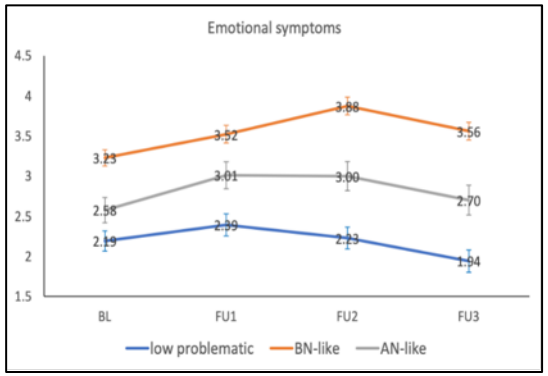
Multi-'omics data integration

Age-dependant multi-omics xQTL maps

Publicly available tissue-specific datasets (e.g., building blood-brain relationships)

Brain & Phenotypic data





Age 14 | Age 19 | Age 23

Molecular signatures & Pathways

Biomarkers

Molecular & neurobiological understanding of mental illness

Thank you

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